



Egharevba, Terry (2017) *Stakeholder perceptions towards conducting pharmaceutical industry-sponsored clinical trials in Sub-Saharan Africa*. PhD thesis.

<http://theses.gla.ac.uk/8451/>

Copyright and moral rights for this work are retained by the author

A copy can be downloaded for personal non-commercial research or study, without prior permission or charge

This work cannot be reproduced or quoted extensively from without first obtaining permission in writing from the author

The content must not be changed in any way or sold commercially in any format or medium without the formal permission of the author

When referring to this work, full bibliographic details including the author, title, awarding institution and date of the thesis must be given

Enlighten:Theses
<http://theses.gla.ac.uk/>
theses@gla.ac.uk

**Stakeholder perceptions towards conducting pharmaceutical industry-
sponsored clinical trials in Sub-Saharan Africa**

Terry Egharevba

BSc, MSc

**Submitted in fulfilment of the requirements for the degree of Doctor of
Philosophy**

**Institute for Health & Wellbeing
College of Medicine, Veterinary, and Life Sciences
University of Glasgow**

September 2017

Abstract

Background: Clinical trials are prospective studies in volunteers to test the safety and efficacy of a drug or intervention in a well-defined, controlled experiment. Pharmaceutical companies spend billions of dollars each year on clinical trials. Yet, despite the rising levels of chronic diseases and evidence suggesting that black patients may respond to treatments differently than their white counterparts, Sub-Saharan Africa is still represented in very few industry-sponsored trials. In addition to any immediate potential therapeutic benefit and the ability to grant patients greater access to drugs that they might not normally be able to obtain, clinical trials may also bring collateral benefits, such as investments in infrastructure and resources. To this end, clinical trials may be useful in helping to address the rising levels of chronic disease in the Sub-Saharan region of Africa. Additionally, it may not always be appropriate to extrapolate data from trials conducted in patients in the West and apply them to patients in other regions of the world, as the literature demonstrates that for certain medicines, treatment effects may differ due to genetic variations between ethnic groups. **Aim:** The aim of the study was to better understand stakeholder perceptions of the issues associated with the conduct of pharmaceutical industry-sponsored clinical trials in chronic diseases in Sub-Saharan Africa. A further goal was understanding what benefit, if any, conducting such trials could confer to the population and region. **Methods:** A multi-methods approach was adopted. The first part of the study focused on the use of semi-structured qualitative interviews with various stakeholders to identify the themes most relevant to the research objectives. The contents of the interview transcripts were thematically analysed, and a quantitative online questionnaire was created on the basis of the themes that emerged from the interviews. This questionnaire was then administered to a larger number of similar stakeholders to corroborate the findings from the first part of the study. **Results:** The interviews identified five main overarching themes. Those themes were as follows: (1) ethical, (2) commercial, (3) medical/scientific, (4) educational, and (5) practical. All five themes are closely related and oftentimes impact one another. The ethical issues largely related to the provision and availability of medicines post-trial and informed consent, as well as to the potential for corruption and fraud by both investigators and pharmaceutical companies operating outside the scope of tightly regulated Western competent authorities and ethics committees. The commercial considerations that were raised primarily centred on the fact that pharmaceutical companies are businesses, many of which have obligations to shareholders,

and on the fact that drug development is tremendously expensive. The majority of the profit generated by pharmaceutical companies comes from their sales in the West, which is why their focus remains on that part of the world. The medical and scientific issues were primarily related to the evolution of Sub-Saharan Africa's disease landscape and pharmaceutical companies' responsibility to their global patients to ensure a robust understanding of how their drugs affect patients of varying ethnic backgrounds in different parts of the world. The educational issues were mainly linked to public awareness regarding what clinical trials are, as well as to the education of investigators, research staff, and ethics committee members. The final theme to emerge was practical issues raised in relation to a lack of infrastructure and oversight. The results of the questionnaire mostly echoed the findings of the interviews. Through their questionnaire responses, participants indicated that they felt that the pharmaceutical industry does have an ethical and scientific responsibility to do more to ensure that its drugs are tested in developing parts of the world, such as Sub-Saharan Africa. However, respondents indicated that pharmaceutical companies should not conduct trials in regions where they have no intention of selling their products and that the three largest barriers precluding the conduct of clinical trials in that part of the world are a lack of adequate infrastructure, a lack of commercial attractiveness, and concerns around unethical behaviour. **Discussion:** Although there are inherent risks and disadvantages associated with participating in clinical trials, the benefits are well known and understood for participants in the West. Therefore, most respondents across the stakeholder groups could see the potential benefits of research for Sub-Saharan Africa. However, many within the pharmaceutical stakeholder group exhibited unfamiliarity with the evolving disease landscape and level of infrastructure within Sub-Saharan Africa. The ethical issues and associated practicalities of conducting trials in that part of the world were likewise not well understood. The results of the study suggest that respondents across all stakeholder groups feel that the pharmaceutical industry needs to do more to make drugs available to patients in developing countries, both commercially and through research. As a justification, they pointed to the industry's ethical and scientific responsibilities to do so. The commercial benefits that the industry could gain from conducting an increased number of clinical trials in Sub-Saharan Africa did not appear to be well understood by the research participants. The results also illustrated that the respondents did not think that chronic diseases should be prioritised over infectious diseases, or vice versa. By carrying out this research, important questions were raised regarding the capabilities of countries within Sub-Saharan Africa, and topics associated with the increasing prevalence of chronic diseases in that region were explored. All stakeholder groups agreed that pharmaceutical companies can play a role in addressing

levels of rising chronic disease through the conduct of clinical trials. The findings of this research led to several recommendations, including allowing countries in the region to participate in bridging studies as a starting point, establishing national databases, and revisiting the restrictive wording in certain current ethical regulations.

Table of Contents

| | |
|---|-----------|
| ABSTRACT | 2 |
| TABLE OF CONTENTS..... | 5 |
| LIST OF TABLES | 11 |
| LIST OF FIGURES | 12 |
| APPENDICES | 13 |
| DEDICATION..... | 14 |
| DECLARATION..... | 15 |
| ACKNOWLEDGMENTS | 16 |
| ACRONYMS | 17 |
| PREFACE..... | 19 |
| CHAPTER 1: INTRODUCTION..... | 1 |
| 1.1 STUDY BACKGROUND AND OBJECTIVES | 1 |
| 1.2 BACKGROUND: SUB-SAHARAN AFRICA | 2 |
| 1.2.1 <i>The region</i> | 2 |
| 1.2.2 <i>Evolution of the socioeconomic and disease landscape</i> | 3 |
| 1.2.3 <i>Chronic diseases in Sub-Saharan Africa</i> | 4 |
| 1.3 CURRENT CLINICAL RESEARCH FOCUS IN SUB-SAHARAN AFRICA | 8 |
| 1.4 CLINICAL TRIAL REGULATORY AND ETHICAL ENVIRONMENT: NIGERIA & GHANA..... | 9 |
| 1.4.1 <i>Clinical trial regulatory approval in Nigeria</i> | 11 |
| 1.4.2 <i>Clinical trial regulatory approval in Ghana</i> | 11 |
| 1.4.3 <i>Clinical trial ethical approval in Nigeria</i> | 12 |
| 1.4.4 <i>Clinical trial ethical approval in Ghana</i> | 12 |
| 1.5 THE POTENTIAL ROLE OF CLINICAL TRIALS AND DRUG RESEARCH IN COMBATING CHRONIC DISEASE..... | 12 |
| 1.6 ETHICAL AND PRACTICAL ISSUES AROUND SUB-SAHARAN AFRICA’S PARTICIPATION IN CLINICAL TRIALS FOR CHRONIC DISEASES | 15 |
| 1.7 CONCEPTUAL FRAMEWORK DEVELOPMENT AND STUDY OBJECTIVES | 17 |
| 1.8 CURRENT CLINICAL RESEARCH FOCUS IN SUB-SAHARAN AFRICA..... | 24 |
| 1.9 CONCLUSION..... | 25 |

| | | |
|---|--|----|
| 1.10 | STUDY OBJECTIVES | 25 |
| CHAPTER 2: KEY LITERATURE ON THE ADVANTAGES AND | | |
| DISADVANTAGES OF PARTICIPATING IN CLINICAL TRIALS.....26 | | |
| 2.1 | BACKGROUND..... | 26 |
| 2.2 | LITERATURE SEARCH | 27 |
| 2.3 | BENEFITS | 28 |
| 2.3.1 | <i>Benefits to the patient.....</i> | 28 |
| 2.3.2 | <i>Benefits to the researcher.....</i> | 31 |
| 2.3.3 | <i>Benefits to society.....</i> | 32 |
| 2.3.3 | <i>Benefits for pharmaceutical companies</i> | 34 |
| 2.4 | DISADVANTAGES | 35 |
| 2.4.1 | <i>Disadvantages for the patient</i> | 35 |
| 2.4.2 | <i>Disadvantages for the researcher</i> | 37 |
| 2.4.3 | <i>Disadvantages for society</i> | 38 |
| 2.4.4 | <i>Disadvantages for pharmaceutical companies</i> | 39 |
| 2.5 | CONCLUSION..... | 39 |
| CHAPTER 3: SYSTEMATIC LITERATURE REVIEW OF STAKEHOLDER | | |
| VIEWS ON THE CONDUCT OF CLINICAL RESEARCH IN SUB-SAHARAN | | |
| AFRICA.....41 | | |
| 3.1 | BACKGROUND..... | 41 |
| 3.1.1 | <i>Rationale and objectives</i> | 41 |
| 3.2 | METHODS..... | 41 |
| 3.2.1 | <i>Types of studies, phenomena of interest, and context.....</i> | 41 |
| 3.2.2 | <i>Search strategy.....</i> | 42 |
| 3.2.3 | <i>Screening and selection of papers.....</i> | 45 |
| 3.2.4 | <i>Methodological quality</i> | 46 |
| 3.2.5 | <i>Narrative synthesis.....</i> | 46 |
| 3.3 | RESULTS | 47 |
| 3.4 | DISCUSSION | 47 |
| 3.4.1 | <i>Stigma/fear.....</i> | 47 |
| 3.4.2 | <i>Therapeutic/preventative misconception</i> | 50 |
| 3.4.3 | <i>Informed consent.....</i> | 51 |
| 3.4.4 | <i>Mistrust</i> | 53 |
| 3.4.5 | <i>Relationship-building and community engagement</i> | 55 |

| | | |
|-------------------------------------|--|-----------|
| 3.4.5 | <i>Research benefits and beneficiaries</i> | 57 |
| 3.4.6 | <i>Infrastructure</i> | 59 |
| 3.4.7 | <i>Researcher perspectives</i> | 60 |
| 3.5 | LIMITATIONS | 61 |
| 3.6 | CONCLUSIONS | 62 |
| CHAPTER 4: METHODOLOGY | | 63 |
| 4.1 | INTRODUCTION..... | 63 |
| 4.2 | RESEARCH PARADIGM | 63 |
| 4.2.1 | <i>Epistemological and ontological starting points</i> | 63 |
| 4.2.2 | <i>Pragmatism</i> | 64 |
| 4.2.3 | <i>Which paradigm: ‘naturalism’ or ‘progressivism’?</i> | 65 |
| 4.3 | MULTIMETHOD RESEARCH | 66 |
| 4.3.1 | <i>Strengths of multimethod research</i> | 66 |
| 4.3.2 | <i>Weaknesses of multimethod research</i> | 67 |
| 4.3.3 | <i>Triangulation/crystallisation</i> | 68 |
| 4.4 | QUALITATIVE STUDY | 69 |
| 4.4.1 | <i>Why include a qualitative perspective?</i> | 69 |
| 4.4.2 | <i>Telephone interviews</i> | 70 |
| 4.4.3 | <i>Qualitative data rigour</i> | 71 |
| 4.5 | QUANTITATIVE STUDY | 74 |
| 4.5.1 | <i>Questionnaires</i> | 74 |
| CHAPTER 5: METHODS | | 77 |
| 5.1 | INTRODUCTION..... | 77 |
| 5.2 | OVERVIEW | 77 |
| 5.2.1 | <i>Interviews</i> | 78 |
| 5.2.2 | <i>Questionnaire</i> | 80 |
| 5.3 | ETHICAL APPROVAL | 84 |
| 5.4 | POPULATION AND SAMPLE..... | 84 |
| 5.5 | THE INTERVIEWS | 86 |
| 5.5.1 | <i>Identifying and contacting the interview participants</i> | 86 |
| 5.5.2 | <i>Interview conduct</i> | 87 |
| 5.5.3 | <i>Informed consent</i> | 88 |
| 5.5.4 | <i>Anonymity and confidentiality</i> | 88 |
| 5.5.5 | <i>Transcription</i> | 88 |

| | | |
|-------------------|---|-----------|
| 5.5.6 | <i>Qualitative data coding and analysis</i> | 88 |
| 5.6 | QUALITATIVE ANALYSIS AND THEME DEVELOPMENT | 89 |
| 5.6.1 | <i>Thematic analysis</i> | 90 |
| 5.7 | THE QUESTIONNAIRE | 95 |
| 5.7.1 | <i>Identifying and contacting questionnaire participants</i> | 95 |
| 5.7.2 | <i>Informed consent</i> | 96 |
| 5.7.3 | <i>Anonymity and confidentiality</i> | 96 |
| 5.7.4 | <i>Data coding and analysis</i> | 97 |
| 5.8 | REFLEXIVITY | 97 |
| CHAPTER 6: | RESULTS | 99 |
| 6.1 | RESULTS | 99 |
| 6.1.1 | <i>Interview respondents</i> | 99 |
| 6.1.2 | <i>Questionnaire respondents</i> | 100 |
| 6.2 | THEME DEVELOPMENT | 103 |
| 6.3 | ETHICAL THEMES | 103 |
| 6.3.1 | <i>Provision of medicines post-trial</i> | 103 |
| 6.3.2 | <i>Informed consent</i> | 107 |
| 6.3.3 | <i>Ethical responsibility to patients globally</i> | 116 |
| 6.4 | UNETHICAL BEHAVIOUR..... | 118 |
| 6.4.1 | <i>Corruption during study set-up and conduct</i> | 118 |
| 6.4.2 | <i>Unethical behaviour by pharmaceutical companies</i> | 121 |
| 6.4.3 | <i>Exploitation of patients</i> | 125 |
| 6.4.4 | <i>Falsification of data for financial gain</i> | 126 |
| 6.4.5 | <i>Fear of being perceived as corrupt</i> | 127 |
| 6.5 | COMMERCIAL VIABILITY AND CONSIDERATIONS | 129 |
| 6.5.1 | <i>Pharmaceutical companies are businesses</i> | 129 |
| 6.5.2 | <i>Drug development is expensive</i> | 131 |
| 6.5.3 | <i>Sub-Saharan Africa's commercial relevance</i> | 133 |
| 6.6 | THE GLOBAL PRESENCE OF THE PHARMACEUTICAL INDUSTRY | 137 |
| 6.6.1 | <i>Global availability of medicines</i> | 137 |
| 6.6.2 | <i>Ensuring global accessibility to medicines</i> | 139 |
| 6.6.3 | <i>Importance of conducting trials in Sub-Saharan Africa</i> | 139 |
| 6.7 | MEDICAL/SCIENTIFIC THEMES | 140 |
| 6.7.1 | <i>The pharmaceutical industry's responsibility to patients globally: Understanding interethnic variations in treatment responses</i> | 140 |

| | | |
|---|---|------------|
| 6.7.2 | <i>Evolution of the disease landscape</i> | 144 |
| 6.7.3 | <i>Lack of epidemiological data</i> | 148 |
| 6.8 | EDUCATION/TRAINING | 151 |
| 6.9 | PRACTICAL/OPERATIONAL THEMES | 154 |
| 6.10 | BIGGEST BARRIERS AND GENERAL CONSIDERATIONS | 157 |
| 6.11 | OTHER CONSIDERATIONS | 160 |
| 6.12 | DISCUSSION AND INTERPRETATION OF RESULTS | 162 |
| CHAPTER 7: DISCUSSION | | 163 |
| 7.1 | STUDY OBJECTIVE 1: UNDERSTANDING THE BENEFITS OF INDUSTRY-SPONSORED RESEARCH FOR SUB-SAHARAN AFRICA | 164 |
| 7.1.1 | <i>Medical/scientific benefits and beneficiaries of clinical research in Sub-Saharan Africa</i> | 165 |
| 7.1.2 | <i>Financial benefits</i> | 171 |
| 7.1.3 | <i>Practical/operational benefits</i> | 177 |
| 7.1.4 | <i>Educational benefits</i> | 180 |
| 7.1.5 | <i>Ethical benefits</i> | 183 |
| 7.2 | STUDY OBJECTIVE 2: UNDERSTAND THE ETHICAL IMPLICATIONS ASSOCIATED WITH RESEARCH IN SUB-SAHARAN AFRICA | 186 |
| 7.2.1 | <i>Informed consent</i> | 187 |
| 7.2.2 | <i>Corruption and unethical behaviour</i> | 191 |
| 7.2.3 | <i>Provision of medicines post-trial</i> | 197 |
| 7.2.4 | <i>The pharmaceutical industry's responsibilities to patients globally</i> | 200 |
| 7.3 | REVISED FRAMEWORK FOR INDUSTRY-SPONSORED TRIALS | 202 |
| 7.4 | RAISING AWARENESS OF CHRONIC DISEASES IN SUB-SAHARAN AFRICA | 208 |
| 7.5 | STRENGTHS AND LIMITATIONS OF THE STUDY | 209 |
| 7.5.1 | <i>Strengths</i> | 209 |
| 7.5.2 | <i>Limitations</i> | 211 |
| CHAPTER 8: CONCLUSIONS AND RECOMMENDATIONS | | 214 |
| 8.1 | CONCLUSIONS | 214 |
| 8.2 | RECOMMENDATIONS | 217 |
| 8.2.1 | <i>Strategic placement of clinical trials</i> | 217 |
| 8.2.2 | <i>Starting with bioequivalence and bridging studies and the establishment of national databases</i> | 218 |
| 8.2.3 | <i>Stakeholder discussions</i> | 219 |

| | | |
|-------------------------|--|------------|
| 8.2.4 | <i>Governments must lead by example</i> | 220 |
| 8.2.5 | <i>Revisiting the interpretation of current regulations</i> | 220 |
| 8.2.6 | <i>Acknowledging and addressing concerns and perceptions of corruption</i> | 221 |
| 8.2.7 | <i>Revisiting pricing structures</i> | 221 |
| REFERENCES | | 310 |

List of tables

| | |
|--|-----|
| Table 1: Annotated framework for ethical principles and benchmarks for multinational clinical research, taken from Emanuel et al. (2004)..... | 22 |
| Table 2: Results of the PubMed searches..... | 43 |
| Table 3: Results of the Science Direct searches..... | 44 |
| Table 4: Number of planned and actual interviewees who participated in interviews. | 86 |
| Table 5: Annotated conceptual framework illustrating the links to the overarching thematic categories identified through qualitative analysis | 94 |
| Table 6: Themes that emerged from coding and analysis. | 104 |
| Table 7: Results of statements 9-11: Informed consent | 108 |
| Table 8: Results of statements 12-17: Ethics and behaviour | 119 |
| Table 9: Results of statements 5-8: Commercial considerations | 136 |
| Table 10: Results of statements 1-4: The global presence of the pharmaceutical industry | 138 |
| Table 11: Results of statements 19-20: Ethical and scientific responsibilities of global pharmaceutical companies | 150 |
| Table 12: Summary of barriers to clinical trials in Sub-Saharan Africa not specifically addressed in the interviews or questionnaire | 159 |
| Table 13: Suggested revisions to the Emanuel et al. (2004) framework specific to industry-sponsored clinical trials..... | 207 |

List of figures

| | |
|---|-----|
| Figure 1: Map illustrating countries in the Sub-Saharan region of Africa..... | 3 |
| Figure 2: Image taken from clinicaltrials.gov on 15 March 2011 of all clinical trials being conducted in Africa. | 10 |
| Figure 3: Image taken from clinicaltrials.gov on 3 March 2017 of all clinical trials being conducted in Africa. | 10 |
| Figure 4: Conceptual framework | 23 |
| Figure 5: Flow diagram outlining articles reviewed, considered, and selected. | 49 |
| Figure 6: Map illustrating the locations of the questionnaire respondents | 101 |
| Figure 7: Barriers to clinical trials in Sub-Saharan Africa..... | 158 |
| Figure 8: Analysis and interpretation of the theme related to the post-trial provision of medicine to trial participants | 286 |
| Figure 9: Analysis and interpretation of the theme related to informed consent..... | 287 |
| Figure 10: Analysis and interpretation of the theme related to the legacy of pharmaceutical companies in Sub-Saharan Africa. | 288 |
| Figure 11: Interpretation and analysis of codes related to pharmaceutical companies' drive for profits, the high cost of treatments, and their interrelatedness. | 289 |
| Figure 12: Analysis and interpretation of themes related to the pharmaceutical industry's responsibility to research differences in treatment outcomes in different ethnic groups .. | 290 |
| Figure 13: Analysis and interpretation of the theme related to Sub-Saharan Africa's changing landscape. | 291 |
| Figure 14: Analysis and interpretation of themes related to the lack of epidemiological data | 292 |
| Figure 15: Analysis and interpretation of themes related to deficiencies in infrastructure | 293 |
| Figure 16: Analysis and interpretation of the themes related to education..... | 294 |

Appendices

| | |
|--|-----|
| Appendix 1: Phases of clinical trials..... | 222 |
| Appendix 2: JBI QARI critical appraisal checklist..... | 223 |
| Appendix 3: Systematic qualitative review summary table | 224 |
| Appendix 4: PRISMA checklist..... | 229 |
| Appendix 5: Research protocol..... | 232 |
| Appendix 6: Interview schedule | 247 |
| Appendix 7: Questionnaire | 254 |
| Appendix 8: Participant letter of invitation (questionnaire) | 262 |
| Appendix 9: Ethics approvals | 266 |
| Appendix 10: Example email to potential participants (interview) | 269 |
| Appendix 11: HCP letter of invitation (interview) | 270 |
| Appendix 12: Pharm letter of invitation (interview)..... | 274 |
| Appendix 13: Example email sent to study 2 (questionnaire) participants | 278 |
| Appendix 14: Codes generated from the thematic analysis of the transcripts | 279 |
| Appendix 15: Analysis and interpretation of categories and themes generated from the transcript analysis..... | 286 |
| Appendix 16: List of respondents who participated in study 1 (interviews) | 295 |
| Appendix 17: List of respondents who participated in study 2 (questionnaire) | 296 |
| Appendix 18: Consent form (interviews)..... | 300 |
| Appendix 19: Published article | 301 |

Dedication

I am dedicating this work to a number of people who have supported me throughout my journey. Firstly, I would like to dedicate this thesis to my entire family, especially my parents and Oga, whose hard work and sacrifice continue to inspire and encourage me. Moreover, my brothers' support and perseverance in their own pursuits has served as an example for me to emulate. This work is also dedicated to Winnie Williams and the Kamara's and all those who have lifted my name in prayer over the past six years. Last but not least, I would like to dedicate this PhD thesis to my beautiful fiancée, Tonisha, for her unwavering support and faith in me, as well as 'the borbors' and LCR who have supported me and given me encouragement during the times I felt like giving up.

Declaration

I, Terry Efeosa Egharevba, hereby declare as the named author that I have conducted the research detailed in this thesis. The research was carried out at the Institute of Health and Wellbeing, University of Glasgow, under the supervision of Professor Jacqueline Atkinson, Dr Rebecca Shaw, Dr Elise Whitley, Dr Samira Ouedraogo and Dr Shona Hilton (due to staff turnover supervisors changed during the course of research). I declare that all the materials presented in this thesis are my own work, apart from those cited and duly acknowledged.

Acknowledgments

‘...but those who hope in the LORD will renew their strength. They will soar on wings like eagles; they will run and not grow weary, they will walk and not be faint.’ (Isaiah 40:31)

God in His infinite grace has given me the strength, patience, and spirit of perseverance to complete this work, and all praise, glory, and honour belong to Him.

I would like to acknowledge and give my sincerest thanks to my academic supervisors, Professor Jacqueline Atkinson and Dr Rebecca Shaw, first and foremost for their patience, enthusiasm, and support. Moreover, I would like to express my gratitude for teaching and encouraging me to think critically, grow intellectually, and write academically. A special thanks goes to Professor Atkinson for staying on with the Institute of Health and Wellbeing long past what her obligations required to see me across the finish line. I would also like to thank Margaret Ashton for her tireless administrative support, which was frequently made more complex through my being based remotely.

A special thank you is also due to my colleagues and friends who took the time to help me with pilot versions of my interview schedule and questionnaire (especially Sarah O’Mahony and Stephen Coates). My sincerest gratitude also goes to Paul Duffy, who introduced me to the world of clinical research and took a chance on me when nobody else would.

To my friends and family who have encouraged and supported me, thank you and God bless you. I would also like to extend my deepest gratitude to my extended family and friends. Moreover, a huge thank you is also due to all of those who were involved in the research as interview respondents or questionnaire participants, as well as to all my employers over the past six years, who have been encouraging, patient, and supportive.

Acronyms

| | |
|---------|---|
| AACI | American Association of Cancer Institute |
| AD | Associate director |
| AIDS | Acquired immunodeficiency syndrome |
| AMANET | African Malaria Network |
| BP | Blood pressure |
| CAQDAS | Computer-assisted qualitative data analysis software |
| CCA | Constant comparative analysis |
| CCOP | Community clinical oncology programme |
| CRA | Clinical research associate |
| CRO | Clinical research organisation |
| CT | Clinical trials |
| CTA | Clinical trial application |
| CV | Curriculum vitae |
| DALY | Disability-adjusted life years |
| DRC | Democratic Republic of the Congo |
| DSMB | Drug safety monitoring board |
| eNOS | Endothelial nitrous oxide synthase |
| EVD | Ebola virus disease |
| FIH | First in human |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GDP PPP | Gross domestic product at purchasing power parity |
| GHS | Ghana Health Service |
| HCP | Healthcare professional |
| HER | Human epidermal growth factor |
| IB | Investigator's brochure |
| ICH GCP | International Conference on Harmonisation of Good Clinical Practice |
| ICF | Informed consent form |
| IEC | Institutional ethics committee |
| IMP | Investigational medicinal products |

| | |
|-------|--|
| IP | Intellectual property |
| IRB | Institutional review board |
| LATAM | Latin America |
| LOC | Local operation companies |
| NCI | National Cancer Institute |
| NHREC | National Health Research Ethics Committee |
| NICE | National Institute for Clinical Excellence |
| NIH | National Institute for Health |
| NME | New molecular entities |
| NGO | Non-governmental organisation |
| PHEIC | Public health emergency of international concern |
| PV | Pharmacovigilance |
| QALY | Quality-adjusted life year |
| R&D | Research and development |
| RCT | Randomised clinical trial |
| SmPC | Summary of product characteristics |
| SSA | Sub-Saharan Africa |
| STI | Sexually transmitted infection |
| TA | Therapeutic area |
| TB | Tuberculosis |
| US | United States |
| WHO | World Health Organisation |

Preface

'Global is not the opposite of domestic. Global health is not foreign health. A global outlook means we recognise that the local and global are united, increasingly interdependent, and interconnected.' - Dr Julio Frenk (Harvard Magazine, 2009)

I began working in the pharmaceutical industry over 12 years ago and have always worked for multinational pharmaceutical or biotechnology companies. Over time, I have been fascinated by several aspects of clinical trials, not least the astronomical costs associated with conducting research and the phenomenal profits that successful drugs can generate for their license holders. Also of interest has been the global nature of clinical research and the potential benefits that it can provide to not only the research subjects, but also the participating hospitals and communities.

One particular aspect of clinical trials that has continued to concern me is the fact that many of the global clinical trials on which I have personally worked over the years have been conducted in a handful of the richest countries, and they have almost always enrolled a disproportionately high number of Caucasian patients. This particular observation became somewhat of an obsession, and I was able to use my master's dissertation to further explore the reasons for such a significant underrepresentation of ethnic minorities in clinical trials (Egharevba, 2008).

With my current research, the aim was to take this investigation one step further and explore the reasons why countries in Sub-Saharan Africa have not, to any significant extent, been involved in many industry-sponsored clinical trials to date. The lack of engagement with these countries exists despite many pharmaceutical companies complaining of an inability to recruit subjects from minority backgrounds to clinical studies. Further, there is evidence within the literature that 10-20% of all trials fail to recruit a single patient and that nearly 50% of clinical trial sites fail to meet their recruitment targets (Steele, 2013; Lo, 2014).

The discussion around the conduct of clinical trials in Sub-Saharan Africa and other developing countries is not a new one. However, to date, this debate does not appear to have featured stakeholder crosstalk, which I believe is required for progress to be made. The failure to initiate and engage in robust discussions involving all key stakeholders—without shying away from potentially sensitive topics, such as socioeconomics, cultural nuances, and political correctness—has, in my opinion, precluded the fostering of more fruitful dialogue and debate on this topic.

The pharmaceutical industry's need for clinical trial subjects, a lack of knowledge around interethnic variations in treatment responses to certain classes of drugs, and a significant underrepresentation of ethnic minorities in clinical trials create a potentially mutually beneficial supply-demand paradigm. With data demonstrating clear increases in levels of chronic disease (De Graft Aikins et al., 2010), there is arguably scope for a greater pharmaceutical presence in Sub-Saharan Africa. A higher pharmaceutical industry presence in Sub-Saharan Africa could, in return, help bring a share of the resources, expertise, and infrastructure required to develop the healthcare systems of the countries in that region and to bring them closer in line with their Western counterparts. Increasing ethnic minority participation in research could also better allow researchers to explore variations in treatment effects between races. Globalisation has led to healthcare systems becoming increasingly dependent on each other, and clinical trials potentially offer one mechanism through which the standard of healthcare in countries throughout the world could become more equal (Marmot Friel, Houwelling, & Taylor, 2008; Weigmann, 2015).

There are, however, a myriad of issues, ethical and otherwise, that have precluded clinical trials from being placed in Sub-Saharan Africa to date. The aim of this study was to investigate the issues associated with the conduct of pharmaceutical industry-sponsored clinical trials in Sub-Saharan Africa with various stakeholder groups, and the focus was on chronic diseases. The reasons that I chose to focus on chronic diseases were twofold: Firstly, as previously mentioned, there is a significant body of literature illustrating the growing levels of chronic disease in the region. Secondly, infectious disease rates are higher in developing countries (and therefore unbalanced when compared to the disease profile of Western countries). Subsequently, to compare the issues specifically related to the conduct of trials in a like-for-like manner, a decision was made to focus on those diseases that affect patients in both parts of the world (developed and developing regions).

To prevent the most obvious confounding factors from diverting the research from its intended focus, countries with stable economies and political environments were selected. However, many of the themes explored are generalisable, not only to other countries in Sub-Saharan Africa but also to other developing countries, as they concern issues that occur throughout the developing world, such as the scarcity of resources and expertise.

This thesis presents the results of my research as follows: Chapter 1 provides an introduction to the topic, briefly describes the region's current clinical trial focus, and offers a high-level overview of the existing ethical and regulatory framework in the two countries of interest. Chapter 2 describes the advantages and disadvantages of clinical research from a general perspective (i.e., in a manner that is not country- or region-specific). Chapter 3 presents the results of a systematic literature review of qualitative studies examining stakeholders' views of clinical trials in Sub-Saharan Africa. That background material provides context for the empirical gap that this research sought to address. Chapter 4 comprises a discussion on the methodology employed within this study. In Chapter 5, the specific methods that were applied during the interviews and questionnaires are covered. Chapter 6 then presents the results of both parts of the study. The final two chapters (Chapters 7 and 8) comprise a discussion on the results of both parts of the research and then draw final conclusions and recommendations, respectively.

CHAPTER 1: INTRODUCTION

1.1 Study background and objectives

Africa bears a disproportionate burden of disease in relation to healthcare funding. In 1990, developing countries carried almost 90% of the global disease burden (measured in disability-adjusted life years [DALYs]), yet were the recipients of only 10% of global healthcare funding. The severity of the most prevalent diseases in the region, combined with tropical disease epidemics, a historical lack of adequate infrastructure and resources, and a dearth of sufficient healthcare facilities, makes the task of delivering adequate levels of patient care in Sub-Saharan Africa a significant challenge (Heyns & Borman, 2008).

Bravemen and Tarimo (2002) reported that in many parts of rural Sub-Saharan Africa, access to hospitals and treatment is difficult due to high levels of poverty coupled with prohibitively high costs for medicines. That factor in turn precludes access to necessary equipment and medication for much of the region's population. Additional challenges related to the use of non-traditional healing (e.g., spiritual healers) have meant that many Africa's poorest patients are more susceptible to inadequate treatment interventions (Asuni, 1979).

Clinical trials are prospective studies in volunteers that enable researchers to measure the risks and benefits of a new therapeutic intervention. These trials follow a well-defined pathway that allows for careful elucidation of positive and negative effects, and they are supervised by health authorities and ethics committees at every phase (Schueler & Buckely, 2014). Appendix 1 provides a brief overview of the various stages of clinical trials.

Clinical trials could potentially help to improve medical care and may play a role in helping healthcare decision-makers direct limited resources to the strategies and treatments that are most effective (National Heart, Lung & Blood Institute, 2014) in their local populations. To this end, the conduct of clinical trials could play a role in helping to address the challenges associated with Sub-Saharan Africa's evolving disease landscape.

1.2 Background: Sub-Saharan Africa

The following sub-sections provide a high-level overview of the Sub-Saharan region of Africa, its changing socioeconomic situation, and the subsequent impact on the prevailing disease landscape.

1.2.1 The region

As illustrated in Figure 1, Sub-Saharan Africa is defined geographically as the 47 countries that lie south of the Sahara Desert. According to the World Bank (2017), the region had approximately one billion inhabitants as of 2015, with an annual population growth of approximately 2.7% per annum. Nigeria has the largest population in Sub-Saharan Africa (182 million people) and accounts for approximately 18% of the continent's total population. The smallest population is that of the Seychelles at 93,000 inhabitants. In geographical terms, the largest country in the Sub-Saharan region is the Democratic Republic of the Congo (DRC), which covers 2.3 million square kilometres (km²), and the smallest is the Seychelles at just under 500 km² (Central Intelligence Agency, 2014). The Sub-Saharan region of Africa contains a number of the poorest countries in the world (World Bank, 2011). According to the International Monetary Fund, the three countries in the region with the highest gross domestic product (GDP) based on purchasing power parity (PPP) per capita are the Seychelles, Equatorial Guinea, and Botswana (International Monetary Fund, 2014). A country's GDP PPP is used to compare standards of living internationally, taking into account local living costs and inflation (Index Mundi, 2011). The three poorest countries in the region (based on GDP PPP) are also the three poorest countries in the world: Zimbabwe, Liberia, and the DRC. The GDP PPP of the richest country in Sub-Saharan Africa, the Seychelles, is approximately 68 times that of the poorest, the DRC, a statistic that highlights the extent of the divide between the richest and poorest countries in the region (World Bank, 2011). According to a World Bank report, the average overall life expectancy at birth for people living in the region was 54 years in 2010, as compared with 79 years in the United States and 80 years in the United Kingdom (Trading Economics, 2010; The World Bank, 2015).

Availability and access to healthcare facilities is a subject of great concern in Sub-Saharan African countries (Makita-Ikouaya, Mombo, Rudant, & Milleliri, 2010). Problems remain regarding not only the range of services but also equality of access. These challenges are due to limitations in resources, funding, training and equipment, and the increasing scarcity of resources (Streefland, 2005).

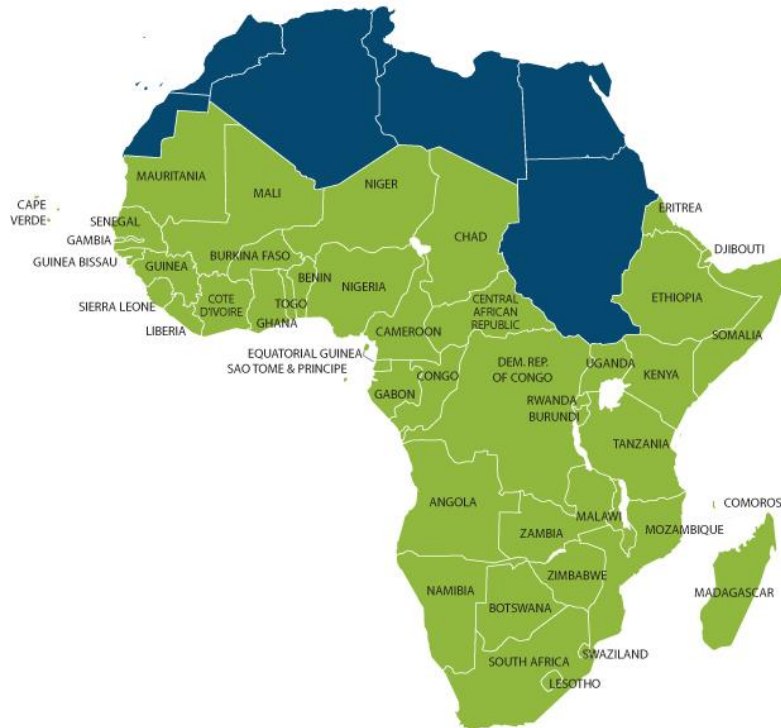


Figure 1: Map illustrating countries in the Sub-Saharan region of Africa. Image taken from the Export-Import Bank of the United States (*Export-Import Bank of the United States, 2011*).

1.2.2 Evolution of the socioeconomic and disease landscape

Although there is a lack of national databases and registries accurately quantifying the prevalence of diseases across countries in Sub-Saharan Africa, the starting position of this research project was that it is generally agreed that levels of chronic disease are increasing in the region. There are a number of changes occurring in Africa in both the socioeconomics and the disease landscape. Heyns and Borman (2008) have asserted that ‘many developing countries in Africa are experiencing a transition from diseases of poverty such as malnutrition, infective and parasitic diseases, towards chronic conditions, such as hypertension, diabetes mellitus, obesity, ischemic heart disease, stroke, chronic obstructive pulmonary disease, and lung cancer.’ Although infectious diseases still account

for 69% of deaths on the continent (Young, Critchley, & Johnstone, 2006), in 2005, the World Health Organisation (WHO) projected that over the following 10 years, the continent would experience the largest increase in death rates from cardiovascular disease, cancer, respiratory diseases, and diabetes as compared with the rest of the world (World Health Organisation, 2005).

The increase in Africa's¹ chronic disease² burden is attributed to a variety of factors, including increased life expectancies, changing lifestyle practices associated with the modernisation of the continent's growing economy, urbanisation, globalisation, and the region's sustained poverty. Although advances in education, job creation, improved housing, sanitation, and better disease control are contributing to improved health conditions, an unintended consequence has been an increase in lifestyle-related diseases, such as sexually transmitted infections (STIs), obesity, and chronic metabolic syndrome. These changes have been largely stimulated by economic growth in the region. Africa's Development Bank reported early in 2011 that 1 in 3 Africans (313 million people) were considered to belong to the middle class (defined as living on between \$2 and \$20 per day). Supplementary statistics, such as an 81% increase in car and motorcycle ownership in Ghana from 2006 to 2011 (Africa Development Bank, 2011), are also indicative of a burgeoning middle class throughout parts of Sub-Saharan Africa. The region's increasing number of people with a higher standard of living and the ability to access improved healthcare has led to a renewed and sustained focus on initiatives to expand healthcare access. The increased focus on healthcare access and quality for more of Africa's citizens has also contributed to the transition from traditional healthcare systems to more modern and well-structured ones.

1.2.3 Chronic diseases in Sub-Saharan Africa

Although the status of chronic diseases in Africa is not the focus of this research project, it is important to consider the current disease landscape of Sub-Saharan Africa to better understand the potential role of clinical trials in that region and in the treatment of chronic diseases.

¹ Where possible references related to Sub-Saharan Africa are used. Where references are not specific then references related to the entire continent are used.

² Chronic disease is a long-lasting condition that can be controlled but not cured (The Center for Managing Chronic Disease, 2011)

1.2.3.1 *Cancer*

As with other chronic diseases, trying to establish the prevalence of all cancers in the Sub-Saharan region of Africa is extremely difficult using published literature. There are numerous papers which have examined the prevalence of specific types of cancers in specific countries or cities within the region, but very little has been published on the prevalence of all cancers throughout the region. For example, Anorlu (2008) stated that there were 70,600 reported cases of cervical cancer in the Sub-Saharan region of Africa, with 54,800 reported deaths (Anorlu, 2008). The incidence of cervical cancer is still considerably high in Sub-Saharan Africa, and the prevalence rate can be up to 15 times higher in poor countries than in industrialised countries due higher rates of infection with human papillomavirus (HPV). The above-mentioned author did, however, acknowledge that this number may not be a true reflection of the incidence levels of the disease, as the rates of cervical cancer, as with most other types of cancer in many African countries, are unknown due to gross underreporting. Very few countries have functional cancer registries, and recordkeeping is minimal or non-existent.

1.2.3.2 *Diabetes*

Type 2 diabetes is by far the most common type of diabetes (90-95% of diabetes cases) and exhibits substantial prevalence rates among people in the Sub-Saharan region of Africa (Levitt, 2008). The prevalence of type 1 diabetes is between 5-10% (Osei & Schuster, 2003; Tuei, Maiyoh, & Chung-Eun, 2010). Peer, Kengne, Motala and Mbanya (2014) reported a type 1 diabetes prevalence of 4.85%, with an expected increase to 5.35% by 2035. That rate is considered high, and epidemiological data for type 1 diabetes in Africa are scarce (International Diabetes Foundation, 2003); nonetheless, its recorded prevalence in Sub-Saharan Africa is much lower than that in temperate countries. Three factors explain this divergence: a lower incidence of type 1 diabetes (according to Oldroyd, Bannerjee, Heald, & Cruickshank, [2005], however, the reasons for the lower frequency remain unclear), underdiagnosis or misdiagnosis, and a poorer prognosis (Beran & Yudkin, 2006).

1.2.3.3 *Cardiovascular disease*

Limited information is available on the prevalence of heart disease in Sub-Saharan Africa. According to Brinks and Aalbers (2009), there is a lack of adequate research in this region on the prevalence of cardiovascular disease, and the data that are available frequently relate to divergent geographical areas and population groups. More recent data described in the literature suggest that the prevalence of hypertension, a predictive condition for cardiovascular disease, has reached—and in certain cases, surpassed—the levels seen in developed countries (Pereira, Lunet, Azevedo, & Barros, 2009; Cappuccio & Miller, 2016). Van der Sande (2003) suggested that approximately 8% of the rural population and 15% of the urban population may have a blood pressure (BP) $\geq 160/95$ mmHg, with the highest prevalence found in southern Africa. Ntusi and Mayosi (2009) estimated the prevalence of hypertension in Sub-Saharan Africa to be between 1-30%. According to Mensah (2006), there were approximately 80 million patients with hypertension in Sub-Saharan Africa in 2000, and projections based on (then current) epidemiological data suggested that this figure will rise to 150 million by 2025.

1.2.3.4 *Respiratory disease*

Data on the prevalence of respiratory diseases in Sub-Saharan Africa are scarce. In two large multinational studies, the prevalence of chronic obstructive pulmonary disease (COPD) in developing countries was twice that in North America. However, the prevalence of respiratory conditions in Sub-Saharan Africa is not well understood (Menezes et al., 2005; Buist et al., 2007). A systematic analysis performed by Adeloye et al. (2014) found an estimated 18.5-43.4 million cases of COPD in Sub-Saharan Africa, a figure representing a 31.5% increase since 2000. The authors largely attributed the rise to Africa's ageing population.

1.2.3.5 *Implications for healthcare*

The impact of chronic diseases in developing countries is not often well recognised, because these types of diseases are often less visible than communicable diseases, progress slowly, and are often times under diagnosed. Further, chronic disease has overtaken the communicable disease burden, in part because of success in reducing the latter, but also

because developing countries are increasingly adopting the unhealthy lifestyles of the developed world (Nugent, 2008). For example, coronary artery disease (CAD) is the leading cause of death, not only in the United States, but also in most of the industrialised world (Center for Disease Control and Prevention, 2011). As the populations of less-developed countries begin to live longer, due in part to the effectiveness of initiatives designed to prevent and control tropical and infectious diseases, one could argue that larger cities in developing countries could begin to see incidence levels of chronic and lifestyle diseases mirroring those observed in developed countries. In the more rural (and subsequently poorer) parts of Sub-Saharan Africa, malignancy and chronic diseases play a lesser role in the disease burden due to the predominance of infective and parasitic diseases, which contributes to a lower average life expectancy (Hotez & Kamath, 2009).

The prevention of pandemic levels of chronic, non-communicable diseases in a sustainable manner will require collaborative efforts (Bloomfield & Kimaiyo, 2011). The implications of a potential pandemic are possibly far greater for countries in the developing world than for those in the developed world for two main reasons. Firstly, more patients suffering from these conditions are likely to go undiagnosed or to be misdiagnosed due to unfamiliarity with symptoms. Secondly, healthcare facilities in Sub-Saharan Africa are likely to face a significant additive effect in terms of costs and resources, as the increased prevalence of these conditions is likely to be in addition to (and not instead of) any currently ongoing infectious disease epidemics. This factor will likely mean that a large proportion of a smaller amount of resources will need to be dedicated to the prevention, diagnosis, and treatment of these conditions. Healthcare providers will need to concurrently tackle infectious diseases, such as AIDS and HIV infection and malaria, which have a much higher prevalence in this region than in the rest of the world (Abu-Raddad, 2006). At present, an estimated 80% of regional health budgets in the Sub-Saharan region have been allocated to communicable diseases, just as they have been for the last decade (World Health Organisation [Regional Office for Africa], 2006). For this reason, many healthcare systems in Sub-Saharan Africa focus on training and developing expertise in communicable diseases while underestimating the importance of building human and material capacity for chronic disease care (Abegunde, 2007; De Graft Aikins, 2010).

The evolution of Africa's disease landscape has not gone unnoticed on the global stage. International health agencies and national governments are beginning to recognise and

tackle the significant global burden of chronic diseases (Fitchett, 2009). The WHO established the goal of reducing global chronic disease by 2% every year between 2005 and 2015, with the aim of preventing as many as 36 million deaths over the course of that decade (Abegunde, 2007). To this end, it has published guidance and recommendations on the prevention of various chronic diseases (e.g., cardiovascular disease and diabetes) (World Health Organisation, 2005). Its aim is to instigate and inform policy changes, including the reprioritisation and reallocation of resources towards chronic disease prevention in developing countries.

1.3 Current clinical research focus in sub-Saharan Africa

Countries on the African continent are represented in only 0.9% of all clinical trials (Thiers, Sinskey, & Bendt, 2008), yet the area is home to around 15% of the world's population (Central Intelligence Agency, 2014). This disparity suggests that there is scope for significant progress with respect to efforts towards facilitating the conduct of more clinical trials in Sub-Saharan Africa. It also indicates that opportunities may exist for developing additional clinical trial capacity throughout the continent (Bairu & Chin, 2012a). Due to the severity of the diseases that affect many people living in the region, many have arguably viewed Sub-Saharan Africa as home to a large, homogenous population suffering from only a single type of disease. The poorest and most vulnerable people living in Africa and suffering from largely infectious diseases have historically been the focus of most research initiatives, as they have garnered the most publicity. As such, most of Africa's participation in clinical trials to date has been focused on research around a handful of disease types considered to represent the most serious threat, such as malaria, AIDS, and HIV (Lang & Lindsay, 2008; Kupfer & Burri, 2009). Scant research has concentrated on the treatment of non-infectious diseases. One reason for this is that interventional research in this area is typically sponsored by pharmaceutical companies who conduct the majority of their work in the West. The reason for this is that access to the high-priced treatments generally associated with chronic diseases in developing countries has traditionally been limited to the wealthy minority (Wemos Foundation, 2013; New, 2014).

Figure 2 and Figure 3 indicate the number of clinical trials being conducted in Africa at the time this research began in 2011, and at the time of its completion in 2017. The figures suggest that progress has been made, and the number of trials conducted in the region has

increased. Nonetheless, this growth, when compared to that seen in Western countries, only represents a relatively small number of trials. Additionally, the bulk of the increase appears to be due to the placement of more trials in South Africa, which is the only country in the Sub-Saharan region that is generally well represented in industry-sponsored clinical trials.

As for the rest of the region, there appears to have been little change. Therefore, various stakeholders must take action by initiating dialogue around the issues raised by this research to ensure that clinical trial access is possible for patients of all ethnic backgrounds and in all parts of the world.

The subsequent chapters enumerate the potential issues associated with participating in a clinical trial. At this point, however, it is worth noting certain disadvantages that are particularly pertinent to patients in developing countries. These include the potentially higher likelihood of exploitation and unfair coercion into trials due to various socioeconomic factors, as well as the potential for corruption on the part of pharmaceutical companies and investigators (Hawkins & Emanuel, 2008; Boers et al., 2010).

1.4 Clinical trial regulatory and ethical environment: Nigeria & Ghana

In developed countries, such as those in the European Union (EU), clinical trials are conducted under the oversight of a competent authority and one or more ethics committees. The requirements for review are outlined in the EU Clinical Trials Directive (Europeans Medicines Agency, 2004), which is a document that puts into law the tenets of Good Clinical Practice (GCP), as described by the International Conference on Harmonisation (2014). Throughout Sub-Saharan Africa, there are similar requirements for oversight that are also based on ICH-GCP. The following sub-sections provide a high-level summary of the regulatory and ethical approval processes that must be followed in the two countries of interest for this study: Nigeria and Ghana.

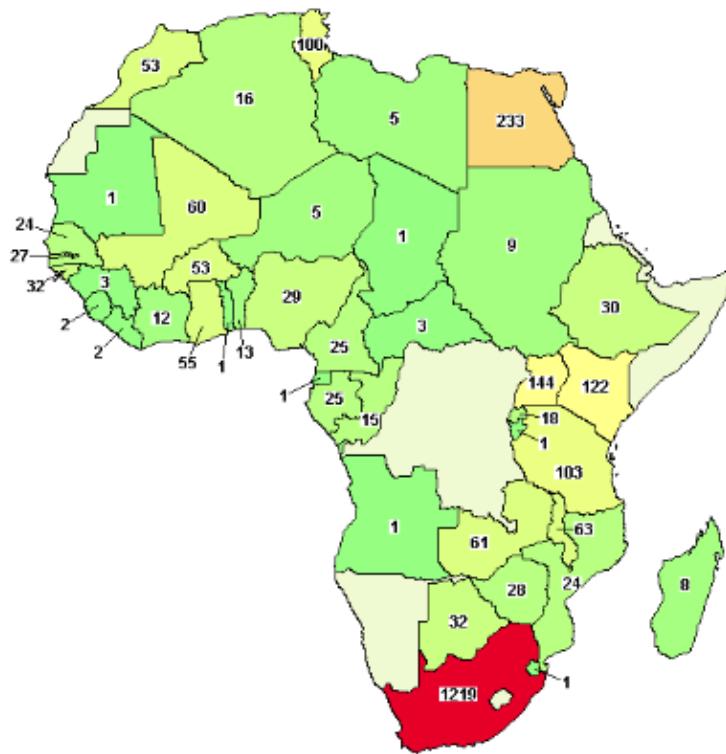


Figure 2: Image taken from clinicaltrials.gov on 15 March 2011. Of all 104,340 trials conducted at the time this image was taken, only 2,251 (2.1%) were being carried out in Africa. Excluding South Africa, less than 1% (1,032) of all trials listed were conducted in Africa.

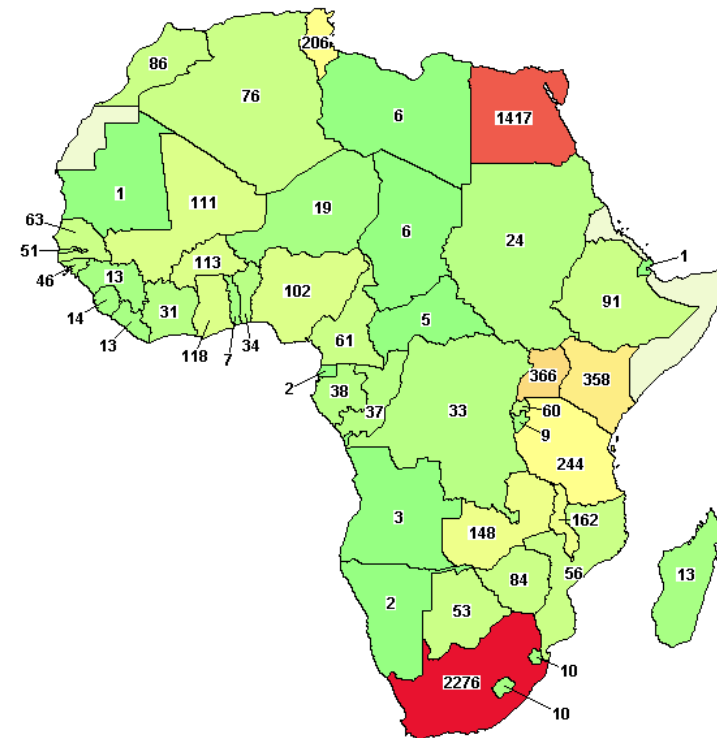


Figure 3: Image taken from clinicaltrials.gov on 3 March 2017. Of 238,072 registered clinical trials, only 5,756 (2.4%) were being conducted in Africa. Excluding South Africa, 1.4% (3,480) of all trials registered were conducted in Africa.

1.4.1 Clinical trial regulatory approval in Nigeria

As summarised by Puppalwar, Mourya, Kadhe and Mane (2015), in Nigeria, the National Agency for Food and Drug Administration and Control (NAFDAC) is the regulatory body that oversees research and clinical trials. NAFDAC ensures safety of the study through primary review of all trial documents before approval and registration and also monitors the safety of the trial before the trial begins, at various stages of the trial, and after the completion of the trial (Nigeria National Health Research Ethics Committee, 2016). The submission package that sponsors must give to the Nigerian competent authority comprises, at a high level: the clinical trial application form, a protocol, an informed consent form (ICF), the investigator's brochure (IB), evidence of agreement between the sponsor and the investigator, evidence of the institutional review board's (IRB) registration with the Nigerian National Health Research Ethics Committee (NHREC), a list of IRB members, minutes of the meeting held to approve the protocol and ICF, evidence demonstrating that the investigator(s) have undergone GCP training within two years, the CVs of the investigators, a sample of all case report forms or electronic case report forms for the study, evidence of insurance coverage for the trial participants, the name and qualification of the trial monitor, and a list and charter of the Drug Safety Monitoring Board (DSMB) (Puppalwar et al., 2015). The NAFDAC has not provided an official timeline for the approval of studies, which may be another factor affecting the willingness of pharmaceutical companies to engage in research in Nigeria.

1.4.2 Clinical trial regulatory approval in Ghana

The regulatory approval process for clinical trials in Ghana is managed by the Ghanaian Health Service (GHS). The purpose of the regulatory guidelines in Ghana are to ensure that clinical trials conducted in Ghana are designed and conducted according to sound scientific principles and ethical standards within the framework of GCP. As part of a clinical trial application (CTA), sponsors are required to show proof of the trial being registered on the Clinical Trial Registry and should submit corresponding evidence. The submission package largely comprises the same documents required by the Nigerian authorities. Furthermore, it also requires material transfer agreements and a specific insurance coverage note for participants demonstrating that they will be covered for the duration of their participation in the trial. Applications to the Food and Drug Board are processed within 60 working days of submission (Ghana Food & Drugs Authority, 2013).

1.4.3 Clinical trial ethical approval in Nigeria

Okonta (2014) described the NHREC as the conscience of the research enterprise. The NHREC was created in 2006 and backed by legislation giving it permission to oversee all Health Research Ethics Committees (HRECs) in Nigeria. Its powers include auditing and instituting disciplinary action where necessary (Erinosho, 2008). The NHREC holistically reviews the ethical aspects of a clinical trial protocol while paying particular attention to the protection of the potential research subjects (Okonta, 2014). The Nigerian Code for Health Research Ethics is similar to most current international research ethics guidelines. It requires that ethics committees in the country be registered and that the registration be renewed every two years. Furthermore, institutes conducting research can have their own internal research ethics committees. Where this is the case, they must be registered with the overarching national research committee (NHREC). Foreign sponsors are required to present the protocol to the ethics committee, which has a maximum of three months from the date of receipt of a valid application to give its decision to the applicant. Members of an HREC must undergo biennial NHREC-approved training.

1.4.4 Clinical trial ethical approval in Ghana

In Ghana, each health research institute has its own IRB. Certain Ghanaian institutions fall under the GHS ethics committee and are therefore also required to send study documents for additional review by the GHS Ethical Review Board in Accra. An ethical approval from the IRB or Institutional Ethics Committee (IEC) at the facility or institution where a trial is to be conducted is required prior to the commencement of any trial activities (Ghana Health Services, 2015; Ramsay De Vries, Soodyall, Norris, & Sankoh, 2014).

1.5 The potential role of clinical trials and drug research in combating chronic disease

Clinical trials could potentially play an important part in managing the increasing levels of chronic disease in Africa. In developed countries, clinical trials have been critical in raising awareness of some diseases and this has led to better treatment outcomes for patients, as diseases are more efficiently diagnosed and treatment algorithms become better defined, more clearly understood, and more widely implemented (Giovanna & Hayes, 2001).

Additionally, as was briefly described in previous sections, there are known interethnic variations in treatment responses to various medications that have been described throughout the literature. For example, endothelial nitric oxide synthase (eNOS), the enzyme responsible for the regulation of cardiovascular homeostasis, is known to have interethnic genetic variants that affect how black patients respond to various treatments (Marroni et al., 2005). Therefore, testing drugs in the appropriate and intended population is a key aspect of clinical trials that could potentially be addressed by increasing Sub-Saharan Africa's participation in clinical trials.

Aside from any immediate therapeutic benefit or risk associated with participating in a clinical trial, clinical research often also brings with it collateral positives and negatives for the individual research participants, the involved healthcare professionals (HCPs), and the community in which the research is conducted. Benefits such as additional funding, resources, and equipment are examples of how a community or hospital can profit from being involved in clinical research.

A more detailed summary of the benefits and disadvantages that clinical trials may bring follows in later chapters. Comprehending the benefits of clinical trials and appreciating the inherent risks at all levels is important for understanding the context for the arguments supporting Sub-Saharan Africa's participation in clinical trials. A better grasp of these advantages and risks facilitates a more robust assessment of how trials may or may not play a role in addressing some of the healthcare challenges that Sub-Saharan Africa faces.

A high-level summary, taken directly from the Wellcome Trust (Wellcome Trust, n.d.), is provided below. This summary has been listed as bullet points for brevity, clarity, and ease of understanding, but they are visited in more detail later on in this thesis.

At a societal/country level, the benefits of research include the following:

- It brings expertise and resources and contributes to the knowledge base regarding particular diseases and interventions.
- It facilitates an understanding of interventions and diseases and therefore has a global public-health benefit.
- It assists in improving community health via:

- Study findings leading to increased performance, quality, and consistency in the delivery of healthcare services.
- Facilitating the implementation of more effective approaches in the diagnosis, management, and treatment of a disease.
- Increasing well-being among community members.
- Contributing to the knowledge base regarding those genetic variations that can lead to differences in treatment outcomes based on race and social ecology.
- Bringing collateral benefits by contributing to local research capacity and providing research-related technical or clinical equipment (which may, in turn, facilitate improvements in diagnostic, medical, and scientific expertise).

These societal benefits then filter down to the research subjects actively participating in clinical trials, allowing them:

- To access treatments that they might not be able to routinely access—in some instances, before these interventions become available to others.
- To enjoy improved care, as the investigators involved in the research directly focus on the medical problem being studied.
- To access treatments for a disease or condition for which no other treatments exist.
- To pursue altruistic endeavours for humanitarian reasons.

These benefits, when framed in the context of a potential impending epidemic of chronic diseases, could be invaluable to both the monitoring and treatment of chronic diseases in Sub-Saharan Africa.

Clinical trials also create another much-needed source of funding for infrastructure, capacity-building, and resources dedicated to these disease types. Fitchett (2009) has argued that one of the key flaws of clinical trials in developing countries has been an overemphasis on results. That focus has meant that issues related to the development of national research capacity, sustainable research, and ownership have not been considered (Fitchett, 2009). Although clinical trials should not be viewed as a panacea for Sub-Saharan Africa's chronic disease problem, they do have the potential to function as a mechanism for addressing their increased prevalence. Another perhaps more contentious benefit of conducting clinical trials in a developing country is that it may be easier to

implement placebo-controlled trials³ (due to less availability of standard-of-care treatments), which produce less ambiguous data. Such results might, in turn, reduce the time needed to approve a new drug (Schulz-Baldes, Vayena, & Biller-Andorno, 2007). Although this could be beneficial to patients around the world, one could also argue that this benefit would only be ethical if the reduced time to drug availability was relevant for the participating subjects.

1.6 Ethical and practical issues around Sub-Saharan Africa's participation in clinical trials for chronic diseases

Changes in population, socioeconomic status, and patterns of disease indicate that Sub-Saharan Africa's involvement in clinical trials may need to be re-addressed. There is no simple approach to such a complex and multifactorial issue involving a diverse group of stakeholders. As such, it is unlikely that there will be agreement from all relevant stakeholders on how best to address all of the concerns in the first instance, particularly as the concept of industry-sponsored trials specifically focusing on chronic diseases is—or would be—relatively new to many countries in the region. It would also need to be ensured that addressing the 'new' phenomenon of rising chronic disease levels did not come at the expense of tackling the communicable diseases that continue to disproportionately affect inhabitants of this region.

Until recently, discussions around Sub-Saharan Africa's participation in clinical trials had gained little traction with the pharmaceutical industry, because such companies had little or no commercial rationale for investing in trials outside of South Africa. However, as described by Su (2012), pharmaceutical companies are encountering new challenges in the typical (Western) countries where trials have traditionally been conducted. Research and development (R&D) costs are increasing each year. Moreover, clinical trial sites are becoming oversaturated, with many companies choosing to use the same locations due to their trial experience. Further, there is a lack of treatment-naïve⁴ patients at many of these sites (Su, 2012), leading to longer recruitment timelines for many trials, particularly those testing first-line treatments. Increased shareholder pressure on pharmaceutical companies

³ A placebo-controlled trial is one in which the effect of a drug is compared with the effect of a placebo (an inactive substance designed to resemble the drug). In placebo controlled clinical trials, participants receive either the drug being studied or a placebo. The results of the drug and placebo groups are then compared to see if the drug is more effective in treating the condition than the placebo is (US Department of Health and Human Services, n.d.).

⁴ A person is considered treatment naïve if they have never undergone treatment for a particular illness.

to be first to market in spite of these challenges suggests a need to reconsider the potential for developing countries, such as those in Sub-Saharan Africa, to participate in industry-sponsored clinical trials.

Sub-Saharan Africa has an expanding middle-class population, and those individuals are beginning to access a healthcare system that is benefitting from increased investment, as well a growing number of well-trained medical professionals. As such, the future of healthcare in Sub-Saharan Africa is currently more promising than it has been for many years (Davis, 2013). However, with emerging epidemics of chronic diseases looming, pressure is mounting to ensure the adoption of a robust and transdisciplinary approach to mitigating the risks that such an epidemic could pose to the region's existing infrastructure. This approach should include thoughtful consideration of what role, if any, clinical trials have in supporting efforts to redress these rising levels of chronic diseases and better understanding how patients' responses to treatment may vary across ethnic groups.

The cases made against the conduct of industry-sponsored trials in this part of the world are arguably less applicable now than they once were. Socioeconomic background is a predictive factor for many chronic diseases; therefore, patients who suffer from these illnesses are more likely to have similar backgrounds with respect to education and literacy than are patients suffering from infectious diseases. This holds true regardless of where the patient lives. The African Library Project reported an 11% increase in adult literacy in Sub-Saharan Africa between 1990 and 2008 (African Library Project, 2013). These figures are skewed by higher rates of illiteracy in the more rural areas of the continent, which also tend to be poorer. As a result, these statistics point to higher literacy rates in larger cities. This suggests a growing number of educated, middle-class population, many of whom will be literate enough to make a balanced and informed decision based on the potential risks and benefits associated with participation in a clinical trial. This factor potentially makes the risk of uninformed or misinformed coercion less likely. Additionally, there are dangers in adopting patronising attitudes towards developing countries that are in a state of transition, particularly when their populations are increasingly afflicted by diseases prevalent in the West (Gilland, 2012).

Increasing the number of clinical trials in developing countries may be of interest to drug companies from a practical perspective. The lower cost of healthcare resources (e.g.,

nursing time and X-rays) may increase pharmaceutical companies' inclination to invest in helping these countries put into place infrastructure at both the local and national level that could be reused in future trials. The cost of doing so is still likely to be significantly less than conducting the trial in the West. Pharmaceutical companies have taken a similar approach with other developing countries, such as India. In 2010, the cost of conducting a clinical trial in that country was said to be, on average, 44% less expensive than in the United States (Bhowmik, Chandira, & Chiranjib, 2010). Integrating such investments into local healthcare structures would require careful monitoring, including the redeployment of staff.

1.7 Conceptual framework development and study objectives

There are numerous examples throughout the literature describing interethnic variations in responses to a number of therapeutic interventions across a broad spectrum of disease indications (Lip et al., 2007; Ford et al., 2008; Isenberg et al., 2009). To that end, numerous researchers, including Agyemang, Addo, Bhopal, De Graft Aikins and Stronks (2009), have called for clinical trials designed specifically to evaluate treatment outcomes in ethnic minority populations. The starting position of the present study was that more clinical research should be carried out in developing countries, including those in Sub-Saharan Africa, to facilitate the inclusion of ethnic minorities and to better understand any interethnic variations in treatment responses to therapeutic interventions.

On a global level, ethnic minorities are underrepresented in clinical trials, including in those in developed countries (Hussain-Gambles Atkin, & Leese, 2004). Therefore, involving minorities from less-developed countries is arguably an appropriate alternative. The need to include ethnic minorities in clinical trials facilitates the inclusion of developing countries and regions, such as Sub-Saharan Africa. However, to appropriately integrate developing countries into clinical trials and to ensure that these trials are run ethically in compliance with applicable regulations, research standards and benchmarks are required.

A conceptual framework, as defined by Miles and Huberman (1994), is the system of concepts, assumptions, expectations, beliefs, and theories that supports and informs a body of research. The conceptual framework adopted for this research was developed using the

model that Emanuel, Wendler, Killen and Grady (2004) proposed in their paper outlining suggested benchmarks for ethical clinical trials in developing countries. The authors' proposal comprised 7 overarching principles, with 31 individual benchmarks associated with them. An annotated version of the framework developed by Emanuel et al. (2004) is presented in Table 1. The table lists all 7 principles and the related 31 benchmarks and expands on the existing framework by adding additional wording which provides context for research in developing countries conducted specifically by pharmaceutical companies. This contextualisation of the principles was derived from both the available literature on the subject and personal experience with conducting clinical trials on behalf of the pharmaceutical industry. The final column specifies the study objective(s) corresponding to each benchmark and principle.

In developing a conceptual framework that adequately addressed both of the study's objectives, I focused on the principle of social value, as presented in Figure 4.

.

The framework presented by Emanuel et al. (2004) was developed for the conduct of research in developing countries, but not specifically for industry-sponsored clinical trials in resource-constrained environments. Therefore, this paper aims to contextualise the results through the principle of social value. Social value was chosen as the most appropriate benchmark upon which to base the conceptual framework. This choice was made as the first objective of this study was to understand the benefits of clinical research in Sub-Saharan Africa, and social value is one such advantage. Although there was an appreciation that all of the principles and benchmarks are relevant for industry-sponsored clinical trials, this research focused on addressing the principle of social value and the associated benchmarks, with reference made to other principles and benchmarks as they arise.

The conceptual framework is presented diagrammatically in Figure 4. It begins with the assertion that there should be greater ethnic minority representation in industry-sponsored clinical trials.

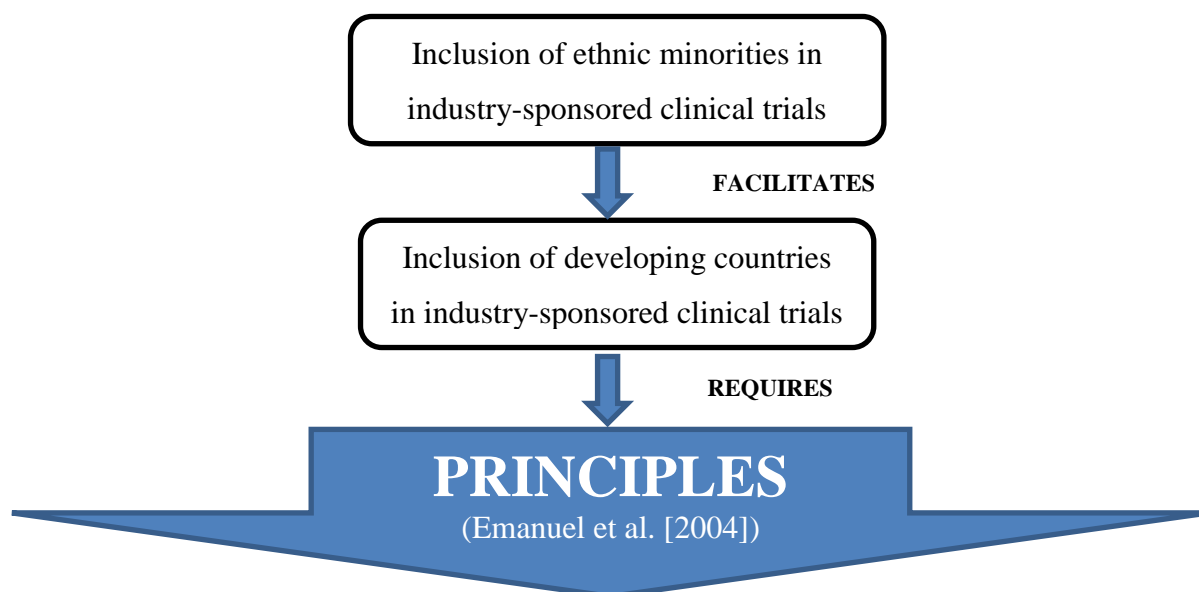
| Principle | Benchmark | Context | Study Objective(s) Addressed |
|------------------------------------|---|---|------------------------------|
| “Collaborative partnership” | “Develop partnerships with researchers, makers of health policies, and the community” | Researchers developing relationships with pharmaceutical companies facilitates knowledge, the sharing of best practices, and access to new techniques and treatments. | Objective 1 |
| | “Involve partners in sharing responsibilities for determining the importance of health problems, assessing the value of research planning, conducting and overseeing research and integrating research into the health-care system” | Interethnic variations in treatment responses represents an issue for HCPs in Sub-Saharan Africa; collaboration with pharmaceutical companies allows for studies that are appropriate and relevant to the region to be conducted. | Objective 1 Objective 2 |
| | “Respect the community's values, culture, traditions, and social practices” | Allow pharmaceutical companies to adopt practices that are culturally appropriate without compromising ethical guidelines. | Objective 2 |
| | “Develop the capacity for researchers, makers of health policies, and the community to become full and equal partners in the research enterprise” | Develop relationships between local healthcare providers and pharmaceutical companies to ensure that research is relevant and appropriate to the local population. | Objective 1 |
| | “Ensure that recruited participants and communities receive benefits from the conduct and results of research” | Benefits may include access to new medicines or equipment and investments in the healthcare infrastructure by pharmaceutical companies. | Objective 1 Objective 2 |
| | “Share fairly financial and other rewards of the research.” | Ensure investigators and study participants (where appropriate) are fairly compensated for trials without incentivising participation in research for financial gain. | Objective 1 Objective 2 |
| “Social value” | “Specify the beneficiaries of research” | The beneficiaries of the research are the populations in which a medicine is being tested, as those individuals will gain information directly relevant to them. This could ultimately improve their treatment and healthcare | Objective 1 Objective 2 |
| | “Assess the importance of health problems being investigated and prospective value to participants” | Treatment of chronic conditions is an important concern for Sub-Saharan Africa due to the combination of increasing levels of such conditions and existing high levels of infectious diseases (Dalal & Beunza, 2011). Potential participants may also benefit from local and national investments in the healthcare infrastructure. | Objective 1 Objective 2 |
| | “Enhance value of research through dissemination of knowledge, product development, long term research partnerships and / or health system improvements” | Value is derived from the understanding of interethnic variations in treatment responses, investments in healthcare, collaboration, and knowledge of the need for potential ethnic variations in treatment regimens. | Objective 1 Objective 2 |

| Principle | Benchmark | Context | Study Objective(s) Addressed |
|--------------------------------------|--|--|------------------------------|
| | “Prevent supplanting the extant health system infrastructure and services” | Ensure that pharmaceutical industry’s investment is in the existing infrastructure, and not in new facilities that do not benefit the local population. | Objective 2 |
| “Scientific validity” | “Ensure that the scientific design of the research realises social value for the primary beneficiaries of the research” | Appropriately designed trials focused on understanding interethnic variations in treatment responses to chronic diseases are inherently of benefit to local populations. | Objective 1 Objective 2 |
| | “Ensure that the scientific design realises the scientific objectives whilst guaranteeing research participants the health-care interventions to which they are entitled” | Ensure appropriate and robust study designs to provide clinically meaningful results, while ensuring that patients are not prevented from accessing treatments to which they would normally have access (e.g., rescue medications). | Objective 1 |
| | “Ensure that the research study is feasible within the social, political, and cultural context or with sustainable improvements in the local health-care and physical infrastructure” | Pharmaceutical companies should ensure that countries selected for clinical trials have a sufficient population to justify their participation and sufficient infrastructure/expertise, even if (sustainable) investment is required. | Objective 1 Objective 2 |
| “Fair selection of study population” | “Select the study population to ensure scientific validity of the research” | Pharmaceutical companies should ensure that inclusion/exclusion criteria, including those regarding allowed concomitant medications and medical history, are developed with the local population in mind. | Objective 1 |
| | “Select the study population to minimise the risks of the research and enhance other principles, especially collaborative partnership and social value” | Pharmaceutical companies should ensure that the study population is appropriate and that there is a clear direct benefit (therapeutic or otherwise) from participation in a trial. | Objective 1 |
| | “Identify and protect vulnerable populations” | Pharmaceutical companies should ensure that processes are in place to avoid incentivising research participation for financial gain and to prevent 'career research subjects' from becoming the norm. | Objective 2 |
| “Favourable risk-benefit ratio” | “Assess the potential risks and benefits of the research to the study population in the context of its health risks” | Chronic diseases are on the rise in Sub-Saharan Africa, and therefore, clinical trials in this region are appropriate in the context of the population's health risks. | Objective 1 Objective 2 |
| | “Assess the risk-benefit ratio of comparing the net risks of the research project with the potential benefits derived from collaborative partnership, social value, and respect for study populations” | Pharmaceutical companies and regulators should holistically assess the risk-benefit ratio of conducting trials in Sub-Saharan Africa, taking into account the potential benefits, such as investments in infrastructure, knowledge of ethnic variations in treatment responses, and potential access to new treatments. They should also assess the potential benefits to trial participants | Objective 1 Objective 2 |

| Principle | Benchmark | Context | Study Objective(s) Addressed |
|---|--|---|-------------------------------------|
| “Independent review” | “Ensure public accountability through reviews mandated by laws and regulations” | Local regulators and ethics committees should review industry-sponsored clinical trials; the appropriateness of trials should not be dictated by external committees. | Objective 2 |
| | “Ensure public accountability through transparency and reviews by other international and non-governmental bodies, as appropriate” | Local regulators should ensure that there is a fair and appropriate mechanism to evaluate clinical trials to ensure their relevance to the local population, and trial progress and results should be accessible to the regulator and subject to public scrutiny. | Objective 2 |
| | “Ensure independence and competence of reviews” | Regulatory bodies and ethics committees should be impartial, accountable, and appropriately trained. | Objective 2 |
| “Informed consent” | “Involve the community in establishing recruitment procedures and incentives” | Pharmaceutical companies should ensure that recruitment and incentives are fair and culturally appropriate | Objective 1 |
| | “Disclose information in culturally and linguistically appropriate formats” | Pharmaceutical companies and local researcher collaboration is required to ensure that consent is obtained in a way that is appropriate for the potential study participant. | Objective 2 |
| | “Implement supplementary community and familial consent procedures where culturally appropriate” | Pharmaceutical companies and local regulators need to collaborate to develop robust processes for ensuring that hierarchical consent processes are implemented that are both respectful of local processes and ensure that candidates have the final word on their potential participation. | Objective 2 |
| | “Obtain consent in culturally and linguistically appropriate formats” | Pharmaceutical companies and local researcher collaboration is required to ensure that consent is obtained in a manner that is appropriate for the potential study participant. | Objective 2 |
| | “Ensure the freedom to refuse or withdraw” | Pharmaceutical companies and local researchers, as part of their collaborative efforts, need to ensure that patients fully understand that participation is voluntary through the informed consent process. | Objective 2 |
| “Respect for recruited participants and study communities” | “Develop and implement procedures to protect the confidentiality of recruited and enrolled participants” | Confidentiality should be ensured and maintained, as is routinely done in trials in the West through the anonymisation of, for example, samples and study data. | Objective 2 |
| | “Ensure that participants know they can withdraw without penalty” | Pharmaceutical companies and local researchers, as part of their collaborative efforts, need to ensure that patients fully understand that participation is voluntary through the informed consent process. | Objective 2 |

| Principle | Benchmark | Context | Study Objective(s) Addressed |
|------------------|--|---|-------------------------------------|
| | “Provide enrolled participants with information that arises in the course of the research study” | Information about developments in treatment and understanding of the disease under investigation should be shared with participants in a way that is understandable to them. | Objective 1 Objective 2 |
| | “Monitor and develop interventions for medical conditions, including research-related injuries for enrolled participants at least as good as existing local norms” | Pharmaceutical companies engaging in research should ensure that clinical trial insurance is in place to reimburse subjects who are harmed as a result of their study participation, as is the case in countries where industry-sponsored trials are routinely conducted. | Objective 1 Objective 2 |
| | “Inform participants and the study community of the results of the research” | Pharmaceutical companies should commit to the transparency of study results at study completion and ensure that findings are presented in a way that highlights their relevance to local populations. | Objective 1 Objective 2 |

Table 1: Annotated framework for ethical principles and benchmarks for multinational clinical research, taken from Emanuel et al. (2004).



| Benchmark | How the benchmarks serve to address study objectives |
|---|---|
| “Specify the beneficiaries of research.” | <u>Objective 1:</u> Identify the benefits of research on chronic diseases in this region and to whom they are of benefit. <u>Objective 2:</u> Address the ethical implications of the benefit(s) conferred to the individual (participant) and other stakeholders. |
| “Assess the importance of health problems being investigated and prospective value to participants.” | <u>Objective 1:</u> Address how conducting clinical trials on chronic diseases may help manage their rising prevalence. |
| “Enhance value of research through dissemination of knowledge, product development, long term research partnerships and / or health system improvements.” | <u>Objective 1:</u> Identify the potential benefits of such research, both therapeutically (for patients) and commercially (for pharmaceutical companies), along with the long-term benefits for the region <u>Objective 2:</u> Understand the ethical implications of using Sub-Saharan Africa’s large patient pool as a mechanism for attracting investment in a healthcare system that should (arguably) be funded by local governments, rather than by for-profit organisations. |
| “Prevent supplanting the extant health system infrastructure and services.” | <u>Objective 2:</u> (a) Understand the ethical considerations associated with corruption and exploitation by local stakeholders. (b) Understand the ethical implications of HCPs conducting research within underfunded healthcare systems. |

Figure 4: Conceptual framework

The principle of social value is an important starting point when attempting to rationalise Sub-Saharan Africa's participation in clinical research, particularly in industry-sponsored trials where potential conflicts of interest may arise. Understanding how various stakeholders potentially involved in the conduct of clinical trials in developing countries perceive the related issues is an essential first step in initiating dialogue on the topic with key decision-makers.

1.8 Current clinical research focus in Sub-Saharan Africa

Within Sub-Saharan Africa, most clinical trials are conducted in South Africa (47.3%). This distribution is largely due to the fact that country has made one of the largest financial investments in healthcare on the continent and that it presumably has a relatively well-developed healthcare system as a result (Fekadu et al., 2014).

Bairu and Chin (2012b) have described the three main types of clinical trial sites that exist throughout Africa as follows: (1) sites managed by not-for-profit organisations; (2) institution-associated sites, which are usually affiliated with a public hospital or an academic centre; (3) and privately owned sites. Proportions vary across countries, but in general, privately owned sites form the majority in South Africa, whereas academic settings are more common elsewhere (Bairu & Chin, 2012b). Although the region has experience with trials in most therapeutic areas (mostly due to South Africa's involvement in large multinational trials), clinical research outside of South Africa has focused mainly on three infectious diseases: HIV/AIDS, tuberculosis, and malaria. Zumla, Petersen, Nyirenda and Chakaya (2015) suggested that the past two decades have witnessed a renaissance in biomedical research, capacity development, and research training activities throughout Sub-Saharan Africa. That resurgence (in addition to focusing on the three above-mentioned diseases) has also incorporated other parasitic infections and comorbidities of communicable diseases with non-communicable diseases (Costello & Zumla, 2000; Zumla et al., 2015).

The focus on infectious disease clinical research, along with the increasing disease burden attributed to chronic diseases, has led to two opposing views on what the region's research priorities should be moving forward. As summarised by Unwin et al. (2001), one perspective holds that focusing nearly exclusively on combating infectious diseases will

offer the greatest health gains, whereas the opposing view suggests that the rapidly growing burden of chronic and non-communicable diseases is a warning sign indicating that priority should be given to proactively preventing them (Unwin et al., 2001).

1.9 Conclusion

Taking into consideration Africa's growing middle class, improving healthcare infrastructure, and increasing pool of medical expertise (particularly in and around large cities), that continent's participation in industry-sponsored clinical research warrants further discussion. The known interethnic variations in treatment responses, as well as epidemiological data suggesting an increasing prevalence of chronic diseases and malignancies, suggest that further work is required to understand the implications of the region's participation in industry-sponsored research.

Although challenges still remain, the factors that have historically excluded Sub-Saharan Africa from industry-sponsored clinical trials, and particularly those examining chronic diseases, may not be as relevant now as they once were. The opportunities for clinical research should detract neither from ongoing or new research on infectious diseases nor work to tackle underlying problems, including poverty. Rather, they should be viewed as complementary, and such trials should be ethically sound, utilising benchmarks such as those outlined by Emanuel et al. (2004).

1.10 Study objectives

The two objectives of this study were:

1. To understand what benefit, if any, conducting industry-sponsored clinical research in chronic disease areas confers to the population and this region.
2. To understand the ethical implications associated with conducting industry-sponsored clinical research in the Sub-Saharan region of Africa, as perceived by various stakeholders both inside and outside the region.

CHAPTER 2: KEY LITERATURE ON THE ADVANTAGES AND DISADVANTAGES OF PARTICIPATING IN CLINICAL TRIALS

This chapter presents a summary of the benefits and risks of participating in clinical trials to facilitate a better understanding of the potential role that trials may play in developing countries.

The aim of this examination of the literature is to outline a broad context in which to understand and explore the research objectives.

2.1 Background

Clinical trials give researchers the opportunity to investigate the efficacy and safety of therapeutic and prophylactic interventions within the confines of a controlled and reproducible protocol. This allows for an assessment of the risk-benefit profile of a compound, device, or procedure and for a decision on whether it warrants further investigation, and ultimately, on whether it should be made available to the wider public. The results of clinical trials are also often used to develop and inform healthcare policy at national and local levels, as evaluations of cost effectiveness often rely on the results of completed trials. Appendix 1 provides further information on the various phases of clinical trials.

Randomised clinical trials (RCTs) are generally considered the gold standard for research, as they often provide the strongest evidence in support of cause-effect relationships and minimise or eliminate bias and confounding variables (Appel, 2006). However, there are also risks and challenges associated with running these trials. With respect to the challenges associated with RCTs, Fuchs et al. listed difficulties in modelling complex human behaviour, concerns around generalisability, limitations in the capacity to recognise a small treatment effect size, and an inability to conduct trials of a sufficient length to mimic treatments of chronic diseases in clinical practice (Fuchs Klag, & Whelton, 2000).

Resnik (2008), addressing clinical research's benefits for society, argued that before a clinical trial is conducted, certain questions need to be asked about the research to ensure that it is necessary and will not put individuals at unnecessary risk. The three most important questions are: (a) Will the research lead to a new public-health intervention? (b) Will it help to improve an educational programme? (c) Will it have important implications for social or economic policy? When the answer to all three of the questions is 'yes', the benefits of participation in clinical trials become more apparent (Resnik, 2008). It is, however, important to understand that there are both inherent risks and benefits associated with conducting human research. The aim of this summary is to explore and describe the advantages and benefits, as well as the disadvantages and risks, associated with the conduct of clinical trials.

The risks and benefits of a clinical trial should be balanced, clarified, and carefully assessed by an ethics committee and regulatory authority. Furthermore, the risks of research should never outweigh its benefits.

2.2 Literature search

Literature searches were conducted using two scientific journal databases: PubMed and Science Direct. The search was limited to papers written in the English language, but there were no time limitations, as it was determined that older papers related to the subject would still be relevant. The search was conducted using both targeted and general strategies. The review started with a high-level search for papers addressing both the benefits and potential disadvantages of clinical trials. It was then further broken down into two separate searches focused on the positive and negative effects, respectively, associated with conducting and participating in clinical trials. Additional searches were performed to identify papers addressing the individual, the community, and society. Supplementary explorations using an internet search engine (Google Scholar) and references in the identified literature were also used to augment the initial results.

The initial search, which used the search terms 'advantage', 'disadvantage', and 'clinical trial' returned thousands of papers. One of the challenges noted early in the search process was identifying literature discussing the potential positive and negative implications of clinical trials as a whole, rather than papers addressing a specific trial or particular disease

Chapter 2: Advantages and disadvantages of trial participation area. The search terms ‘benefits’, ‘positives’, ‘disadvantages’, ‘advantages’, ‘clinical’, ‘medical’, ‘trials’, ‘risks’, ‘research’, and ‘community’ were used in various combinations. The search was filtered to return results that listed these keywords in the abstract, title, or keywords.

This search and review of the literature was not intended to be a systematic review. Nevertheless, it was felt that the variety of search strategies, including both broad and targeted techniques, led to a sufficiently thorough review of the literature pertinent to the topic.

2.3 Benefits

2.3.1 Benefits to the patient

It can be argued that the benefits and disadvantages of clinical trials may differ depending on a number of factors, including the study’s type (e.g., phase, indication, design) and location. Both the advantages and drawbacks may be highly dissimilar for those participating in a study in a developed country versus in a developing country. For example, access to a gold-standard medication may not necessarily be seen as an advantage to a person in the United Kingdom with free access to that treatment. On the other hand, it may be a benefit for a patient in a developing country, where access to such medicines is not possible due to either a lack of availability or prohibitively high costs.

Braunholtz, Edwards and Liliford (2001) argued that the benefits of participation in clinical trials are clear, particularly if trial participation gives subjects an improved chance of receiving a new and more effective treatment. Participation is also beneficial if trial clinicians become better informed or more careful (due to the feeling of being under observation), if they are required to follow a carefully researched and designed protocol for those in the trial, or if trial participation simply makes patients feel more useful. The authors argued that this feeling of usefulness may even improve treatment outcomes.

Few would argue that clinical trials do not offer at least a limited benefit to the individuals who participate in them. The perceived benefit from simply participating in a clinical study, which is observable even in the absence of treatment efficacy, is known as the protocol or Hawthorne effect. Braunholtz et al. (2001) defined the Hawthorne effect as the

benefit gained from improved routine care within a trial. This effect is said to be a result of changes in patient or clinician behaviour due to increased knowledge or interest, or due to the feeling of being 'observed'.

The Hawthorne effect has been substantiated through a number of research studies examining patient attitude towards their participation in clinical trials. One such study assessed responses to, and attitudes towards, participating in research through a questionnaire mailed to research participants at the conclusion of the three-year treatment period of the oncology trial. Overall, 'careful medical follow-up received' (43%) and 'being part of a research effort' (24%) were the most frequently cited important benefits, while the 'amount of time taken to attend clinic' (32%) and 'side effects' (20%) were the most commonly mentioned unpleasant aspects of trial participation. Most surveyed patients viewed the study as 'very or extremely important' to their general health (62%) and their skin cancer condition (88%). As a result of participation, they claimed to feel 'much or somewhat better' physically (52%) (Tangrea, Adrianza, & Helsel, 1992).

This is consistent with data collected in an earlier study by Mattson, Curb and McArdle (1985), who investigated the drivers for enrolment in clinical trials for patients who were participating in trials examining the use of aspirin or beta-blockers to prevent myocardial infarction. They found that for 44% of the respondents, the largest driver was that medical monitoring, laboratory tests, and physical examinations that they received provided them with additional clinical information about their condition. The advantage of having a second opinion of their condition was also emphasised by patients. A similar proportion of patients (38%) stressed the emotional benefits of reassurance. They noted the significance of having peace of mind, increased personal awareness, and a sense of being better educated about cardiovascular disease risk factors and how to control them. Interestingly, less frequently cited were the actual physical benefits, such as health improvement, early diagnosis of disease, and the prevention of new health problems. Eight percent of the patients mentioned increased interaction with individuals concerned about them and their problems as positives associated with their trial participation (Mattson et al., 1985).

Altruism, as defined by Jones (2002), is the performance of cooperative, unselfish acts for the benefit of others, and it is occasionally a driver for patient participation in clinical trials. This is of benefit to a patient because it allows them to feel as though they are

contributing to the furthering of knowledge around their disease. Additionally, it is interesting to note is that in one study conducted by Rosenbaum et al. (2005), researchers concluded that women who reported altruism (or at least one altruistic reason) for participating in a clinical trial investigating the use of oestrogen for stroke prevention were more likely to adhere their study medication regime than were other participants. It is important to note, however, that altruism may not be the sole or primary reason that patients participate in clinical trials. A study conducted by Truong, Weeks, Cook and Joffe (2000) on the parents of paediatric oncology patients participating in a clinical trial found that although cancer trial participants commonly reported that altruism contributed to their decision to enrol, it was rarely their primary motivation for taking part in the study. Participants in early phase trials and those with poor prognoses are the least likely to be driven by altruism (Truong et al., 2000). These differences in responses may be partially related to the fact that adults are more likely to be altruistic where it concerns them than where it concerns their children. However, a number of papers (Simon, 2006; Jansen, 2009) have also prompted a debate on whether altruistic reasons for participating in a clinical trial are good, bad, or even ethical. That said, further exploration of that debate would be beyond the scope of this literature review, given the number of considerations that need to be taken into account. For the purposes of this discussion altruism will be considered an advantage for patients given its role as a motivating factor for prospective subjects to enrol onto studies and due to it being listed as a positive effect associated with trial participation in many of the papers discussed within this review.

Another potential benefit for patients participating in clinical trials, and particularly for patients in countries where healthcare is not provided free of charge, is that patients frequently receive free healthcare while participating. In their paper investigating patient and physician attitudes towards participation in clinical trials in the United States, Fenton, Rigney and Herbst (2009) noted that 21% of all surveyed cancer patients who had taken part in a clinical trial listed the fact that their costs of care were covered in the trial as a reason for participating. It is worth noting that this benefit may be less relevant in countries other than the United States featuring government-funded healthcare. This benefit is ethically important, particularly for trials in areas such as cancer care where the cost of treatment can be extremely high. The fact that medicines to which patients may not otherwise have access, or which might come at an extremely high cost, become available through trial participation is ethically challenging, and that topic lends itself to a completely separate debate. This concern arises because money, when serving as a

Chapter 2: Advantages and disadvantages of trial participation

motivating factor, can impair judgment or compromise voluntary decision-making (Grady, 2005). It may cause differences in both reasons for participation and actual recruitment to studies in countries with a subsidised healthcare system versus an insurance-based healthcare system.

2.3.2 Benefits to the researcher

Patients are not the only individuals who can benefit from participation in clinical trials. Healthcare practitioners, in their role as investigators, often gain from involvement in clinical trials through enhanced acclaim, publications, access to new treatments, or the opportunity to learn new skills and techniques. Being well regarded in a particular field can lead to promotions and access to better professional opportunities. Practitioners are also frequently able to generate income as a result of their participation and can secure additional funding for resources and/or equipment at their research centre. The funding provided by pharmaceutical companies can be substantial, and although a percentage of clinicians use that money to fund research nurses or administrators, not all do, as certain countries allow the researchers to keep that money as personal income. This factor raises an ethical debate in itself, as it could lead to a conflict of interest and could influence an HCP's judgement on the suitability of trial patients. Investigators, when questioned as part of a study conducted by the National Cancer Institute's (NCI) Community Clinical Oncology Program (CCOP) on the perceived advantages or benefits of participating in a clinical trial, gave several reasons for their involvement. One respondent commented that being actively involved in research protocols kept him abreast of developments in his field, including changes and trends. That knowledge helps him and his team stay up to date and to feel as though they were contributing to a greater effort. It also put them in a position to be able to offer patients cutting-edge treatments that they might otherwise be unable to provide. He concluded that ultimately, the two major benefits were the ability to offer new drugs to patients and changes in how he and his colleagues practiced oncology. Another respondent in the same study indicated that it was important that his centre participate in trials as it allowed his team to offer a much broader spectrum of treatment options to patients, noting that such variety is particularly appealing in the oncology setting (McAlearney, Song, & Reiter, 2012).

2.3.3 Benefits to society

Research by Emanuel et al. (2004) concluded ethical research must have social value in terms of generating knowledge that will ultimately lead to improvements in the treatment of patients. Kryzanowska et al. (2011) argued, however, that ‘demonstrating and measuring the benefits of clinical research, and therefore the value to any health system of supporting a research infrastructure, is extremely challenging. Healthcare professionals, policymakers and the public at large seem to recognise that clinical trials and studies are worthwhile and are broadly supportive, as reflected in regular and sustained financial support from governments’. Evidence supporting this statement include the United States National Institute for Health (NIH) budget of \$31.2 billion and the United Kingdom’s healthcare research budget of £1.7 billion as well as by public support for health research charities (e.g., Cancer Research UK, approximately £400,000) (Kryzanowska, Kaplan, & Sullivan, 2011). Typically, early studies are valuable only because the information that they generate informs additional research that could cumulatively change healthcare. According to Emanuel et al. (2004), priorities may shift during a study, and therefore, the cooperation of a diverse group of stakeholders is needed to make changes on the basis of the results of ongoing research. Consequently, trying to determine the social value of research is always probabilistic and involves judgments about the usefulness of a sequence of research (Black, 2001).

The benefits and social value of research might include employment and training for community members to augment healthcare services for the entire community. This could include, for example, training community members as clinical support or ancillary workers (e.g., phlebotomists). In both developed and developing countries, the conduct of clinical research may also bring improvements to the healthcare infrastructure, such as the training of personnel, the building of new facilities, or the provision of an affordable drug (Grady, 2005).

The community surrounding a hospital may also benefit from clinical research due to that institute’s enhanced ability to recruit and retain talented physicians. A hospital administrator surveyed in the previously mentioned NIH CCOP survey described a recent physician recruitment effort: ‘...one of the specific questions that they [the physician candidates] had for us was what research we do here.’ These institutions often benefit from

increased 'status' within the community and become seen as pioneering centres in term of medical treatment (Fenton et al., 2009).

Clinical trials demonstrating the efficacy of a particular intervention are not the only studies that are important. Rather, trials that meet their primary objective and those that do not are equally important. Through clinical trials, researchers are able to identify treatments and interventions that do not work. That knowledge, in addition to preventing patients from receiving ineffective treatments or interventions with unfavourable side-effect profiles, could save governments, healthcare institutions, and health plans money, thereby benefiting entire countries. This is because the results of clinical trials are often used to inform healthcare policy at the national and local level. Payers often make assessments on the value of medicine using cost-benefit analyses, such as the cost per quality-adjusted life year (QALY) calculation employed by the United Kingdom's National Institute of Clinical Excellence (NICE) ((Raftery, 2001). Using the results of a cost-benefit analysis allows healthcare policymakers and payers to make informed decisions, particularly in cash-strapped reimbursement environments, as to whether a particular treatment, device, or intervention warrants the price charged by its manufacturer or license holder.

A patient's entry into a clinical trial can also relieve part of the financial pressure on healthcare institutions and systems, as the sponsors of clinical trials often cover the costs of patient assessments which are done as a result of their participation. Many of these assessments would otherwise be carried out in routine practice (and would therefore be chargeable to the institution or reimbursement body). A pilot study conducted by the American Association of Cancer Institute (AACI) demonstrated that the average medical charges for patients enrolled in clinical trials were less than those for patients receiving standard therapy (Bennett et al., 2000). Additionally, certain guidelines governing the conduct of clinical trials include wording to ensure that provision is made for participating patients to receive continued treatment following their enrolment in such a trial. Earlier versions of the Declaration of Helsinki, for example, made the sponsor of a trial responsible for providing treatment to subjects following their participation (Wolinksi, 2006). When such arrangements are in place, they can also relieve financial pressure on healthcare institutions tasked with providing this long-term treatment for some patients.

In their paper examining clinical trials within the context of substance dependency, Timmermans and McKay (2009) concluded that ‘while randomised clinical trials are imperfect substitutes for clinical care, they do constitute a fragile and sporadic therapeutic niche in a country (the United States) with fundamental problems in access to healthcare...and a profit-driven pharmaceutical development and approval process’ (Timmermans & McKay, 2009).

2.3.3 Benefits to pharmaceutical companies

Pharmaceutical companies are required by law to provide evidence of safety and efficacy for the products that they develop before they are allowed to sell them to the public. However, the conduct of clinical trials is of benefit to pharmaceutical companies for a number of reasons. In particular, the data collected from clinical trials allow companies to test the effectiveness and safety of their medicines and make informed decisions about which assets are best suited for further investment, and ultimately, for selling at a profit. Pharmaceutical companies often focus on developing drugs for which there is a market or for which a market can be created, as opposed to focusing on the development of products for which there is a significant need or social value (DuVal, 2005). Conducting their own trials (as opposed to having the trial conducted by an independent external partner or investigator) may also allow for a pilot to be halted prematurely if no benefit is being demonstrated. That flexibility can save significant amounts of money and resources, as well as prevent negative press for failed trials. This also permits pharmaceutical companies to manipulate data to present a drug favourably in terms of its efficacy or safety profile, even when the data may suggest otherwise. Conducting research on their own products also allows pharmaceutical companies to control what data and results are shared in the public domain. When trials are positive, pharmaceutical companies may benefit from publishing papers in leading academic journals and presenting results at large conferences, as doing so increases their press and generates interest from potential prescribers (ultimately boosting sales when the product is eventually marketed) (Chopra, 2003). Additionally, announcing the results of positive clinical trials for promising drugs may have rapid effects on a company’s share price and economic forecast.

2.4 Disadvantages

2.4.1 Disadvantages for the patient

There is evidence within the literature to suggest that the perceived disadvantages associated with participation in clinical research can differ greatly between academics and patients. Furthermore, the perceived disadvantages of participating in clinical trials can vary from trial to trial. A research study conducted by Lidz, Appelbaum, Grisso and Renaud (2004) interviewed subjects who were participating in a variety of clinical trials, and the results suggested that subjects often sign consent forms to enrol in clinical trials with only a modest appreciation of the risks and disadvantages of participation. This discord between expectations and reality has been described as the therapeutic misconception (Lidz et al., 2004). Clinical trials are inherently filled with risks due to the often-unknown safety profile of drugs being tested. This is true particularly for phase I-III trials, as in phase IV studies, which occur in the post-marketing setting, side effects and safety profiles are usually well understood. Risks include side effects from medicines, as well as a lack of efficacy, unknown safety profiles, and the potential to receive a placebo in blinded trials. Certain placebo-controlled clinical trials also entail the risk that participation might preclude the use of symptomatic or rescue treatments due to the potential for results around efficacy and safety signals to be confounded. Although the risks of such trials should be carefully reviewed by an ethics committee or IRB, in some instances, fear of being withdrawn from a trial may lead to patients delaying the use of essential treatments. Additionally, in some disease areas, there could be a natural worry that persons with severe and/or terminal disorders may be so desperate for a cure that they are particularly vulnerable to exploitation in high-risk research studies (Kim et al., 2009). Another more general point to note is that if patients find the consent process traumatic, if it results in a loss of faith in clinicians or treatments, or if trial participation leads to reduced access to better treatments then worse outcomes could be the result (Resnik, 2008).

There are a number of factors that may contribute to a patient being more vulnerable to exploitation, and these are not limited to the type of disease from which that individual suffers. Amongst other variables, a patient's likelihood of being exploited can also be partially determined by socioeconomic factors. The nature of the physician-patient relationship may be affected by socioeconomic factors and also plays a role in a patient's

vulnerability, as some patients fail to distinguish between clinical care and research. Miller and Rosenstein (2003) described this as the ‘therapeutic orientation’, arguing that many patients see both trials and routine care as scientifically guided and therapeutically oriented activities conducted within the context of the physician-patient relationship.

A further disadvantage for terminally ill patients is the significant time element associated with their participation in a clinical trial, which could potentially detract from their ability to fully benefit from their end-of-life care and could cause significant distress for their family. Wilcox and Schroer (1994) examined patients’ perspectives on trial participation in an asymptomatic carotid atherosclerosis study and reported that more than half of the subjects saw no disadvantages to participation, whereas Tangrea et al. (1992) considered patients participating in a chemoprevention trial and revealed a number of disadvantages raised by patients; these were covered earlier in this review. Another disadvantage associated with clinical trial participation, specifically after licensing authority is granted, lies in the nature and design of phase IV clinical trials (post-marketing). Most post-marketing studies, which are often carried out to reassure prescribers and regulatory authorities regarding the safety and efficacy of a drug and to provide the aforementioned with longer term data, require extensive follow-up of patients and take many years to complete by which time the results and conclusions may seem stale or irrelevant (Garfield, 1999).

Lidz et al. (2004) summarised the negative points associated with patient participation in clinical trials, particularly those that are double-blind and placebo-controlled in nature. Firstly, subjects are typically assigned to treatment conditions randomly, rather than on the basis of an individualised judgment as to which treatment would best meet their personal needs. Secondly, subjects may receive placebos for reasons unrelated to improving their condition, something that would not occur in ordinary clinical settings. Also, other adjunctive medications or treatments may be prohibited for the subject, not because they would cause harm in conjunction with one of the experimental treatments, but precisely because they could be helpful and could thus create confusion about the source of any positive responses observed. Lastly, a protocol, rather than patients’ responses to treatment, will often determine the dosage of medication that an individual subject receives. In certain situations, physicians may normally increase the amount of a prescribed medication in response to a patient's failure to improve on the current dose;

however, many study protocols restrict their ability to do so and thus prohibit researchers from trying to ascertain the optimal dose for each patient (Lidz et al., 2004).

Although all of the points raised by Lidz et al. (2004) are valid, it may be that some of their arguments did not fully consider the experimental nature of the drugs used in most exploratory work. For instance, determining the optimal dose of an experimental medication on the individual patient level, based on treatment response, brings with it a host of ethical and medical challenges and concerns. Additionally, the prohibition on adjunctive treatments is not always due to the potential for a treatment to confound the results. Rather, it may stem from the potential for unknown or poorly understood drug interactions to occur.

A lack of efficacy or dangerous side effects can often have serious consequences, which is particularly relevant for phase I or first-in-human (FIH) studies. Although rare, early development studies may entail an increased likelihood of dangerous side effects causing lifelong sequelae. This outcome was demonstrated in a 2006 study investigating the use of a CD28 super-agonist antibody. All six phase I volunteers in that study experienced multi-organ failure, as Attarwala and Hunig described in their respective papers on the events that occurred during that trial (Attarwala, 2010; Hunig, 2012).

There are many clinical trial sites that use research as their sole means of income in that they have been specifically established to conduct clinical trials. In such an environment, there may be greater incentives for investigators to enrol higher numbers of patients to meet financial pressures. In emerging markets or developing countries, there is an arguably greater potential for exploitation, which could lead to patients being unnecessarily exposed to medications or procedures that could be dangerous. There is also an increased potential for unscrupulous clinical trial investigators to enrol patients who are not suitable for a particular study to generate money for themselves or their research site.

2.4.2 Disadvantages for the researcher

For investigators, clinical trials may have certain disadvantages, especially if they are conducted on top of normal clinical duties. One study conducted by Lynch, Gorelick, Raman and Leurgans (2001) identified perceptions towards clinical trials in an African-American Physicians Association in the United States. In rank order, physicians indicated

that the disadvantages of a clinical trial included: additional paperwork or telephone calls that might arise as a consequence of patient participation (56%), blind drug assignment (42%), excess patient care costs (21%), the loss of a patient from a medical doctor's practice (17%), and negative effects on managed-care status for a medical doctor's practice (10%).

2.4.3 Disadvantages for society

Most of the social disadvantages associated with clinical research are unrelated to clinical research in the broad sense. The disadvantages instead relate directly to the results of specific clinical trials themselves. Moreover, most of these drawbacks are not truly disadvantages but are rather limitations of clinical trials. For example, generalising the results of a randomised controlled trial to a larger population can be extremely difficult, as due to stringent inclusion and exclusion criteria, clinical trial populations are not necessarily representative of the general population. While not suggesting that there is a better alternative, generalising data from a controlled sample does not always give researchers an indication of what may be observed (e.g., safety profile and efficacy) when the drug is made available to the general public. Furthermore, organising trials for diagnostic and surgical techniques has its limitations, as forming a control group is not possible. Another consideration is that statistically significant results do not mean that the findings are clinically important (Earl-Slater, 2001). Additionally, there is a risk that false negative results (e.g., from studies that have been insufficiently powered) may influence clinical practice or that statistically significant results might lead to treatment guidelines being implemented on the back of a trial not demonstrating any real clinical significance.

As previously mentioned, in areas where the primary aim of conducting clinical trials is to generate income, the primary focus of institutions and healthcare providers may be on ensuring that these trials go well. That aim could lead to a reallocation of resources from normal clinical practice to clinical trials, as well as a shift in priorities. Even in the absence of financial pressure, there is always a risk that for the overzealous investigator, research priorities may take precedence over individual patient needs.

2.4.4 Disadvantages for pharmaceutical companies

For pharmaceutical companies, the disadvantages of conducting clinical trials relate mostly to their cost, time, and resource demands. Sertkaya, Wong, Jessup and Beleche (2016) analysed data from 2004 to 2012 on the cost of clinical trials and found that phase II proof-of-concept study costs ranged from \$7 million for a cardiovascular study to \$19.6 for a haematology study. That same paper found that phase III confirmatory study costs spanned from \$11.5 million to \$52.9 million (Sertkaya et al., 2016). Additionally, clinical trials that do not meet their primary objectives may impact stock prices and create negative press for companies. There is also a high failure rate for clinical trials in later, more expensive phases of development, such as phase III pivotal trials, as many such initiatives fail to meet their objectives (Kola & Landis, 2004) or to recruit enough patients to conduct a full analysis.

As there are so many stakeholders involved in the conduct of clinical trials, it can be difficult for companies to ensure that everybody is adhering to the rules. When individuals are not compliant, the negative press can cause significant reputational damage, even if the company has taken all reasonable steps to ensure that trials are conducted appropriately.

2.5 Conclusion

Clinical trials are an imperative part of the drug development process. Few would argue against the importance of testing new medicines in a small subset of the population before making them accessible on a larger scale, as doing so protects the health and wellbeing of the general public.

In the absence of a perfect and risk-free mechanism for testing treatment options, clinical trials will likely remain our only way of assessing the safety and efficacy of pharmacological treatments, medical devices, and surgeries. Clinical trials have the ability to benefit many, and not just those who are directly involved as either participants or researchers. In addition to the other collateral benefits for patients, trials may provide an alternative treatment option when no known treatment exists, and they may also allow for closer medical follow-up. Clinicians and healthcare practitioners receive the opportunity to offer their patients alternatives to standard treatment while remaining at the cutting edge of

medical technology and therapeutic interventions relevant to their particular field. They may also benefit from additional resources funded by trial work. Pharmaceutical companies gain from obtaining data to inform their asset and pipeline development decisions, and healthcare policymakers can use the results of such trials to inform healthcare policy at multiple levels.

However, clinical trials are not without their disadvantages. Aside from the obvious immediate risks to patient safety due to a lack of efficacy, unfavourable safety profiles, and patients being prohibited (where ethical) from accessing approved treatments that could confound trial results, clinical trials are also administratively burdensome for site staff and can be flawed in their ability to assess a treatment's effectiveness among the general population. For pharmaceutical companies, trials are extremely expensive and require a significant amount of resources. While not perfect, clinical trials offer many advantages and these should be considered along with their potential drawbacks.

CHAPTER 3: SYSTEMATIC LITERATURE REVIEW OF STAKEHOLDER VIEWS ON THE CONDUCT OF CLINICAL RESEARCH IN SUB-SAHARAN AFRICA

3.1 Background

3.1.1 Rationale and objectives

The rationale for conducting this systematic literature review is to better understand the experiences, perceptions, and views of various stakeholders in relation to the conduct of clinical trials in Sub-Saharan Africa. Although there have been systematic literature reviews examining studies focused on individual facets of the clinical trial process in Sub-Saharan Africa, no such appraisal seems to have explored studies addressing stakeholders' perceptions of the clinical trial process as a whole. For example, Adjei and Enuameh (2015) conducted a review of perceptions and beliefs related to blood draws for clinical trials conducted in Africa, and Nalubega and Evans (2015) performed a systematic review addressing the views and experiences of patients participating in HIV research in Sub-Saharan Africa.

The aim of this systematic review is to identify, review, and report on qualitative research studies addressing the views, experiences, attitudes, perceptions, and understandings of individuals from all relevant stakeholder groups on the conduct of clinical research in Sub-Saharan Africa. The focus is on better understanding the issues that stakeholders are raising, as opposed to reviewing studies quantifying the level of agreement with topics that have already been raised.

3.2 Methods

3.2.1 Types of studies, phenomena of interest, and context

This literature review considered all published articles reporting on qualitative studies conducted with any stakeholder group involved or associated with the conduct of interventional clinical trials in Sub-Saharan Africa. Studies that addressed the perceptions of stakeholders in relation to observational research were not considered. Stakeholder

groups included: patients, regulators, HCPs, and community workers. Studies conducted in North Africa were not considered, as countries north of the Sahara Desert are different in their racial and socioeconomic composition.

3.2.2 Search strategy

A three-step search strategy was used, with PubMed and ScienceDirect queried for published studies. PubMed was searched first, as it is considered one of the most comprehensive literature databases in the fields of medicine, nursing, and healthcare systems (US National Library of Medicine, 2002). Searching on PubMed also provides access to several other databases, including MedLine. There are a number of studies that have demonstrated that the use of one database is not sufficient for a systematic literature review, while the use of two or more provides more reliable coverage (Minozzi Pistotti, & Forni, 2000). Including ScienceDirect as an additional database was a way to ensure that all relevant papers were captured, and this strategy was further augmented by performing a supplementary Google Scholar search. A 2013 study conducted by Gehanno, Rollin and Darmoni (2013) found that searches on Google Scholar returned all of the same studies included in 29 Cochrane systematic reviews which comprised 738 original studies. In doing so, the authors demonstrated its reliability as a tool to ensure a comprehensive search strategy.

The search terms used were various combinations of the following: ‘clinical trials’, ‘clinical research’, ‘views’, ‘perception’, ‘opinion’, ‘stakeholder’, ‘qualitative’, ‘interview’, ‘Africa’, and ‘Sub-Saharan’. Following an analysis of the title, abstract, and index terms, a second search was then performed using any keywords that were not part of the original search terms. Finally, the references from each analysed article were reviewed to check for additional studies or relevant literature. Summaries outlining the results of the two main databases that were searched are presented in Table 2 and Table 3.

| Search terms | Results | Reviewed |
|---|---------|----------|
| Medical Subject Headings (MeSH): Clinical trials AND MeSH: Africa south of the Sahara Title/abstract: perception | 8 | 3 |
| MeSH: Clinical trials AND MeSH: Sub-Saharan Africa AND Title/abstract: perception | 1 | 1 |
| Title/abstract: clinical trial AND Title/abstract: Sub-Saharan Africa AND Title/abstract: perception | 6 | 4 |
| Title/abstract: clinical research AND Title/abstract: Sub-Saharan Africa AND Title/abstract: stakeholders | 3 | 0 |
| MeSH: views AND MeSH: clinical research Africa | 149 | 15 |
| MeSH: perception AND MeSH: clinical trial Africa | 167 | 11 |
| MeSH: stakeholder view AND MeSH: clinical research AND Title/abstract: Africa | 1 | 1 |
| MeSH: perception AND Title/abstract: clinical research Africa | 62 | 1 |
| MeSH: interview AND MeSH: clinical trial Africa | 219 | 18 |
| MeSH: qualitative AND Title/abstract: clinical trials Africa | 239 | 31 |

Table 2: Results of the PubMed searches

| Search terms | Results | Reviewed |
|---|---------|----------|
| pub-date > 1995 and TITLE-ABSTR-KEY(clinical trial Africa) and TITLE-ABSTR-KEY(qualitative) | 7 | 3 |
| pub-date > 1995 and TITLE-ABSTR-KEY(perception) and TITLE-ABSTR-KEY(trials Africa). | 21 | 2 |
| pub-date > 1995 and TITLE-ABSTR-KEY(interview clinical trial Africa) | 15 | 7 |
| (perception clinical trials) and ABSTRACT(Africa) | 263 | 4 |

Table 3: Results of the Science Direct searches

3.2.3 Screening and selection of papers

When searches were complete, all papers were screened for appropriateness and selected based on a set of six pre-existing criteria which are listed in the below.

1. Data:

Only studies conducting empirical research were included in the literature review. Existing literature reviews and/or meta-analyses were not included.

2. Language:

Only studies published in the English language were considered for this review.

3. Timeframe:

Papers written between 1996 and the present were included. Those written prior to 1996 were not considered appropriate, given shifts in the disease and socioeconomic landscapes, as well as changes in clinical trial regulations within the last 20 years.

4. Participants:

There were no restrictions on the trial population participants (e.g., paediatric, adult) or the sponsor of the research (industry, charity, non-governmental organisation [NGO]). However, only studies assessing the opinions of stakeholders on the conduct of interventional clinical trials were included.

5. Geographic spread:

Only studies focused on the conduct of clinical trials in Sub-Saharan Africa were included in this literature review. Studies assessing the opinions of stakeholders in North Africa were excluded.

6. Research methodology:

Only studies that used qualitative methods to assess stakeholder attitudes toward the conduct of clinical trials were reviewed. Those using purely quantitative methods were not included. Studies that used mixed (qualitative and quantitative)

methods were selected, but only qualitative data are included in the results of this review.

3.2.4 Methodological quality

This literature review was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), an evidence-based set of guidelines outlining a minimum set of criteria used to report systematic literature reviews (Moher, Liberati, Tetzlaff, & Altman, 2009). The studies' appropriateness for inclusion was assessed using the Joanna Briggs' Qualitative Assessment and Review Instrument (QARI) (Joanna Briggs Institute, 2003), a 10-point evaluative tool that provides a structured way of reviewing and appraising qualitative research. This tool was used to ensure that the papers included met the criteria for quality (i.e., for study selection), as opposed to employing it to systematically assess the quality of each study. A copy of the Joanna Briggs' QARI can be found in Appendix 2.

3.2.5 Narrative synthesis

Narrative synthesis describes the way in which a researcher brings together research from various sources to provide an overall picture of current knowledge. (Snilstveit, Oliver, & Vojtkova, 2012).

This review used an approach to narrative synthesis that Thomas, Harden and Newman (2012) have described as 'thematic summary'. The conceptual framework of this overall study was used to categorise the findings of the studies identified for inclusion in this review into similar groups of relevance for the reader (Thomas et al., 2012). The findings from each study were separately reviewed and synthesised before being brought together within an aggregative narrative informed by themes and topics identified during the development of this project's conceptual framework.

3.3 Results

The studies screened and assessed for eligibility are summarised in Figure 5.

In sum, 101 individual records were reviewed. That figure represents the total number of papers selected for initial review following both the PubMed (77) and ScienceDirect (24) searches. Once duplicates were removed, 74 records remained to be screened. Of the 74 items screened, 23 papers were excluded for not relating to the phenomenon of interest (i.e., interventional studies), for being quantitative in nature, for not being written in English, or concerning research conducted outside of Sub-Saharan Africa. Of the 51 studies that were fully assessed for eligibility, only 3 were excluded (as they were not related to interventional research).

3.4 Discussion

Several key and interlinked themes emerged from the review of the literature. The findings are presented under the appropriate theme headings in the sections which follow.

Notably, much of the published qualitative literature on stakeholders' perceptions of clinical trials in Sub-Saharan Africa is related to HIV/AIDS. Further, most of these studies, including Venables and Stadler (2012) and Moodley, Staunton, de Roubaix and Cotton (2015), were conducted in South Africa. This may have limited the diversity of the opinions reported throughout the literature, as the issues in that country may not be the same as in other countries in the region. As a result, certain themes reported in the literature are more relevant to those particular disease indications than to others. A summary table outlining the key attributes of the studies discussed in this review can found in Appendix 3.

3.4.1 Stigma/fear

The available literature on participants' perspectives of HIV/AIDS trials reported several common themes related to participation in trials in this disease area. These included discouragement from family members/colleagues, the need to overcome the fear of being

tested for HIV/AIDS, and a general mistrust of healthcare providers and researchers (Nyblade, Singh, Ashburn, Brady, & Olenja, 2011; Tarimo et al., 2011a).

For example, Nyblade et al. (2011) conducted focus groups with 133 participants, along with 82 individual interviews with respondents from 2 centres in Nairobi, Kenya. The respondents were current participants in an ongoing preventative AIDS vaccine clinical trial, and many reported stigma and discrimination that impacted their daily lives as one of the largest negative impacts of their involvement. Also reported was discord within marital or partner relationships, a loss of economic support, the potential for physical violence, and a loss of relationships (Nyblade et al., 2011). The importance of understanding the effects of trial participation on personal relationships was further qualified by Venables and Stadler (2012). That study, which involved interviews with participants in a trial investigating the use of microbicide to prevent the transmission of HIV with female patients, emphasised the importance of partner dynamics for clinical trial participants. The authors concluded that engaging male partners of female research subjects to build and strengthen relationships between researchers and research participants was advisable for HIV trials (Venables & Stadler, 2012).

In earlier studies with similar respondent groups, researchers also established that the impact of participating in HIV trials was such that involvement could also lead to changes in health-seeking behaviour on the part of participants (Stadler, Delany, & Mntambo, 2008; Tarimo et al., 2011).

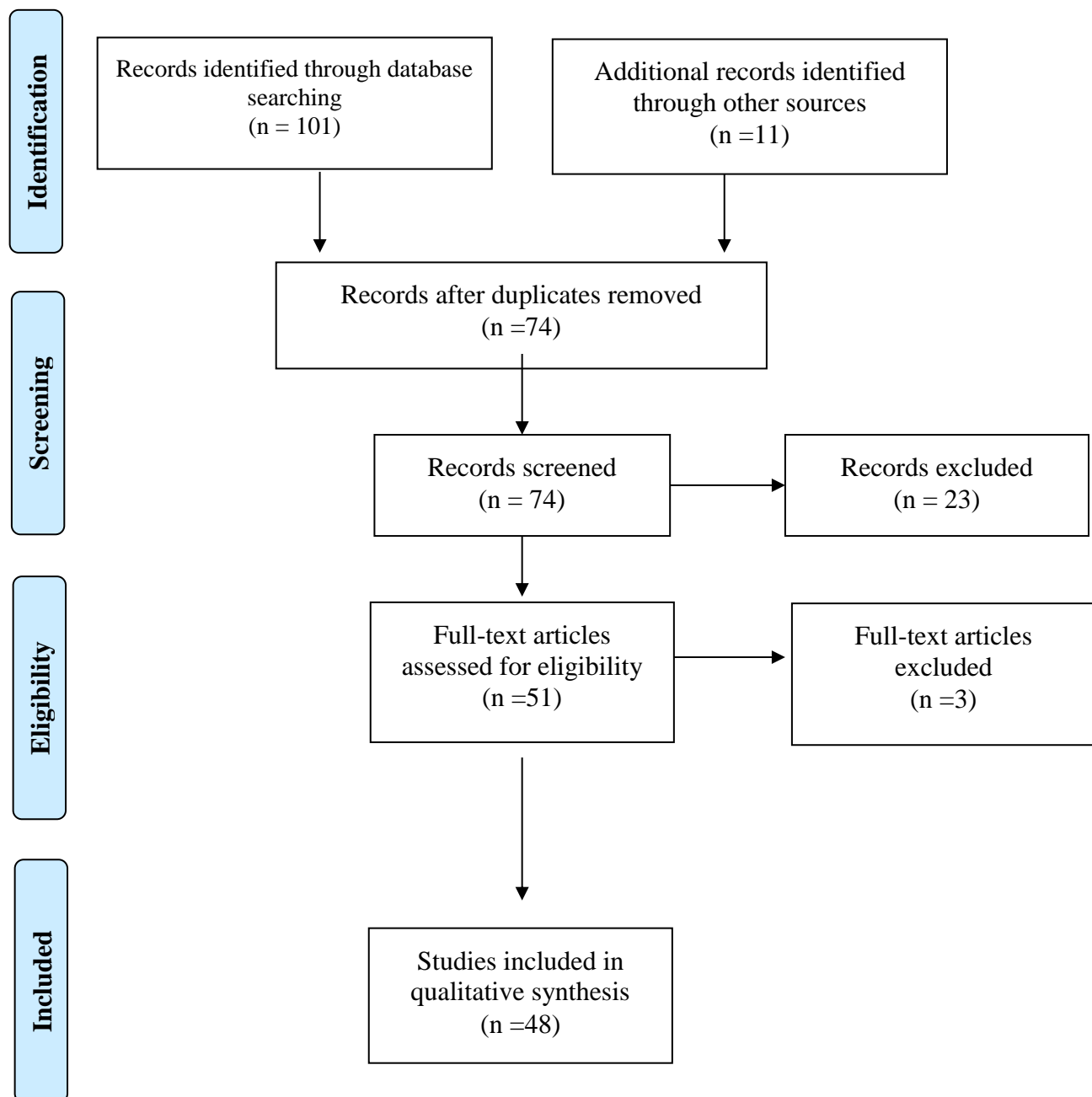


Figure 5: Flow diagram outlining articles reviewed, considered, and selected (Liberati, Altman, Tetzlaff, Mulrow, & Gotzsche, 2009)

3.4.2 Therapeutic/preventative misconception

A study similar to that of Venables and Stadler (2012) found serious issues regarding preventative misconceptions (Woodsong et al., 2012). A preventative misconception is a misunderstanding in which research participants make an ‘overestimate in probability or level of personal protection that is afforded by being enrolled in a trial of a preventive intervention’ (Simon, Wu, Lavori, & Sugarman, 2007). The researchers conducting the focus group and interview-based study in Malawi, Zimbabwe, and South Africa were trying to understand reasons for participation in a preventative microbicide trial. The authors found numerous examples of preventative misconception among participants, and they discovered that patients were participating in the trial because they believed the medicine would be effective in preventing the transmission of HIV (Woodsong et al., 2012). Those results thus highlighted potential inadequacies within the informed consent process.

The issue of preventative or therapeutic misconception was not only related to research associated with HIV/AIDS clinical trials. Evidence of therapeutic or preventative misconception has also been found by researchers in other disease indications. For example, Malan and Moodley (2016) reported results from a qualitative study investigating the perceptions of South Africans participating in phase III oncology trials. They found that therapeutic misconception clearly existed within some patients, as evidenced by comments indicating that participants felt the clinical trial’s purpose was mainly for personal benefit. Further comments implied an underestimation of the risks and optimism about the outcome (Malan & Moodley, 2016). Mfutso-Bengo et al. (2008) found, in contrast, that therapeutic misconception was not a significant driver of participation in clinical trials in Malawi across a number of therapeutic indications. Rather, overcrowding in government hospitals and hospitals often lacking drugs meant that participating in a clinical trial often gave research subjects access to better ancillary care than that received by non-participating community members (Mfutso-Bengo, et al., 2008). Osamor and Kass (2012) found that most trial participants in a study in Southwest Nigeria took part because they wanted to know more about their disease, and not because of a perceived therapeutic benefit.

3.4.3 Informed consent

A significant proportion of the available literature offering qualitative perspectives on clinical trials in Sub-Saharan Africa deals with the issue of informed consent. Given its apparent importance as a topic for consideration in the discussion around the conduct of clinical trials in Sub-Saharan Africa, this literature review reports on this theme in more detail than that given to other, less frequently discussed issues.

Toe et al. (2013) used a mixed-methods approach involving focus group, interviews, and a quantitative survey at the Daffra Health Centre in Burkina Faso to assess whether parents' decisions to enter their child(ren) into a paediatric malaria trial were being made before the parents and children were consented. The interviews and focus groups revealed that most parents bringing their children in to see the study doctors had heard about the study in the community and had already made a decision to allow their child to participate in the trial before being taken through the consent process. The potential for their children to access free healthcare was the primary driver for this decision, in accordance with earlier referenced work by Mfutso-Bengo et al. (2008). It is, however, worth noting that this study was conducted in a particularly socially disadvantaged area of Burkina Faso, and consequently, its results may not be representative of patients in less disadvantaged areas. The authors concluded that informed consent in areas with poor access to healthcare does not always achieve its goal of allowing participants to freely choose to take part in a trial, as participation is often the only way to access free healthcare (Toe et al., 2013). On the basis of similar findings in an earlier study, Gikonyo, Bejon, Marsh and Molyneux (2008) recommended that greater attention be paid to 'diverse social relationships that are essential to the successful application of informed consent procedures.' Further, the authors suggested that current guidelines may not be an adequate response to the complex and constantly evolving ethical issues faced by researchers in resource-constrained environments (Gikonyo et al., 2008).

Molyneux, Wassenaar, Peshu and Marsh (2005) held focus group discussions with community members living in a rural area of Kenya located close to a large research unit. In this study, subjects were asked about their perceptions of the informed consent process during interviews. The researchers sought to ascertain whether participants felt that consent was needed, and if so, who should provide it. The authors also wanted to better understand

if the participants had any special concerns about the informed consent process. They reported general agreement on the need for autonomous consent, at least at the household level, but only after consent from community leaders had been given to conduct research in the community. In line with the previously discussed findings related to therapeutic misconceptions, the results also revealed that respondents had difficulties distinguishing research from routine clinical care (Molyneux, Wassenaar, Peshu, & Marsh, 2005). Leach et al. (1999) found slightly different results related to the need for community leader consent for a trial, as they reported that many did not feel it was necessary for consent to be given at that level. That paper was, however, written six years earlier, and it is possible that the prevailing opinion had evolved and/or that the need for consent at the community level is specific to various communities. The authors also found, perhaps unsurprisingly, differences in the need to obtain community leader consent in urban areas. More specifically, less than 1% of parents approached in an urban area to have their child participate in a clinical trial of *Haemophilus influenza* type B conjugate vaccine felt it necessary, versus 25% of those parents in rural areas (Leach et al., 1999).

Molyneux et al. (2013) performed in-depth interviews with parents, trial staff, and healthcare workers and examined the use of deferred consent in emergency trials (in this case, a paediatric trial in critically ill children with severe febrile illness and shock). In the deferred consent process, verbal assent to the trial is obtained from the parent/guardian when the child is admitted to the hospital, with a delayed full informed consent process following after the child has stabilised. The study's results indicated that the interviewees felt that deferred consent worked in the interest of all parties by ensuring that treatment was not delayed, and that by deferring the consent process, time was given to parents to fully assess the information and withdraw their previous assent, if they were not happy. The authors also found, however, that in some instances, poorly delivered preliminary information undermined the validity of the assent and compromised the guiding principles of deferred consent (Molyneux et al., 2013). This highlights the challenges of providing truly informed consent and accords with evidence elsewhere within the available literature suggesting that even after granting their consent, not all patients understand or retain the information that has been given to them, as summarised in a paper by Ndbele, Wassenaar, Masiye and Munalula-Nkandu (2014). The authors reported that almost two-thirds of patients enrolled in a randomised, double-blind, placebo-controlled clinical trial investigating the use of microbicide in Malawi did not have a full grasp of the aspects of the trial that were deemed critical to understanding the study itself. The structured

questionnaire interviews carried out with respondents indicated that while the site staff had adequately explained the definition of each aspect of the trial, several key elements were probably not covered in a manner sufficient to provide a solid and comprehensible justification for their use, leaving several patients confused (Ndbele et al., 2014).

Most of the published literature addressing informed consent alluded to scope for improvements to in the consent process in Sub-Saharan African countries. Changes that are needed include ensuring that information related to the use of placebos is provided in a way that is comprehensible (Hill, Tawiah-Agyemang, Odei-Danso, & Kirkwood, 2006). Moreover, improved interpersonal communication skills and relationship-building capabilities are required for all staff to guarantee that subjects are comfortable providing consent and to ensure that subjects do not feel as though they are ‘negotiating with authority’ when consenting. Additionally, making certain that subjects understand the roles of, and differences between, research units, aid organisations, and routine healthcare is an important factor for consideration in the consent process in resource-constrained environments (Molyneux et al., 2005; Van Loon & Lindegger, 2009).

3.4.4 Mistrust

There were numerous examples throughout the literature highlighting issues of mistrust and misconceptions around procedures associated with clinical trials, with blood draw cited most frequently. Leach et al. (1999), who were assessing participants’ views on the clinical trials process, had a respondent summarise the reasons for that mistrust in quite comprehensive terms:

‘I don’t trust experimental vaccines and moreover these vaccines brought here to Africa by scientists cannot be trusted. Because these Europeans know we are poor people and so accept any terms and conditions, they are using Africans like guinea-pigs and Africa as a dumping place for so much waste.’

Quoted in Leach et al. (1999)

A recent study by Chatio, Baiden, Achana, Oduro and Akazili (2016) in Northern Ghana surveying parents whose children were enrolled in a clinical trial assessing the efficacy of rectal artesunate found that while most were aware of the role that clinical trials play in

reducing the occurrence of diseases, many were not pleased that blood samples were being taken from their children. A number of the parents feared that their children's blood could be tested for HIV, while others harboured suspicions that the blood samples would be sold to local and international partners (Chatio et al., 2016). Fairhead, Leach and Small reached analogous conclusions in a similar earlier study in Gambia (Fairhead et al., 2006).

Boahen et al. (2013) looked specifically at perceptions of blood draws for clinical trials in a study conducted between 2010 and 2011. As part of that effort, 12 focus group discussions were held alongside 8 in-depth interviews with community members in the Kintampo District of Ghana. Most respondents indicated that there were no cultural beliefs that discouraged them from giving blood, but some indicated that there were fears that the blood could be used for rituals. To dispel this misconception, the interviewees strongly recommended that researchers thoroughly explain the reasons for taking blood, particularly in instances where patients may not be ill. The respondents offered this advice, as they were largely familiar and comfortable with giving blood when ill but struggled to understand the need to do so when healthy (Boahen et al., 2013). Contrary to these findings, however, were the results of Stadler and Saethre (2010) who were investigating rumours linked with blood and reimbursements related to an interventional microbicide gel trial looking at the prevention of HIV transmission in South Africa. A rumour around the study was started that suggested that subjects were being reimbursed for their participation in the trial, as well as being paid for their blood in a 'blood for cash' scheme. During interviews, participants in the trial accused the research team of being paid a significant amount of money for the blood, suggesting that the cash received for that blood was the reason that the researchers could afford to drive expensive cars. Participants also indicated that when they asked the researchers why so much blood was needed, they were told it would take too long to explain. This finding again highlights the role that education plays in building trust and relationships with communities and research participants (Stadler & Saethre, 2010).

Concerns specifically related to the amount of blood drawn, particularly in paediatric trials, were also an issue raised in several articles, including Leach et al. (1999), Liheluka et al. (2013), and Dial, Ceesay, Gosling, D'Alessandro and Baltzell (2014). Similar apprehensions related to the use of endoscopic biopsies and their potential application in witchcraft were raised by Kingori, Muchimba, Sikateyo, Amadi and Kelly (2010). They conducted interviews with mothers whose children were involved in a paediatric

malnutrition study, and some participants suggested that the doctors and nurses on the study were Satanists and that the children's body 'parts' removed during endoscopies would be used in medical students' lessons or sold to drug manufacturing companies (Kingori et al., 2010).

3.4.5 Relationship-building and community engagement

Several themes emerging from the literature pointed toward the need for relationship-building and engagement between researchers and the communities with which they are involved for research purposes.

3.4.5.1 Relationship-building

An important topic in the discussion on the conduct of clinical trials in Sub-Saharan Africa is that of the relationship between the clinical investigator and research participant, particularly in socioeconomically poor regions. A relatively small amount of published research has been conducted with stakeholders outside the patient group. One exception is a study by Zvonareva and Akrong (2015) based on 42 in-depth interviews in Ghana and South Africa with multiple stakeholder groups. The respondents involved had varying levels of experience in clinical trials and the discussion's aim was to better understand their views and attitudes towards clinical research and the role of research subjects. The results illustrated that across stakeholder groups, opinions were largely the same. In addition, the investigators who were involved in the research preferred to look at their patients as partners with whom they were jointly working to find ways to address local health needs. The respondents (both potential and previous clinical trial participants) had a solid fundamental understanding of what clinical research is and why it is important, and they indicated that they were likely to be more engaged if they felt there was transparency, that investigators cared about them, and that the researchers were accountable in some manner. Of note, however, is that the study was conducted at a university, and the socioeconomic background of the respondents was not clear from the article (Zvonareva & Akrong, 2015). The idea of patients feeling as though they are partners in a study, working together with researchers to find a cure, was also a theme that also emerged from a separate study by Zvonareva, Engel, Ross, Berghmans, Dhali and Krumeich (2015) examining potential and past participants' perspectives on the benefits of clinical trial involvement.

3.4.5.2 *Community engagement*

The need for community engagement, widespread educational strategies, and sensitisation before the outset of a clinical trial emerged from research conducted by a number of authors. Koen, Essack, Slack, Lindegger and Newman (2013) reported on the importance of meaningful and long-term (as opposed to crisis-driven) community engagement in research examining the perspective of negative trials results and stakeholder engagement (Koen et al., 2013). Dial et al. (2014), who reported on a study investigating barriers to participation in a mass malarial drug administration effort in Gambia, concluded that widespread education were key to sensitising communities to clinical trials. Similar conclusions were reached by Akazili et al. (2016), who highlighted the importance of educating trial participants on the potential side effects of new drugs. The process of sensitising communities should be continuous, and potential trial participants must be given information in a way that it is readily understandable and comprehensive in terms of both the trial and the investigational product to be administered (Buregyeya et al., 2015; Dial et al., 2014).

3.4.5.3 *The use of locals to build trust with communities*

One potential mechanism of engaging communities and providing reassurance to research participants may be the use of ‘village reporters’ (VRs). Village reporters are community members who are tasked with supporting research conducted by units in East Africa. Chantler et al. (2013) assessed the impact of VR use across a number of studies in which VRs were interviewed and invited to participate in focus groups. The authors concluded that the VRs’ unique position of being from, based in, and familiar with the community may leave those individuals more capable than researchers of engaging with locals and earning their trust. However, the article also described issues that remain to be addressed regarding the use of VRs; these regarded attachment to, and relationships with, researchers and the community that could compromise their impartiality (Chantler et al., 2013). Kamuya, Marsh, Kombe and Geissler (2013) reported separately on the use of VRs and their community engagement role and reached similar conclusions (Kamuya et al., 2013).

3.4.5.4 *Formative research as a tool for community engagement and researcher education*

The literature raises the topic of the need for education, not only for communities but also for researchers themselves. In particular, Westerners conducting research in Sub-Saharan Africa must inform themselves as to what is acceptable. An interesting study by Corneli et al. (2007) looked at formative research (research that occurs before a study is designed) as a means of informing the development of clinical trial protocols. Formative research was thought to have the potential to make protocols more culturally acceptable (including reducing the amount of blood required for blood draws, a prevalent topic throughout much of the literature, as previously discussed). The authors found that involving the community in research prior to protocol finalisation allowed them to better understand the cultural nuances in need of consideration and allowed them to incorporate those elements into the trial design at an early stage. Doing so ultimately led to the successful implementation of a well-designed and culturally sensitive clinical trial (Corneli et al., 2007).

3.4.6 Research benefits and beneficiaries

Another theme featuring prominently throughout the literature is related to better understanding the benefits and beneficiaries of research conducted in resource-constrained environments. Zvonareva et al. (2015) conducted interviews with 24 respondents in South Africa. Of these individuals, approximately 38% had experience participating in clinical trials. The interview questions were all aimed at gaining further insight into perspectives on the benefits associated with clinical trials in terms of both medical care and the longer-term, post-trial advantages. The authors reported that the respondents did not cite money as a valid reason to take risks with their own health. However, they did see improvements in one's community as a more enticing reason to participate in trials. The participants felt that it was not right to want anything in return for participating in a study, as they saw their role in research as helping their community (some likened it to donating blood). The study revealed that more important than financial compensation was the ancillary care that the research participants received, an outcome similar to the findings of Mfutso-Bengo et al. (2008). The participants felt that because they were helping researchers with their study, the investigators should, in turn, be concerned enough about the well-being of patients to ensure that they have adequate access to healthcare beyond their participation in the trial (the participants had limited healthcare access in this particular part of South Africa)

(Zvonareva et al., 2015). The results of an earlier study by Lairumbi, Parker, Fitzpatrick and English (2012) were similar to those of Zvonareva et al. inasmuch as the interviewees felt that individual-level access to investigational products and care were important drivers of participation. They also mentioned being motivated by possibilities for community improvement through infrastructural development, ‘brain gain’ (i.e., the retention of qualified staff), and technology transfer. However, there was some discord with Zvonareva’s research, as those interviewed highlighted compensation for time and effort as a significant driving factor for participation in clinical trials (Lairumbi et al., 2012). These findings are more in agreement with the outcome of other studies. For example, participants in Shaffer et al.’s (2006) study in Kenya felt that they should receive compensation, given the risks associated with their involvement (Shaffer et al., 2006). Masiye, Kass, Hyder, Ndbele and Mfutso-Bengo (2008) also reported access to better healthcare as a significant driver for mothers who had chosen to enrol their children in a malaria study in Malawi (Masiye et al., 2008). Njue, Kombe, Mwalukore, Molyneux and Marsh (2014) argued that concerns about undue financial incentives in low-income communities may often be misplaced and that greater attention should be given to avoiding unfairness (Njue et al., 2014).

In instances in which the investigators are beneficiaries and receive payment for enrolling subjects in clinical trials, potential conflicts of interest are always an issue. Work by Essack et al. (2009) concluded that potential power issues could develop in cases in which the principal investigator is paid significant sums for enrolling subjects in a trial. Such an outcome could, in turn, impact the ethical conduct of the research (Essack et al., 2009). The issue of financial reward as an incentive for clinical trials in resource-constrained environments was best summarised by Stadler and Saethre (2010), who referenced a comment made by a former South African minister of health:

‘In a community that is poor, providing financial gain or compensation could prove to be perverse incentives. As we know, the poor may become desperate to receive incentives despite risk’ Quoted in Stadler & Saethre (2010).

Of note, however, is that the issue of financial reward is not exclusive to developing countries, as doctors in the West are also paid to include patients in clinical trials.

3.4.7 Infrastructure

The levels of clinical trial infrastructure across Sub-Saharan Africa differ, with South Africa generally considered to have the most developed and robust infrastructure, and consequently, the most experience with clinical trials. However, Siegfried, Volmink and Dhansay (2010) carried out research to establish the need for a dedicated initiative to support the conduct of clinical trials, focusing particularly on research methods training and statistical support. The authors found that stakeholders were largely in agreement with the establishment of such a unit but felt that consideration needed to be paid to sustainability from a resource (human and financial) perspective (Siegfried et al., 2010).

Angwenyi et al. (2015) looked at the opinions of 99 healthcare providers involved in the conduct of clinical trials at centres in Ghana, Kenya, and Burkina Faso. The authors wanted to understand how the long-term and wider benefits of clinical trials' contributions could potentially impact routine healthcare in resource-constrained environments. They found that facilities involved in trials benefitted from equipment upgrades, support with essential drugs, and access to trial vehicles. Those sites also tended to be assigned qualified trial staff, which benefitted routine clinical care. However, these benefits were often short-term and generated concern around what would happen at the trial's end (Angwenyi et al., 2015). Liheluka et al. (2013) summarised the secondary benefits of trial participation as improvements to routine healthcare services and the provision of resources. In that particular study, these resources took the form of a new laboratory and radiology facilities (Liheluka et al., 2013).

Infrastructural issues at the macro-level, such as access to public transport in rural areas, also play a key role in the viability of clinical research in developing countries. Research on participants in rural areas of Sub-Saharan countries has reported patient concerns with getting to appointments, having to return home late at night, and the implications for their personal safety (Magazi et al., 2014). This is an issue that researchers should potentially consider in both their trial designs and their outreach strategies to ensure that there are safe and efficient ways for patients to reach trial visits. Another option is to limit the area for patient recruitment to the research facility's immediate proximity. Magazi et al. (2014) reported that participants enrolled in a study investigating the efficacy of various forms of tenofovir for the prevention of HIV were frustrated with the lack of staff available to see

them at their scheduled visit time and with the long waiting times and associated inconvenience.

3.4.8 Researcher perspectives

Much of the available published literature focuses on the perceptions and opinions of communities and clinical trial subjects, rather than on those of the researcher. Only 13 of the papers reviewed concentrated on the perspective of the researcher, and of those, only 2 papers (Siegfried et al., 2010; Van Loon & Lindegger, 2009) explicitly solicited the opinions of pharmaceutical company representatives. Although there were several examples (e.g., Siegfried et al. [2010], Koen et al., [2013], and Angwenyi et al. [2014]) highlighted earlier in this review, the literature does not report on the opinions of researchers to the same degree that considers those of participants. All of the other papers reviewed (29 out of 44) focused on the opinions of trial subjects (or their guardians), social workers, or community members.

Recently, however, a study by Vischer et al. (2016) investigated the advantages and challenges of working with GCP-ICH E6 guidelines, which aim to protect the rights, safety, and well-being of trial subjects while ensuring data integrity and a high level of quality. The study team conducted interviews with 60 clinical trial staff members at different levels in research centres in Kenya, Ghana, Burkina Faso, and Senegal. It found that most respondents felt that the guidelines were useful but were concerned with the overcautious application of parameters regarding informed consent, raising questions about their applicability and sensitivity to cultural beliefs and needs (Vischer et al., 2016). For example, the authors highlighted how traditionally, communication takes place orally within some cultures and how the need to give research subjects a document to both read and sign contradicts the nature of the spoken agreement through which many arrangements are made. The verbal nature of agreement and consent was also a topic addressed by Molyneux et al. (2013) in their discussions around paediatric deferred consent and the need to ensure verbal assent in emergency situations.

Another topic raised by local researchers in Kenya, as described by Lairumbi et al. (2012), is researchers' difficulties in trying to convince potential subjects to participate in clinical trials without adequate compensation or reward. The article also cited related concerns

about the primary motivators of study participation in poorer settings. Researchers who were interviewed as part of that study also identified ‘brain gain’ as a key benefit to research in Kenya. These infrastructural benefits include researchers’ replacement of old equipment, which hospitals may otherwise struggle to replace, as well as access to medical and public-health tools and proven interventions that may otherwise not be available (Lairumbi et. al., 2012). Research methods training and statistical support were mentioned by researchers in a separate research study conducted by Siegfried et al. (2010) as benefits of conducting clinical trials in Kenya. Angwenyi et al. (2015) suggest that sponsors consider the resource gap (human and otherwise) that will remain when funding for studies is no longer being received and the impact that this may have on patients if a centre’s ability to deliver services is affected.

3.5 Limitations

There were several limitations within the literature reviewed. The first relates to an imbalance with respect to countries that have been involved in research assessing the perceptions of clinical trials. Although Sub-Saharan Africa comprises 49 countries, only 12 of those countries were represented in the studies included in this review. Additionally, within the few countries represented in the literature, most research was conducted in rural areas, with a dearth of publications on research conducted at large teaching hospitals in the regions’ larger, more developed cities. In many cases, the educational and socioeconomic backgrounds of the respondents was not reported, which may have also created a bias in the nature of the issues raised regarding the opinions of the community and the extent to which they impact the conduct of research in the region.

Another limitation within the available literature relates to use of studies assessing the perceptions of trials that have been conducted largely in the domain of infectious disease, and more specifically HIV/AIDS. These diseases, along with malaria, were the most frequently discussed conditions in the literature. Little was published on perceptions of trials conducted in chronic diseases, with the exception being authors such as Malan and Moodley (2016), who reported on trials in oncology.

3.6 Conclusions

There is a significant body of literature addressing the perceptions of research participants in clinical trials conducted in Sub-Saharan Africa. Nevertheless, most research appears to have been conducted in a handful of countries and has largely concentrated on infectious diseases, and particularly HIV. The types of issues raised across the literature are similar and interlinked. Most fall under the umbrella of a handful of key issues, including: the benefits and beneficiaries of research, informed consent, issues around blood draws, and education/understandings regarding clinical trials and trial conduct. Moreover, the literature, to a large extent, reflects the views, perceptions, and opinions of participants or potential participants. Although some published studies have addressed the views of researchers, the voices of other stakeholder groups—including HCPs with no interest in research, regulatory personnel, government officials, and members of the pharmaceutical industry—are heard less often.

Gaps in the current literature include a lack of qualitative research assessing perceptions of trials related to chronic diseases, as well as scant research adequately capturing the opinions of non-participant stakeholder groups involved in the conduct of clinical trials. There is little published research discussing the opinions of stakeholders who are not current and/or potential patients, and a greater diversity of relevant stakeholder opinions is required to move discussions around Sub-Saharan Africa's participation in clinical research forward.

CHAPTER 4: METHODOLOGY

4.1 Introduction

As a researcher, it is important to consider and understand which of the numerous existing methodologies is most appropriate for answering the research questions or for gaining insight into the phenomenon under investigation. Methodology refers to the underlying logic leading to a particular method or set of methods being chosen and focuses on the theoretical concepts that inform that choice of methods. In describing the methodology, the researcher provides a justification, rationale, and context for the methods used (Schneider, 2014).

This chapter begins by describing the philosophic underpinnings that informed and shaped this mixed-methods inquiry. The chapter moves from that theory to consider the strengths and weaknesses of the study's methodology.

4.2 Research paradigm

4.2.1 Epistemological and ontological starting points

As a researcher, declaring a research paradigm is an essential step in orienting the audience around one's study. According to Bracken (2010), 'declaring ontological and epistemological beliefs is important as they underpin the adoption of strategies and methods used by empirical researchers.'

Ontology is a branch of philosophy that concerns itself with the 'what is' (Floredi, 2003). O'Gorman and MacIntosh (2015) described it as providing insight into a researcher's view of the world. This view ultimately guides the methodology that a researcher employs to answer his or her research question(s). Ontological assumptions are generally divided into two configurations: objective and subjective. An objective viewpoint believes in a single reality that can be measured and tested and that exists even when not being observed or experienced (O'Gorman & MacIntosh, 2015). In contrast, a subjective perspective suggests that multiple realities and experiences exist (Lincoln & Guba, 1985).

Epistemology is the study of knowledge and asks the question of ‘how do we know what we know?’ (Creswell, 2003). Defining an epistemological position is important, as it helps the researcher’s audience know how they have evaluated new information and made fundamental decisions (Hofer, 2001).

4.2.2 Pragmatism

Pragmatism, as defined by Tashakori and Teddlie (2002) and Creswell and Plano Clark (2007), is a paradigm that encompasses a range of philosophical viewpoints. It focuses on the research problem and then uses a variety of approaches to develop knowledge about that problem; in doing so, pragmatism embraces both objective and subjective ontological positions. As argued by Feilzer (2010), it ‘supports the use of a mix of different research methods and modes of analysis and a continuous cycle of abductive reasoning while being guided primarily by the researcher’s desire to produce socially useful knowledge.’

Taking a pragmatic approach allows the researcher to circumvent some of the contentious issues of truth versus reality and argues that philosophically, there are singular and multiple realities that are open to empirical enquiry. As such, pragmatism aims to solve practical problems in the ‘real world’ (Rorty, 1999; Creswell & Plano Clark, 2007). As Creswell (2003) summarised in his discussions around the various available research paradigms, pragmatism operates with several assumptions:

1. ‘Pragmatism is not committed to any one system of philosophy and reality.
2. Individual researchers have a freedom of choice.
3. Pragmatists do not see the world as an absolute unity.
4. Truth is what works at the time.
5. The pragmatist researchers look to the “what” and “how” to research, based on the intended consequences and where they want to go with it.
6. Pragmatists agree that research always occurs in social, historical, political, and other contexts.’

Powell (2001) further argued that ‘to a pragmatist, the mandate of science is not to find truth or reality, the existence of which are perpetually in dispute, but to facilitate human problem-solving.’ Epistemologically, it means that any way of thinking or conducting

research that leads to a practical solution is useful, and pragmatism does not claim that one method is better than another (Scott, 2007).

There are arguments against the use of pragmatism as a research paradigm, including suggestions that it lacks universal intellectual appeal and that its all-inclusive approach is too cautious to be of any use. Others take issue with its ‘flexible approach to “truth” and “ethics”’ (Mintz, 2004).

Proponents of pragmatism support its stress on concrete facts, flexibility, experimentation, and practical, workable solutions to real-world problems (Mintz, 2004). Creswell’s sixth assumption of pragmatism—namely, ‘pragmatists agree that research always occurs in social, historical, political, and other contexts’—is particularly relevant and one of the key reasons that this philosophical worldview was adopted (Creswell, 2003). That assumption suggests that research is influenced by the cultural, historical, and political context in which it occurs and that consequently, there is a cultural, historical, and political dependency on each person’s reality. This point was considered particularly relevant given the diverse backgrounds of the stakeholders involved in this research, and it is important to keep in mind when considering the nature and context of the issues that were raised. Appreciating these variations in reality allows one to better understand the reasons for divergences in opinions.

4.2.3 Which paradigm: ‘naturalism’ or ‘progressivism’?

Holliday (2007) distinguished two major paradigms of qualitative research, ‘naturalism’ and ‘progressivism’. He considered that ‘qualitative research has grown from both the intermingling and divisions, resulting in a complex family of interrelated methods and approaches’. In naturalism, the researcher becomes fully involved in the research setting, either overtly or covertly, for a lengthy period of time. Naturalists believe that substantiation is gained through establishing the ‘real’ nature of the social world through sufficient weight of description by ‘being there’ using an unobtrusive approach. On the other hand, progressivists argue that there is no ‘there’ until it is constructed (Gubrium & Holstein, 1997). While there is much debate between naturalists and progressivists over whether a definitive picture of the ‘truth’ or the ‘real’ nature of the social world actually exists, Holliday (2007) has stated that:

‘The progressive break from naturalism does enable a far greater variety in procedure and scope, in which data is presented more creatively, with more openness about who the researcher is and how she spins validity through argument.’

A review of the literature suggested that this study was located within the progressive paradigm. Central to the progressive paradigm is the desire to actively engage with stakeholders to obtain their views on key areas; thus, telephone interviews seemed an appropriate data collection method to consider.

4.3 Multimethod research

The terms ‘mixed method’ and ‘multimethod’ are sometimes used interchangeably within the literature. According to Morse (2003), a mixed methods design is the adding of various qualitative and quantitative strategies within a single research project. Morse argues ‘these strategies are supplemental to the major method and serve to provide clues that are followed up within the core method.’ This approach requires the conduct of two or more research methods—each conducted separately and complete in itself—in one project, with the results later triangulated to form a complete whole (Tashakori & Teddlie, 2002; Morse, 2003).

Johnson, Onwuegbuzie and Turner (2007) described multimethod research as the adoption of different approaches or methods to be used in parallel or in sequence, but not in an integrated manner until inferences are made. The authors also clarified that the mixing of methods need not be restricted to quantitative and qualitative, but may include different means of data collection within the same research paradigm, such as qualitative participant observation with qualitative in-depth interviews (Johnson et al., 2007).

4.3.1 Strengths of multimethod research

Combining both quantitative and qualitative components can assist researchers in corroborating findings, as well as in generating fuller, more robust data. That approach also allows for results obtained from one method to augment insights attained with a

complementary method. A qualitative-quantitative pairing can provide greater insight into the perspectives of individuals, thereby yielding a more comprehensive understanding of the topic being investigated (Curry, Nembhard, & Bradley 2009).

One of the greatest advantages of multimethod research over a single-method study, according to Creswell (2003), is that using multiple methods allows the researcher to ask exploratory and confirmatory questions in the same study. Using more than one method is a strategy for overcoming each method's weaknesses and limitations (Brewer & Hunter, 1989). Multimethod research also allows researchers to triangulate their data. That is, it facilitates the validation of data and results by combining a range of data sources or methods. In that way, 'fresh or paradoxical factors' can emerge, which could stimulate further work and ultimately widen the scope of the study (Tashakkori & Teddlie, 1998). In summary, collecting different types of data through diverse methods from a range of sources provides a wider coverage, which may result in a fuller picture of the topic under study than would have otherwise been achieved (Bonoma, 1985).

Stange, Crabtree and Miller (2006) also suggested that using multiple methods allows researchers to follow emerging questions, rather than limiting their inquiry to those questions that are amenable to a particular method. This capability brings together numbers, narratives, descriptions, hypothesis testing, hypothesis generation, and an understanding of meaning and context to provide robust insight into the research topic being studied (Stange et al., 2006).

4.3.2 Weaknesses of multimethod research

Not all researchers feel that a multimethod strategy is an appropriate way to carry out research. Certain methodological purists have argued that researchers should always work within either a qualitative or quantitative paradigm (Johnson & Onwuegbuzie, 2004). One such assertion suggests that quantitative and qualitative methods have traditionally been associated with different epistemologies. Qualitative methods align themselves with an interpretative epistemology and quantitative methods with positivist approaches. Meeto and Temple (2003) acknowledged, however, that social scientists are increasingly recognising that there are problems in attempting to fix an epistemology to a particular quantitative or qualitative method, particularly when researchers are attempting to use both

types of approaches within a single study. Different methods use different processes to produce findings, and the distinctions between these processes are valuable in contextualising data generated in disparate ways.

Other weaknesses of multimethod research described within the literature include considerations around it taking longer to execute than studies employing a single methodological approach. Additionally, multimethod studies can be more expensive and require that the researcher learn about multiple methods and approaches and understand how to mix them appropriately. Combining qualitative and quantitative data can also present other problems regarding, for example, how to qualitatively analyse quantitative data and how to interpret conflicting results (Johnson & Onwuegbuzie, 2004). Driscoll, Appiah-Yeboah and Salib (2007) criticised the use of multiple methods due to the potential loss of depth and flexibility that occurs when qualitative data are quantified and argued that qualitative data are multidimensional and provide insight into a host of interrelated conceptual themes.

4.3.3 Triangulation/crystallisation

Using a multimethod approach allows for triangulation, which some researchers associate with qualitative data rigour. Triangulation involves the use of different sources of information or methods of data collection to enhance the credibility and validity of research (Koc & Boz, 2014). Methodological triangulation implies the use of at least two methods, usually qualitative and quantitative ones, to address the same research problem (Morse, 1991). This study used qualitative and quantitative tools for data collection in a design referred to as a ‘quantitative follow-up’. In that approach, a smaller quantitative study helps evaluate and interpret results from a principally qualitative analysis. One of the disadvantages of this approach is that such a study design promotes the perception that qualitative results must be treated as tentative until they have been validated by quantitative results (Morgan, 1998).

Not all researchers believe that triangulation necessarily confers academic rigour. Richardson (1991) suggested that it is more helpful to think of the captured data as representing complementary, rather than competing, perspectives and used the term ‘crystallisation’ as an alternative to triangulation. As discussed by Mays and Pope (2000),

critics have argued against triangulation as a tool for having one method validate the results of another, as adopting that perspective suggests that a single method in isolation does not adequately address a research question. For the purposes of this research, however, the different sources of data were used to provide comprehensiveness, which Mays and Pope (2000) suggested is a more realistic goal.

4.4 Qualitative study

4.4.1 Why include a qualitative perspective?

Reviewing the literature revealed that gaps existed in relation to stakeholder perceptions of the conduct of industry-sponsored clinical trials in developing regions. The overall orientation of qualitative research is quite different from that of quantitative research, and the decision to use a qualitative approach was partially based on the fact that the literature revealed these gaps in knowledge of perceptions. Indeed, the exploratory nature of the inquiry predisposed the study to employ the inductive techniques used in qualitative research, rather than the deductive techniques of quantitative research. In deductive research, the researcher begins with theory before embarking on empirical research and analysis. Using deductive reasoning, the researcher derives a testable proposition or hypothesis from that theory in advance of the research process (Mason, 2002). A mathematical approach ‘seeks to transcend the particular by higher and higher reaching for abstraction, and in the end disclaim in principle any explanatory values at all where the particular is concerned’ (Bruner, 1986). Similarly, Seale (1999) described deductive reasoning as follows:

‘Propositions, logically deduced from theoretical statements, are operationalised in research projects, tested against the objectively observed, factual nature of the real world, thus determining the truth or falsity of propositions, which in turn influences the content of theories.’

In contrast, in inductive research the process of scientific discovery begins with data generation from which theory is then extrapolated. Mason (2002) considered inductive reasoning as developing ‘theoretical propositions or explanations out of the data, in a process which is commonly seen as moving from the particular to the general’. As such, inductive modes of thinking are particularly useful when the aim is to describe, explore,

understand, or explain a particular phenomenon. They may consider the ‘what’, ‘why’, and ‘how’ of the phenomenon, albeit not in terms of ‘how many’ or ‘how frequently’ (Gantley, 1999). Maykut and Morehouse (1994) asserted:

‘The goal of qualitative research is to discover patterns which emerge after close observation, careful documentation, and thoughtful analysis of the research topic. What can be discovered by qualitative research are not sweeping generalisations but contextual findings. This process of discovery is basic to the philosophic underpinning of the qualitative approach.’

According to Holliday (2007), the choice of a research approach should grow naturally from the research questions. Qualitative studies set up research opportunities designed to lead the researcher into unforeseen areas of discovery and are useful in exploring behaviour within specific social settings rather than in broad populations. To this end, the rationale underpinning this study’s choice of qualitative methods was that they offered a more suitable approach for exploring the subjective aspects of industry-sponsored research in Sub-Saharan Africa; such elements would not have been readily accessible via quantitative methods.

4.4.2 Telephone interviews

Kvale (1983) defined the qualitative research interview as ‘an interview whose purpose is to gather descriptions of the life-world of the interviewee with respect to interpretation of the meaning of the described phenomena’. Telephone interviews were selected as the most appropriate way to conduct the qualitative part of this research, because they allowed access to interviewees in different geographical areas at a time suited to them and also provided a means of circumventing the logistical constraints associated with conducting face-to-face interviews with stakeholders in various geographical locations. Although telephone interviews offer a number of benefits over asynchronous methods of interviewing, they are not without shortcomings. While the interviewer can engage in a dialogue with people who are not easy to access, one of the disadvantages of the telephone interview is the reduction of social cues. The interviewer does not see the interviewee, and so body language and other non-verbal signals cannot be used as a source of extra information. However, other social cues, as such as the speaker’s voice and intonation, are

still available, and enough such cues remain to allow for the utilisation of telephone interviews without problem (Opdenakker, 2006).

Kassianos (2014) summarised additional issues with telephone interviews in qualitative research by highlighting the limited rapport with interviewees (which reduces the potential richness of data) and the fact that they may exclude participants who cannot access a telephone. However, it is also worth noting that qualitative telephone interviews allow respondents to be more relaxed than they would be at an in-person meeting, and therefore potentially more willing to talk freely and to disclose sensitive information. To that end, data from telephone interviews are considered to be ‘rich, vivid, detailed, and of high quality’ (Novick, 2008). In addition to telephone interviews, more recent technological advancements such as Skype allow for participants to be either telephone interviewed or interviewed via video chat which confers further benefits over traditional telephone interviews alone. In summarising the benefits of Skype, Oates (2014) concluded that Skype allows researchers the opportunity to reach participants who are geographically spread in a way that is safe and cheap whilst still allowing for rapport and collaboration to occur.

4.4.3 Qualitative data rigour

May and Pope (1995) noted that qualitative data is often criticised for being open to research bias and lacking in terms of scientific rigour, reproducibility, and generalisability. To this end, Shenton (2004) argued that qualitative data rigour is needed to ‘demonstrate that a true picture of the phenomenon under scrutiny is being presented.’ Shenton listed four criteria that a researcher should satisfy to demonstrate academic rigour: (1) credibility, (2) transferability, (3) repeatability, and (4) confirmability.

Qualitative content analysis and its systematic approach to data analysis were employed in this study, as were purposive sampling, multiple coding, and triangulation. While qualitative research is not given to mathematical abstractions, it is nonetheless systematic in its approach to data collection and analysis.

4.4.3.1 Multiple coding

Multiple coding is the process through which more than one coder is used to code a dataset to increase validity (Olson, McAllister, Grinnell, Walters, & Appun 2016). Barbour (2001) described it as a mechanism for ensuring that the qualitative equivalent of inter-rater variability does not bias the outcome of qualitative research. However, Barbour cautioned against the multiple coding of entire datasets (on the grounds of economy in terms of both cost and effort) in her paper discussing the use of procedural checklists for ensuring rigour in qualitative research. Barbour did, however, advocate having another person review segments of data or emergent coding frameworks. Barry, Britten, Barber, Bradley and Stevenson (1999) described this secondary review of coding as a core activity of academic supervision sessions.

4.4.3.2 Purposive sampling

While statistical ‘representativeness’ is not a key objective of qualitative research, sample selection is nevertheless one of its important strategic elements. Qualitative samples aim to encompass diversity and to compose a structured, rather than random, sample, guided by the focus of the research questions (Barbour & Kitzinger, 1999). Similarly, Mason (2007) considered that the aim of the sampling strategy is to produce a relevant range of contexts or phenomena in relation to the wider universe, but not to represent it directly. This shift away from an emphasis on ‘representativeness’ and on the need to be able to generalise findings to larger populations has meant a move from systematic random sampling towards more theoretically motivated sampling. To capture as much of the full spectrum of stakeholder views as possible, this study used a purposive sampling strategy that incorporated the philosophical principles underlying grounded theory’s approach to theoretical sampling.

Purposive sampling has been described by Teddlie and Yu (2007) as a method used in qualitative studies wherein units (e.g., individuals, groups of individuals, or institutions) are selected based on their potential ability to answer a research study’s questions. Purposive sampling allows for particular persons to be deliberately selected for the important information that they can provide that could not be obtained as effectively from other sources (Maxwell, 1997). This contrasts with convenience sampling, which draws on

sample populations that are both easily accessible and willing to participate in a study (Teddlie & Yu, 2007). Purposive sampling is one mechanism through which researchers can demonstrate rigour, as it ensures that multiple views on the same topic of inquiry are captured and assists in providing a full understanding of all possible perspectives on the topic being researched (Belle & Stewart, 2004).

4.4.3.3 Deciding on qualitative content analysis

To identify the best approach, various texts on qualitative methods were read, and that review indicated a qualitative content analysis approach drawing on the principles of grounded theory, such as the constant comparative method, would be appropriate. Qualitative content analysis is a research technique that is widely used by qualitative researchers (Hsieh & Shannon, 2005). Krippendorff (2004) defined content analysis as ‘a research technique for making replicable and valid inferences from texts (or other meaningful matter) to the contexts of their use’. Downe-Wambolt (1992) described the process as ‘a research method that provides a systematic and objective means to make valid inferences from verbal, visual, or written data in order to describe and quantify specific phenomena’. While content analysis can be used for all types of written texts, Bengtsson (2016) suggested that researchers be mindful when choosing the data collection method, as it can affect the depth of the subsequent analysis. He contended that open-ended, written questions, for example, ‘cannot provide the same depth that an interview can provide, as the researcher has the opportunity to deepen the discussion with the informants.’

As a novice researcher, I deemed grounded theory useful to consider as a research method, given that it involves the use of inductive logic or evidential support to generate new theories by having the investigator collect and analyse data and then generate a hypothesis (Strauss & Corbin, 1990). This systematic approach to data analysis and subsequent theory generation is considered to confer rigour, but my research was less concerned with theory development and more focused on answering key research questions using inductive coding methods. As such, I needed to consider other approaches.

The research questions that this study aimed to address were as follows:

- How can clinical trials provide a beneficial opportunity to address rising levels of chronic disease in the Sub-Saharan region of Africa without being exploitative?
- How is it possible for the relationship between Western pharmaceutical companies and developing countries in Sub-Saharan regions to be mutually beneficial?
- Do any potential ethical concerns outweigh any potential benefit that these countries stand to gain, and in what way?
- How do pharmaceutical companies incorporate ethical and social responsibilities with respect to their engagement with developing nations?

Research questions of this kind require a qualitative approach to inquiry (Ormston et al., 2014), and qualitative content analysis aims to systematically describe written or oral data in the way that the researcher questions specify (Moretti et al., 2011; Schreier, 2012; Cho & Lee, 2014). It uses inductive thematic analysis to code and identify the content of transcripts, and coding can be strengthened by using constant comparative analysis (CCA). CCA is a method in which the researcher cross-compares new codes that emerge across all the transcripts to ensure that each code has all pertinent data. Similarly coded data are assigned to clusters or categories according to the obvious fit. In this way, the researcher is forced to continuously compare data across all transcripts, which allows for the generation of themes that are richly detailed. Moreover, CCA can encourage researchers to move away from describing issues in specifics to thinking more abstractly about the data that they have collected (Lawrence & Tar, 2013; Fram, 2013).

4.5 Quantitative study

4.5.1 Questionnaires

There are a number of benefits associated with administering questionnaires as a research method. Not only can large amounts of information be collected from a large number of people with logistical ease and over a short period of time, but also online questionnaires allow access to individuals who may not otherwise be so readily accessible. Online questionnaires can also be relatively quick to create and disseminate and can be much more cost-effective than their paper-based equivalents (Wright, 2005).

Wright (2005) also argued that questionnaires can be analysed more objectively than other data collection methods. However, Bridger (2014) contended that the act of making sense of quantitative data (i.e., analysing what the numbers in the scale mean) is an interpretative process that requires a form of subjective reasoning. Subjectivity in questionnaires is also important to consider. Specifically, it can be difficult to know how each person has interpreted a question, as individual respondents may understand each question in a unique manner.

There are also further disadvantages to this type of data collection strategy. With questionnaires, there is often no way to tell if a respondent has put much thought into a question or if he or she has provided an honest response. While the latter may also be said for other types of data collection, such as interviews, in those cases, other social cues can arguably help the researcher determine whether a respondent is not being honest or has failed to think through a response. Another argument against the use of quantitative questionnaires is that in developing the survey, the researcher determines what is important (Barbour, 1999). That consideration was one of the main reasons that this study adopted an exploratory (i.e., sequential) multimethod approach as using the thematic outputs from the interviews was intended to reduce the researcher bias in developing the questionnaire.

Collecting quantitative data while simultaneously allowing for respondents to add qualitative information allowed for further exploration of the extent to which the participants felt particular topics were relevant. It also gave those who were not involved in the interviews the opportunity to raise new topics. One limitation of conducting the study in this way, however, is that although the qualitative aspects of the questionnaire responses are captured and analysed, there was no way of further quantitatively analysing any new issues raised. The impact of this limitation is discussed in further detail in Chapter 7.

4.5.1.1 Likert scale

The Likert scale is a psychometric response scale in which respondents are asked to indicate their level of agreement with a given statement. The responses are used to obtain preferences or the degree of accord with a set of statements (Bertram, 2007).

The main advantage of using Likert scaling is that such measurements have demonstrated a high level of reliability and are generally easy for respondents to understand (Li, 2013). The ease with which Likert scale questions are understood may lead to a greater level of response than, for instance, a questionnaire mainly comprised of open-ended questions.

One of the biggest disadvantages of using the Likert scale is the issue of ordinal versus interval scaling. There are two schools of thought amongst researchers (Joshi, Kale, Chandel, & Pal, 2015) about whether Likert scales provide interval data, as suggested by Grover and Vriens (2006), or ordinal data, as argued by Fisher and Marshall (2009). These debates are relevant, as some researchers, such as Cohen, Manion and Morrison (2000), have argued that if the Likert scale is considered interval, then it is incorrect to assume that the intensity of feeling between options (e.g., ‘strongly disagree’ and ‘disagree’) is equivalent to the intensity of feeling between other consecutive categories, which can make interpretation of the results difficult.

Another weakness pointed out by Li (2013) is the closed format of questions, wherein respondents are forced to make a choice from among given options that may not match their exact opinions. Respondents have to either select an answer from an insufficient range of responses or select an ‘acceptable’ answer in the closed format, thereby contributing to the previously mentioned challenge of interpretation. The drawbacks of employing an odd-numbered scale relate to the middle or neutral response, which may seem to be an ‘easy way out’. The presence of that option may mean that respondents do not consider the merit of each response. It can also be difficult to know what meaning participants assign to the word ‘neutral’. To circumvent this issue, an open-ended text box was provided with every question, allowing the respondents to clarify or expand on their response or to raise other issues, thereby adding a richness to the quantitative data collected.

CHAPTER 5: METHODS

5.1 Introduction

This chapter provides a detailed description of the design and conduct of the study. These explanations are included to illustrate how subjectivity was managed and scientific rigour maintained. Consistent with this aim is the final section, which describes the problems encountered during the research process, reflects on my potential impact on the process in my role as the facilitator, and details how the analysis was executed.

5.2 Overview

The overall aim of the study was to understand the perceptions of various stakeholders towards the conduct of pharmaceutical industry-sponsored clinical trials in Sub-Saharan Africa.

As is further detailed below, the study had two parts: interviews and a questionnaire. A number of factors led to the decision to conduct a multimethod study. Little was known about the topic, and therefore, interviews seemed to be an appropriate choice to gain insight into stakeholders' perspectives and the issues of importance to them. Attempting to realise that goal from the literature alone would have limited the potential area of interest. It was, however, recognised that accessing suitable interviewees would be difficult due to logistical (geographic) constraints. Due to the anticipated challenges of conducting a high number of interviews, it was felt that the use of a complementary method would be appropriate. Had it been possible to conduct a larger number of face-to-face interviews with a balanced number of stakeholders by travelling to Ghana and Nigeria, a fully qualitative study may have provided sufficiently robust data to preclude the need for the complementary questionnaire. Nevertheless, semi-structured interviews followed by a quantitative questionnaire proved effective in identifying and exploring the most relevant topics. The use of the questionnaire as a complementary method of data collection was considered an appropriate means of adequately corroborating the interview findings and ensuring that a full and robust dataset was collected.

5.2.1 Interviews

Qualitative methods are particularly useful when working in underexplored research areas, such as stakeholder perceptions of industry-sponsored clinical trials, particularly in developing countries. Such an approach also has particular utility when the research is not seeking to test hypotheses but is instead aiming to capture the complexity of a phenomenon (Bryman, 2016). The flexibility of a qualitative methods approach provides a means of capturing data on more abstract concepts, such as ethics, fairness, and the balancing of these two concepts with commercial interests.

The aim of the interviews was to understand the opinions and experiences of various stakeholders on the conduct of industry-sponsored clinical research in Sub-Saharan Africa in chronic diseases. Open and exploratory approaches enable participants to articulate their experiences using their own vocabulary and allow the researcher to observe the nuances of language use in ways that other, more structured data collection techniques may preclude (Bryman, 2016). The greater sense of control that exploratory approaches provide to participants may be particularly appropriate when research is of a sensitive nature (e.g., when it explores issues of morality, ethics, and fairness). Semi-structured approaches enable the both participants and researcher to steer the focus and direction of the research and findings (Bryman, 2016). By encouraging deep reflection and meaning-making, qualitative methods provide an opportunity to instil in participants a sense of expertise and experience (Visser, Stappers, Van der Lugt, & Sanders, 2005).

5.2.1.1 Interview schedule development

The interview schedule was developed using information obtained from the literature reviews, conceptual framework, and personal experience working in clinical research within the pharmaceutical industry. An effort was made to not only include the issues most commonly identified from the literature but also provide space for new topics to emerge, as there was an appreciation that various individuals and groups of stakeholders may have particular areas of interest or relevance. Due to the study adopting a methodology based on a pragmatic worldview, there was a recognition that social, political, and cultural factors might be relevant for stakeholders and that a semi-structured approach would allow for such contexts to be adequately captured. A decision was made that questions on ethics alone might not solicit full and honest responses (due to their potentially sensitive nature),

and so the ethics-related questions were embedded in a wider interview touching on multiple topics, not just ethics. During the development of the interview schedule, a decision had to be made as to whether to discuss a smaller number of issues in more detail or a wider breadth of issues in less detail. The choice was made to cover fewer issues during the interviews, as a wider breadth of topics could be more easily addressed with the questionnaire employed in the second part of the study.

5.2.1.2 *Piloting the interview transcript*

Two pilot interviews were conducted with colleagues to ensure that the questions themselves, their flow, and the overall approach were appropriate. The following minor revisions were made to the interview schedule following the piloting stage:

- Changes to the verbiage used in certain questions sought to enhance clarity and consistency. For example, there were instances where the terms ‘clinical trial’, ‘clinical study’, and ‘clinical research’ were used in reference to a single concept.
- The order of questions was revised to facilitate a more natural flow between themes. For example, questions were grouped by topic.
- Questions that included wording that was considered leading were revised to be more neutral.
- Questions that were considered duplicative were either consolidated or removed to reduce the overall length of the schedule. For example;

Before feedback:

“In your opinion does the pharmaceutical industry have any ethical responsibility to involve poorer countries in clinical research?”

“Do pharmaceutical companies have a moral obligation to include patients from developing countries in clinical trials of new medicines?”

After feedback:

“In your opinion does the pharmaceutical industry have any ethical responsibility to involve poorer countries in clinical research”

~~“Do pharmaceutical companies have a moral obligation to include patients from developing countries in clinical trials of new medicines?”~~

5.2.2 Questionnaire

The aim of the questionnaire was to gather data and commentary from a larger number of stakeholders in response to the specific questions or issues raised in the interviews. Despite the interviews' focus on chronic diseases, the questionnaire did not specifically emphasise that topic. Rather, it addressed issues associated with the conduct of all industry-sponsored clinical trials in Sub-Saharan Africa.

5.2.2.1 Questionnaire development

The questionnaire was created based on the themes identified in the conceptual framework, with a particular focus on those that arose from the qualitative data analysis. Those themes and issues that arose during the interviews and that were considered important (because of either the topic itself or the frequency with which it was mentioned) were covered.

The questionnaire can be found in Appendix 7. It consisted of four parts:

- Four mandatory questions asked for basic information about the participant. These questions were denoted with an asterisk (*).
- Eighteen Likert scale statements measured the respondents' level of agreement. These statements also included free-text boxes to allow the respondents to add further information.
- One question asked respondents to rank items from a number of options provided.
- Two open-ended questions.

Three online questionnaire software options (Zoomerang, SurveyGizmo, and Survey Monkey) were reviewed before selecting Survey Monkey, which was chosen for the ease with which numerous question types could be formatted and its clear dashboard, which reported metrics in a way that allowed for simplified analysis of the quantitative data. The questionnaire, once live, was hosted at the following URL:

<http://freeonlinesurveys.com/app/rendersurvey.asp?sid=2nso98va928ya90494176&refer=www%2Efacebook%2Ecom>.

5.2.2.1.1 Use of Likert scale questions

The questionnaire mainly comprised Likert scale questions. A number of other scales, such as numerical and adjectival scales, were also considered. However, the themes of interest had already been identified during the interviews, and the goal of ascertaining the levels of agreement with those emergent themes lent itself to the Likert scale. Some Likert-type scales were also considered during the development of the questionnaire wherein frequencies (e.g., never, sometimes, or very often) or importance (e.g., not important, somewhat important, or very important) would have been used, however the purpose of the questionnaire was to understand respondents' agreement or disagreement with the themes which had already come out of the earlier interviews and therefore these were not considered appropriate.

The decision to use an odd-numbered five-point Likert scale was made because of the potentially sensitive topics covered in the questions. For that reason, the respondents were offered an 'out', or an opportunity to avoid making a weighted comment by selecting a neutral response. To facilitate the interpretation of the neutral responses, each question also gave respondents the opportunity to leave a comment to explain the reason for their choice.

5.2.2.1.2 Use of closed and open-ended questions

The questionnaire also used one closed question and one open-ended question to collect further information on some of the issues that were being raised that could not be explored through the use of Likert or Likert-type questions. The closed-ended question asked the participants to rank issues in order of importance, and the open-ended one asked them to

describe additional issues not covered in the questionnaire. Neither topic would have been suitable for Likert-type questions.

5.2.2.2 *Piloting the questionnaire*

A first draft of the paper-based questionnaire was reviewed by my supervisors and piloted with two colleagues. The pilot participants were asked to consider its wording, order, clarity, and structure. Additionally, the results were assessed to ensure there was no strong endorsement of a single response to a particular question (including the neutral response) and no responses to a particular question suggesting that it may have been sensitive or poorly worded. Additionally, discussions were held with the pilot participants to discuss the nature of the questions and ensure that there were no items that were effectively duplicates.

Following piloting, a number of changes were made:

- The interspersing of negatively and positively worded statements was introduced as comments received suggested that the use of continuously negatively or positively worded questions meant there was a chance that respondents were less likely to read the question in a great amount of detail and therefore were likely to be less considered in their responses.
- Clarifying language was added to questions that were vague or difficult to understand. For example, one of the original questions was separated into two questions, as follows:

Before piloting:

‘Investigators in the Sub-Saharan region of Africa are more likely than those in the West to exploit patients in clinical trials or falsify data for financial gain.’

After piloting:

‘Investigators (clinicians) in Sub-Saharan Africa are more likely than those in the West to exploit patients in clinical trials.’

‘Investigators in Sub-Saharan Africa are more likely than those in the West to falsify data for financial gain.’

A pilot participant pointed out that the original question would better serve its purpose if it were instead split into two questions.

- Additional feedback highlighted an inherent bias in the wording of certain questions, and so alternative phrasings were suggested for several questions to prevent any researcher bias or reflection of my own personal opinions. Such subjective language could have potentially influenced the outcome of the research to a certain extent. For example, the following change was made on the basis of feedback suggesting the use of less confrontational wording:

Before piloting

‘Any efforts by pharmaceutical companies in Sub-Saharan Africa should focus on infectious diseases as opposed to chronic diseases.’

After piloting

‘Any efforts by pharmaceutical companies in Sub-Saharan Africa should focus on infectious diseases ~~to~~ rather than on chronic diseases.’

- Questions that were considered duplicative were removed. For example, the second question below was considered replicative and removed, as illustrated:

Before piloting

‘Pharmaceutical companies in the West do not always conform to GCP.’

‘Pharmaceutical companies in the West are behaviourally poor.’

After piloting

‘Pharmaceutical companies in the West do not always conform to GCP.’

- Feedback related to grammatical and typographical errors was incorporated, and suggestions to be consistent with wording (e.g., ‘pharma’ versus ‘pharmaceutical’) were also addressed.

Following these revisions, the questionnaire was built online using the Survey Monkey software. Once the questionnaire was live, it was tested on the two colleagues who had been involved in the initial pilot to gather feedback on their experience with the questionnaire software and the presentation of the questions. No further changes were made to the questionnaire, although challenges being able to read all of the text entered into the comments field were noted (as the comments box only displayed a limited number of characters on screen). As there was no clear remedy for this issue, and as the two colleagues who piloted the questionnaire felt that it was a minor point, no further action was taken.

A copy of the plain language statement that accompanied the link to the questionnaire is included in Appendix 8.

5.3 Ethical approval

A protocol including ICFs and interview prompts (see Appendix 6) was submitted to the Medicine, Veterinary, and Life Sciences (MVLS) College Ethics Committee before any potential interviewees were approached. The submission outlined the plans for a two-part study and indicated that the questionnaire, which was to be developed from the interview responses, would be submitted after the first part of the study was complete.

An additional application to authorise the use of Skype was later submitted to the MVLS Ethics Committee, and approval was granted before any Skype interviews were conducted.

Once the interviews had been completed and analysed, a final paper version of the questionnaire (see Appendix 7) was sent to the MVLS College Ethics Committee, alongside the plain language statement (Appendix 8). Ethics approval (Appendix 9) was received before the online version of the questionnaire was created.

5.4 Population and sample

To explore as wide a range of views as possible, a variety of stakeholder groups was considered. The goal in doing so was to produce the most unbiased and robust possible

summary of opinions from a diversity of stakeholders with a vested interest in clinical trials, drug development, and healthcare in the region. The same population was targeted for both the interviews and the questionnaire.

The four stakeholder groups that were initially identified were:

1. Policymakers/influencers, including government representatives, members of international health organisations, and charities working within the selected countries.
2. Local HCPs who had responsibility for patient care.
3. Where they existed, patient advocacy groups (which may have included patients and staff). Any patients interviewed or surveyed by questionnaire would not have been asked any questions relating to their own situation.
4. Senior pharmaceutical industry representatives (associate director level and above) who were involved in the clinical development of medicinal products and the global placement of clinical trials.

At an early stage, including the general public in the interviews was considered. However, doing so was deemed impractical due to geographical constraints. There were also questions regarding whether the general public would have sufficient knowledge of clinical trials to participate. While it may have been interesting to engage patients based in Sub-Saharan Africa, it was felt that the most practical way to do so would be through patient advocacy groups.

The initial aim was to conduct a total of 24 interviews across stakeholder groups. The breakdown of stakeholders who were targeted for contact and actually reached is summarised in Table 4. These planned numbers were considered sufficient to obtain a clear and balanced view of the issues related to the primary research questions. There was no explicit requirement for interviewees to have had experience in clinical trials.

| Stakeholder Group | Number from Nigeria (planned) | Number from Nigeria (actual) | Number from Ghana (planned) | Number from Ghana (actual) | Total (planned) | Total (actual) |
|---|-------------------------------|------------------------------|-----------------------------|----------------------------|-----------------|-------------------------------------|
| Government representatives | 2 | 0 | 2 | 1 | 4 | 1 |
| Local HCPs | 3 | 3 | 3 | 3 | 6 | 6 |
| Patient advocacy group representatives | 2 | 0 | 2 | 0 | 4 | 0 |
| Pharmaceutical industry representatives | --- | --- | --- | --- | 10 | 9 South Africa (1) Europe (8) |
| Total | | | | | 24 | 16 |

Table 4: Number of planned and actual interviewees who participated in interviews.

5.5 The interviews

5.5.1 Identifying and contacting the interview participants

To ensure rigour in the qualitative data, a purposive sampling strategy (as described in the previous chapter) was used. Relevant stakeholders were identified from a variety of sources, including literature reviews (for HCPs, this task was largely carried out on the basis of academic journal review contributions). Healthcare advocacy and government websites were employed with the goal of identifying potential government respondents. Two of the stakeholders identified from the pharmaceutical group were identified through existing connections from previous professional experience, as well as through snowballing techniques. Snowballing, also referred to as chain sampling, is a method of identifying potential participants through ‘asking participants for recommendations of acquaintances who may qualify for participation’ (Robinson, 2014).

Potential interviewees were contacted by email (see Appendix 10 for an example). These emails were tailored specifically for each stakeholder group and contained a brief introduction of myself and the study. Attached to each email was a copy of the research participant letter of invitation (see Appendix 11 and Appendix 12), which outlined the

study in more detail and explained what would be required of respondents in the event they chose to participate. The study protocol was requested on two occasions, and it was sent to potential interviewees who requested it prior to their interview. The method of interview for each stakeholder is described in the results chapter, as well as in Appendix 16. The responses from the candidates were logged and tracked on an Excel spreadsheet.

It was recognised early in the process of trying to identify respondents that there were few readily identifiable people who fell into the category of charity/advocacy group representatives based in the Sub-Saharan region of Africa. Three attempts were made to contact members falling into this stakeholder group by way of emails to generic mailboxes; however, no return contact was received. It was subsequently decided to make no further effort to contact members from this stakeholder group and to focus on the other identified categories.

5.5.2 Interview conduct

One of the biggest challenges identified with the interview method was encouraging stakeholders based in Sub-Saharan Africa to agree to a remote interview. As many participants were HCPs working in resource-constrained environments with numerous commitments, they often had only a limited amount of free time to participate in an interview. As a result, arranging mutually convenient times for the interviews proved to be difficult in almost every instance. Most interviews conducted with the HCP stakeholder group were held in the early morning or late evening, when the interviewee was at home. On two occasions, the respondents asked for the interview questions to be emailed to them so that they could respond by email. That request was not granted, and attempts were instead made to engage these respondents during the second part of the study.

Interviewees who agreed to participate in the study were contacted at a prearranged time that suited them. Where it was practical to do so, in-person interviews were conducted with the pharmaceutical respondents (4 of 16 interviews). Two of the 16 interviews were conducted via Skype. Holding the interviews via Skype when possible helped to overcome some of the weaknesses of telephone interviews, such as the lack of non-verbal cues (Sullivan, 2012). All other interviews (10 of 16 interviews) were conducted by telephone.

All interviews were audio-recorded using a Dictaphone, with an iPhone employed on the three occasions where technical difficulties were encountered with the Dictaphone.

5.5.3 Informed consent

At the start of the interview, I explained the aim of the research and gave the participants the opportunity to ask any questions. Each interviewee was informed that his or her responses would be recorded and transcribed and was asked to provide informed consent before recording began. Those who were interviewed face to face signed a hard copy of the ICF, which I then retained. Those who were interviewed via Skype or telephone provided verbal consent before the recording of the interview session began. All interviewees, with the exception of one, agreed to participate once they learned the interview would be recorded. The single interviewee who declined to have his responses recorded was not interviewed. Despite the spread in the geographical locations of the various stakeholders, all interviews were conducted in English and lasted between 25 and 35 minutes.

5.5.4 Anonymity and confidentiality

Reasonable steps were taken to ensure the anonymity of the participating interviewees. The respondents were given unique codes to replace their names, and these codes only identified the stakeholder group to which they belonged. The ICFs (where physical copies were collected) and the details listing the unique identifier of each respondent were kept separately and securely. The information gathered from each respondent was confidential and only accessible to myself and my supervisors. Some of the responses were potentially commercially sensitive, and therefore, those responses were not included in the final thesis.

5.5.5 Transcription

The audio-recordings for each of the semi-structured stakeholder interviews were assigned a unique identifier. I transcribed them verbatim following each interview.

5.5.6 Qualitative data coding and analysis

To ensure qualitative data rigour, multiple coding was used (see Chapter 4). During the analysis, the codes/categories generated from the transcript review, as well as the more

detailed codes derived and the corresponding emergent, overarching theme categories, were reviewed by my two supervisors to ensure agreement and consistency in coding across transcripts. The more detailed categories and themes were reviewed to confirm that they were reflective of the codes comprising them. The codes, categories, and overarching theme types, as well as the more detailed themes that later emerged, are presented in Appendix 14 and Appendix 15.

The data from each of the audio-recordings were examined using thematic analysis. The use of technology to facilitate qualitative data handling dates back to early 1980s, when the first software programmes designed to aid qualitative data analysis were created (Drass, 1980). Over the next decade, the popularity of computer-assisted qualitative data analysis software (CAQDAS) increased, and such programmes have become more advanced in both their scope and function. In this study, the process of coding was aided by the qualitative data analysis computer software package Nvivo.

Each of the transcripts was initially coded sentence by sentence using this software. In some instances, multiple codes were assigned to the same sentence. Although no previously defined coding frame was used (to allow the coding process to maintain a degree of flexibility), the coding of the transcripts was informed by the conceptual framework and the background literature reviews that were performed prior to the interviews. During the coding process, similar codes were grouped together and category themes were identified. The code categories generated from the interviews (depicted in Appendix 14) were exported from Nvivo into an Excel spreadsheet, with each category aligning itself with one of the identified overarching themes (e.g. practical or medical). Once the categories had been sorted into their overarching theme type and grouped, more descriptive and detailed themes were created.

5.6 Qualitative analysis and theme development

Thematic analysis of the interview transcripts and reviewing of the codes generated a total of 10 detailed themes (one of which was labelled ‘other’ to capture those codes that did not fit under a different heading). A summary of the detailed emergent themes is presented in Table 6 with richer descriptions following.

5.6.1 Thematic analysis

Thematic analysis is a method that allows researchers to identify and analyse patterns in qualitative data (Clarke & Braun, 2013). Many texts were consulted regarding various approaches to analysing interview data. Crucially, there appeared to be various ways of carrying out that task, but the literature was in agreement that analysis must be executed in a systematic and rigorous fashion reflecting the breadth of the data. Braun and Clarke (2006) described six phases of thematic analysis, which the following sub-sections use to outline the process employed in this study.

5.6.1.1 Familiarisation with data

Braun and Clarke (2006) suggested that the first phase of thematic analysis should involve the researcher familiarising himself or herself with the data to fully grasp the depth and breadth of the content. This aim was achieved through the transcription of the interviews, as described earlier in this chapter. The process of transcribing each interview facilitated familiarity with the topics and issues raised therein and helped to identify recurring themes and trends on an ongoing basis. Lapadat and Lindsay (1999) suggested that interview transcription may also help develop the interpretive skills required during the subsequent, more detailed analysis.

Although there are varying conventions of transcription required for other specific forms of analysis such as conversation or discourse analysis, the same level of detail is not required in thematic analysis (Braun & Clarke, 2006) and therefore the interviews were simply transcribed verbatim.

5.6.1.2 Generating the initial codes

The first step in thematically indexing the data to make them more manageable for interpretation was coding the transcripts. After each transcript had been typed, it was read and re-read in full, and significant observations were noted for each transcript. The task of generating the initial codes was performed using Nvivo. Coding is one of the most important processes in the analysis of qualitative data, as it involves the steps necessary for organising and making sense of transcribed data (Basit, 2003). According to Braun and

Clarke (2006), a researcher must make a decision at an early stage as to whether to provide a rich description of the data or a detailed account of one particular aspect of the dataset. Initial coding for this study was performed with the objective of delivering a rich description of all the data received, as further, more detailed descriptions of topics could be investigated using the questionnaire.

Coding was inductive and performed at the semantic level (i.e., identifying codes based on their surface meaning without looking for meaning beyond what was said) to try to condense the data into a summary format (Thomas, 2006). This was done with an appreciation that further interpretation would occur once all of the data had been coded and categorised. In an attempt to avoid hierarchical thinking and to keep the codes free of organisation at this stage, the initial coding of the transcripts used the free-node option in Nvivo. Richards (1999) recommends free nodes are useful when categories are being created from the data early in the coding process. During this early stage in the analytical process, no limits were placed or expectations formulated on the number of free nodes. As such, the initial coding of the transcripts gave rise to 459 free nodes. To make sense of the significant number of codes, the next stage sought to retrieve and bring together all data extracts that were pertinent to a particular free node. This allowed me to read and re-read extracts both out-with context and within the original transcript so that I could collapse the nodes together or develop new nodes. In accordance with the tenets of CCA, once each transcript was checked to ensure that the nodes were being systematically applied across the transcripts, I printed out all of the codes generated and highlighted similar codes with the same colour to help visualise links and similarities. In the early stages, this mapping of the codes helped to connect the codes to themes describing the data. However, as I became more familiar with the data and began to think more conceptually about the data-mapping process, the codes became a useful way of developing ideas and linking them into mind maps, as presented in Appendix 15.

Generating descriptive codes allowed for patterns in the data linked to the literature to be observed before the more analytical codes were developed later. Any emergent titles from the codes within each transcript were noted, following the protocol typically adopted by grounded theorists during inductive coding.

5.6.1.3 *Searching for and reviewing themes*

The third and fourth phases of thematic analysis involve reviewing and categorising the list of codes and searching for themes before naming them. One important decision required within thematic analysis that seems to lack a systematic approach is determining what codes will count as a theme. Braun and Clarke (2006) argued that while it is preferable for there to be multiple instances of a theme across a dataset, repetition should not necessarily qualify data as a theme. The authors suggested that the researcher's judgment is necessary to determine the individual themes. They further argued that the 'keyness' of a theme is not necessarily dependent on quantifiable measures but is instead contingent on whether it captures something important with respect to the overall research question (Braun & Clarke, 2006).

Many of the codes generated could be collapsed into a single code title. Those that were considered significant and that occurred most frequently were clustered together to create superordinate codes and themes. These superordinate codes were organised into a table and are presented in Appendix 14 beside the corresponding themes. Through an iterative process, code clusters were continually compared against each transcript, as is typically done in CCA. Further work was then performed to link the various superordinate codes by mapping them onto a diagram to illustrate both the relationships between codes and themes as well as their interrelatedness. Mind maps depicting these relationships can be found in Appendix 15 (Figure 8 through Figure 16). The mind maps were created using online software MindMup (<https://app.mindmup.com>). The central, more detailed themes are presented in blue boxes, while the superordinate codes are in grey boxes. The red dotted lines illustrate the relationships between codes.

5.6.1.3.1 *Constant comparative analysis*

As described earlier, CCA was adopted to strengthen the research methods. This approach involved coding the data and identifying and naming superordinate codes. These superordinate codes were then revised and refined as various discrete units of text with similar meanings were pooled together. This facilitated analytical interpretation of the data, and that process informed the development of the more detailed themes. As described by Taylor and Bogdan (1984):

‘in the constant comparative method, the researcher simultaneously codes and analyses data in order to develop concepts; by continually comparing specific incidents in the data, the researcher refines these concepts, identifies their properties, explores their relationships to one another, and integrates them into a coherent explanatory model’.

5.6.1.4 *Defining and naming themes*

The fifth step of thematic analysis involves interpreting and refining the identified themes. Braun and Clarke (2006) asserted that in this phase, it is important that the researcher does not simply paraphrase the content of the data but also provides additional information in the form of descriptive terms indicating what is interesting about the data and why those points are noteworthy. Each of the 10 themes identified is aligned with 1 of 5 broad topics—namely, ethics, finance, medical/science, practical/operational, and education/training—each of which was related in some capacity to both Emanuel et al.’s (2004) framework and the conceptual framework developed for this study. A modified version of this study’s conceptual framework is presented in Table 5. It illustrates how the five overarching theme types are related to Emanuel et al.’s (2004) benchmarks that were incorporated into this study’s framework. The detailed themes derived from the analysis and interpretation exercises are described in Table 6.

5.6.1.5 *Producing the report*

The last phase of thematic analysis relates to final analysis and reporting, providing textual examples of the codes and themes generated and linking them to the original research question(s). This step should help convince readers of the validity of the analyses (Braun & Clarke, 2006). The results of this step are presented in the following chapters, which describe the qualitative data collected from the interviews. Further insights are offered in the discussion in Chapter 7.

| Benchmark | Context in Relation to Addressing Study Objectives | Related Overarching Topic |
|---|---|---|
| Specify the beneficiaries of research | <u>Objective 1:</u> Identify the benefits of research in chronic diseases in this region and identify to whom they are of benefit. | Ethical Medical/scientific Finance Practical/operational |
| | <u>Objective 2:</u> Address the ethical implications of the benefit(s) conferred to the individual (participant) and other stakeholders. | Ethical Finance Education Medicine/science |
| Assess the importance of health problems being investigated and prospective value to participants | <u>Objective 1:</u> Understand how the conduct of clinical trials in chronic diseases may or may not aid in the diagnosis and treatment of chronic conditions and how potential participants may also benefit from local and national investments in, for example, healthcare infrastructure. | Medical/scientific Finance Education Practical/operational |
| | <u>Objective 2:</u> Understand the ethical implications of not conducting research in chronic diseases in a population that is experiencing a sharp increase in chronic disease prevalence. | Medical/scientific Ethical |
| Enhance value of research through dissemination of knowledge, product development, long term research partnerships and / or health system improvements | <u>Objective 1:</u> Understand the potential benefits of such research, both therapeutically (for patients) and commercially (for pharmaceutical companies), along with the long-term benefits for the region and for pharmaceutical companies. | Medical/science Finance Practical/operational |
| | <u>Objective 2:</u> Understand the ethical implications of using SSA's large patient pool as a mechanism for attracting investment in a healthcare system that should (arguably) be funded by local governments, rather than by for-profit organisations. | Ethical Finance Practical/operational |
| Prevent supplanting the extant health system infrastructure and services | <u>Objective 2:</u> (a) Understand the ethical considerations associated with corruption and exploitation by local stakeholders. (b) Understand the ethical implications of HCPs conducting research within underfunded healthcare systems. | Ethical Practical/operational Financial |

Table 5: Annotated conceptual framework illustrating the links to the overarching thematic categories identified through qualitative analysis

5.7 The questionnaire

The questionnaire could be accessed by clicking on the previously referenced link. The link was included in the body of the email inviting potential respondents to participate at their earliest convenience. Respondents were unable to submit the questionnaire if the mandatory questions were not completed but had the option to skip any other questions with which they may have felt uncomfortable answering. It is not known if any questionnaires were started but not submitted due to this requirement.

Once all questionnaires had been completed, the data were accessed using the reporting dashboard within Survey Monkey. To facilitate the analysis, the data were subsequently transferred from the online data repository to Excel.

5.7.1 Identifying and contacting questionnaire participants

Potential survey respondents were identified through the same techniques used in identifying the interview respondents and were contacted by email. The email contained a short outline of the study and included a plain language statement approved by the ethics committee containing more detailed background information and a description of what would be required of participants. The email also contained a direct link to the questionnaire.

An example of the email sent to potential questionnaire respondents is included in Appendix 13.

The requirement for those from within the pharmaceutical industry to be senior-level representatives was relaxed for the questionnaire. The reason was that senior staff members (e.g., associate director or equivalent and above) of pharmaceutical companies are more likely to influence the direction of their respective companies and to therefore have a greater influence on the direction of the industry as a whole. The issues that group believed to be most relevant had already been elucidated during the interviews and informed the questionnaire's development. The questionnaire then allowed for the exploration of these issues in greater detail with people from various levels within the pharmaceutical industry. Additionally, relaxing that criterion allowed for a greater number of respondents from various functional areas to be identified and approached, leading to a larger and more varied sample. This variation in the sample was analysed to identify whether there were any easily discernible trends highlighting important differences in opinion between the more senior respondents and the more general pharmaceutical population. By relaxing this criterion, it became possible to ascertain whether pharmaceutical industry decision-makers' opinions and priorities cascaded through staff of decreasing levels of seniority and to identify whether those at lower levels of the industry agreed with those at the top.

Snowballing was also used as a means of identifying additional respondents which impacted the geographical spread of respondents.

5.7.2 Informed consent

Completion of the questionnaire was taken as inferred consent. The suggestion that participation would infer consent was made clear in the letter of invitation that accompanied each email sent to potential respondents.

5.7.3 Anonymity and confidentiality

As with the interview participants, reasonable steps were taken to ensure the anonymity of the participating respondents. Respondents were not prompted to provide any personal information that could identify them. Each respondent was assigned a unique code which only identified the stakeholder group to which he or she belonged. Any commercially sensitive responses or responses that identified a specific organisation have not been

included in the final thesis. This is true except for where governmental, NGO, and charity bodies were referenced in the free-text responses

5.7.4 Data coding and analysis

The outputs from Survey Monkey were transferred to Nvivo, and the thematic analysis was performed on any free-text comments entered in response to the questions. Basic calculations were carried out on the numeric outputs for each question to produce descriptive statistics. The numeric data were also analysed through creating Excel spreadsheets for the purpose of more clearly viewing inter- and intra-respondent group trends.

5.7.4.1 Descriptive statistics

Descriptive statistics were used to describe the quantitative data collected from the questionnaire. The purpose of the questionnaire was to gather complementary data to validate and more fully describe the themes that emerged from the semi-structured interviews. As such, it was designed to corroborate and expand on the qualitative data collected during the semi-structured interviews, rather than to be a fully powered, stand-alone survey. The sample size was small, and respondents skewed towards the pharmaceutical stakeholder group. Analyses of the data are therefore based on descriptive, rather than inferential, statistics.

5.8 Reflexivity

Shacklock and Smyth (1998) defined reflexivity as the ‘conscious revelation of the role of the beliefs and values held by researchers in the selection of a research methodology for the generation of knowledge and its production as a research account’. In contrast to the naturalistic paradigm defined by Holliday (2007), which suggests that substantiation is gained via minimal researcher interference using a ‘fly-on-the-wall approach’, this study required that I actively ask questions, probe for explanations, and check responses to clarify ambiguous statements (where possible). Therefore, during the interviews, I often prompted stakeholders to explain, confirm, or justify their position so that their opinions could be examined in greater depth. However, the decision to intervene needed to be

balanced with the skill of remaining silent (Barbour & Kitzinger, 1999), and I tried to carry out these interviews in a non-threatening, non-judgmental manner to avoid giving stakeholders the impression of being under judgement. In general, I felt that my role was to keep the interviews focused on the questions but to allow enough time and silence for the interviewees to consider their response to me. However, despite my attempts, as a person working in the industry, I did not come to this project with a completely neutral outlook, and there were occasions during early face-to-face interviews when my facial expression or tone in response to questions may have indicated disagreement. However, I quickly learned to adapt my interviewing style to offer a more neutral stance to reduce my influence on the data.

CHAPTER 6: RESULTS

6.1 Results

The results of both parts of the study are presented alongside each other. In most instances, the interview outputs are presented first, as it was the qualitative responses that provided the framework upon which the questionnaire was built. However, this order of presentation was not appropriate in all instances. The questionnaire responses are grouped and presented under the appropriate theme headings.

6.1.1 Interview respondents

Ninety-eight emails were sent to various stakeholders, and 22 responses (22%) were subsequently received. Initially, a response rate of approximately 25% had been estimated. Sixteen (16%) interviews were eventually conducted. Of the remaining six respondents, five did not respond to further correspondence related to organising a day and time for the interview. The remaining respondent declined to be recorded at the start of the interview, and therefore, no interview was conducted. All of the interviewees, with the exception of one, had had some type of involvement in clinical trials, either in the past or in their current role. All interviewees had at least five years' experience in their current role and/or field. A further breakdown of the respondents and additional details on each one can be found in Appendix 16.

At the time of the interviews, all respondents in the pharmaceutical stakeholder group (n=9) worked at the manager level or above and had roles in the R&D department of their respective organisation. Most (n= 8, 89%) held a position equivalent to associate director or above. One respondent, while currently not working for a pharmaceutical organisation, had done so previously. At the time of the interview, however, this person was working for a non-profit venture that manages and develops an R&D portfolio and was therefore deemed suitable for interviewing. All respondents were based in Europe, with the exception of one respondent based in South Africa.

Five of the six respondents (83%) who fell under the HCP stakeholder category were physicians. The one respondent who was not a physician was a patient-facing member of a clinic's staff, performing basic tasks associated with collecting patient samples from research trial participants. All of the HCP participants were based in either Ghana or Nigeria.

Despite contacting six individuals who would have fallen under the government/policymaker respondent group, only one person responded and was interviewed. The interviewee was based in Ghana and was working for the country's Food and Drugs Board.

6.1.2 Questionnaire respondents

Two-hundred-and-thirty-seven emails were sent to potential respondents, and 75 (32%) questionnaires were eventually completed. A detailed breakdown of the respondents, including their title, number of years in their present field, and experience working in both clinical trials and in Sub-Saharan Africa, can be found in Appendix 17.

Respondents in the following countries participated and completed a questionnaire (see Figure 6): Egypt, France, Ghana, Liberia, Nigeria, South Africa, Spain, Uganda, the United Kingdom, and the United States.

For the questionnaire, the three stakeholder groups that were approached were the same as those interviewed in study 1.



Figure 6: Map illustrating the locations of the questionnaire respondents

Of the 75 respondents, the largest percentage, 77% (n=58), were from the PHARM⁵ stakeholder group, followed by 15% (n=11) from the HCP group and 4% (n=3) from the OTHER group. The REG group represented only a small percentage of those surveyed (n=1, 1%), as did one respondent who was identified as REG/HCP. The PHARM stakeholder group represented a larger percentage of respondents in this part of the study than in the interviews, where PHARM respondents represented 56% (n=9) all participants (n=16). In contrast, HCPs were not as well represented in this part of the study as in the interviews, as they comprised 38% (n=6) of the interviewees versus 15% (n=12) of the questionnaire respondents. Although the ability to detect differences between groups was limited, the greater number of PHARM respondents may have had an influence on the overall results presented in this chapter, as it discusses in more detail at a later point.

⁵ Throughout this thesis, PHARM will refer to respondents from the pharmaceutical industry, REG will refer to respondents from within regulatory bodies, and HCP will refer to healthcare professionals

The average (mean) number of years in the current role was 5.1 years for the entire group of respondents. For the HCP group, the mean was 11.8 years—a figure 6.7 years higher than the average number of years in post for the PHARM group, 5.1 years. That said, on the basis of personal experience, I suspect that the divergence was likely due to a higher probability of PHARM stakeholder group members to have more frequently changed roles and/or titles on several occasions through their careers. With the benefit of hindsight, it would have been better to collect the number of years that the respondent had spent in the industry as opposed to the number of years in the current role, as that figure would have been a more accurate reflection of experience.

Ninety-five percent of the respondents (n=71) had some experience working in clinical trials, while 5% (n=4) had none. Twenty-five percent (n=19) of those surveyed had experience in working in Sub-Saharan Africa, while the majority (n=71, 75%) had no such experience.

The respondents were asked to indicate their agreement with various statements on a 1-5 scale, with 1 meaning ‘strongly disagree’ and 5 meaning ‘strongly agree’. The questionnaire responses were grouped into similar thematic categories as those from the interviews. The results of the responses to each question can be seen in Table 7 through Table 11.

Respondents were also given the opportunity to add free text to expand on their responses to individual questions throughout the questionnaire. The questionnaire respondents are identified with parentheses—HCP(1)—as opposed to the underscore (e.g., HCP_1) used to identify the interview respondents. For clarity, ‘questionnaire’ or ‘interview’ is also written before the respondent identifier to ensure that it is evident which part of the study a quotation represents. It is important to note that in the example just given, HCP_1 and HCP(1) are two completely different respondents. Quotations taken from free-text responses to the questionnaire are written verbatim in italics.

6.2 Theme development

Thematic analysis of the interview transcripts and reviewing of the codes generated a total of 10 themes. In order to facilitate the review, a summary of the themes which were identified can be found in Table 6 with more detailed descriptions following.

6.3 Ethical themes

6.3.1 Provision of medicines post-trial

The provision of medicine post-trial was one of the ethical concerns most frequently raised by stakeholders across all groups (i.e., pharmaceutical industry representatives, HCPs, and government representatives). In the context of the conceptual framework, this particular issue is relevant, as it speaks to the key principle related to specifying the intended beneficiaries of research. If trials are to be conducted in ethnic minority populations and in patients in developing countries, it is important that sponsors understand that those individuals are among the beneficiaries of that research. One mechanism for guaranteeing that is the case is to ensure that, amongst other things, the drug tested is made available in trial region at dose levels or as part of treatment regimens appropriate to the researched population. Within this theme were sub-themes related to why medicine should be provided post-trial and associated implementation problems. Many of the participants who raised the lack of post-trial access to trial medication appreciated that the issue was not exclusive to Sub-Saharan Africa but one that also affected trials in developed and developing countries elsewhere in the world.

| Theme Type | Detailed theme |
|------------------------------------|---|
| Ethical themes | <p>(1) The provision of medicine post-trial is one of the most frequent ethical concerns raised by stakeholders in multiple groups. This is not an issue exclusive to the sub-Saharan region of Africa, but is of particular concerns in this region due to the countries socioeconomic climate.</p> <p>(2) Informed consent is an issue that has numerous challenges associated with it in developing countries due to lower levels of literacy, lack of understanding of the clinical trial process and cultural differences which mean that the western informed consent process may not necessarily fit the region.</p> <p>(3) The legacy of pharma companies in some countries, both developed and developing, is contentious. The potential for patients and / or HCPs to be exploited is greater in developing countries because of socioeconomic conditions which exist in these regions. Sub-Saharan Africa also has a legacy of corruption and fraud at numerous levels and there is concern that this could affect both investigators and / or pharma companies (and potentially ethical and regulatory bodies).</p> |
| Commercial themes | <p>(1) Pharmaceutical companies are businesses that ultimately exist to generate profit. This single fact dictates many of the decisions they make. Africa's lack of commercial attractiveness is an important factor which has precluded clinical research being performed in region to date.</p> <p>(2) The cost of drug development is high which leads to drug companies charging high prices for products produced. The costs of these medicines in sub-Saharan Africa are prohibitively high and cast doubt on the appropriateness of conducting trials in this region as accessibility will be limited to a wealthy few.</p> |
| Medical/scientific themes | <p>(1) Pharmaceutical companies have a responsibility to research the differences in response to treatment for patients based in different parts of the world to ensure both safety, and efficacy of products made available globally.</p> <p>(2) Due to changing socioeconomic conditions in the region, the disease landscape of sub-Saharan Africa has changed such there are rising levels of chronic diseases. This, however, should not take focus away from existing priorities which include the prevention and treatment of infectious diseases.</p> <p>(3) Much of the problem of prioritising research efforts in sub-Saharan Africa come from the lack of epidemiological data for the region. A lot of work is needed to be able to quantify the extent of the problems before efforts can be made to tackle them.</p> |
| Practical/operational theme | <p>(1) Deficiencies in infrastructure and ethical & regulatory review framework and processes, whether perceived or actual, have precluded pharma companies from placing clinical trials in the sub-Saharan region of Africa. These deficiencies (if / where they exist) need to either be redressed or where deficiencies are only perceived, capabilities need to be communicated to pharma companies to attract more research. Further research being conducted in the region will contribute and develop existing infrastructure further.</p> |
| Educational theme | <p>(1) Education at multiple levels is key to driving the increase of clinical research in sub-Saharan Africa. This includes education of the public, education of pharma, and education of healthcare professionals in the region.</p> |

Table 6: Themes that emerged from coding and analysis.

6.3.1.1 Responsibility: cost and availability

The issue of responsibility for providing medicines post-trial and their cost and availability is of particular concern due to the socioeconomic climate of countries in this region. This topic is primarily related to the commercial availability and affordability, or lack thereof, of drugs sold in the region. The central question in this respect concerns who is responsible at the end of the trial for providing patients with post-trial medication. This was one of several issues raised throughout the course of the interviews that was identified as universal in nature.

'If the medicine's not available, and it's thought to be effective, then that's a universal ethical consideration that needs to be factored in, not just specific to your territories.' (Interview: PHARM_4)

'It's a difficult question, because essentially, if we go down the route of supplying patients lifelong on products, we basically won't be able to do those studies in those areas.' (Interview: PHARM _5)

The case of Brazil was highlighted, as in that country, the government expects not only the trial drug but also the patient's other medications to be supplied by the pharmaceutical company for the rest of that individual's life:

'I think that is a copout by that government. They should be supplying that or ensuring that there's a decent healthcare system, especially a rich country such as Brazil.' (Interview: PHARM_5)

The responsibility of pharmaceutical companies to provide medicines post-trial and how that relates to the Declaration of Helsinki, one of several guidelines covering the conduct of clinical trials and the responsibilities of sponsor organisations embarking on such research, was cited exclusively by stakeholders in the pharmaceutical group. This may potentially speak to a lack of familiarity with the ethical guidelines that govern the global conduct of clinical trials on part of the HCP stakeholder group:

'I know historically, the pharmaceutical industry hasn't had a particularly good record in developing countries in general, particularly with respect to informed consent and also with the availability of treatments for chronic disease after trials have ended, which is one of the reasons for the change in, I think it was the 2004 Declaration of Helsinki.' (Interview: PHARM_7)

Referencing this particular version of the guidelines is important, because the Declaration of Helsinki is one of the few sources of specific guidance in relation to who is responsible for providing drugs to trial patients post-study. However, multiple versions of the document exist. Depending on which version a pharmaceutical organisation chooses to adopt, this document may put full responsibility for the post-trial provision with the entity sponsoring the trial, generally the pharmaceutical company.

Although there was only one pharmaceutical respondent who was based in Africa, it is worth noting an apparent disconnect in expectations between this participant and the other pharmaceutical representatives based outside of that continent. Most respondents (all of whom were based outside of the region) felt that providing post-trial medication should not be the responsibility of the pharmaceutical companies sponsoring the trial. The single pharmaceutical respondent based in the region, however, commented:

'So, we do not do any trials unless the pharmaceutical company ensures that it's going to be registered or they will provide medication until such time that there is an endpoint of the trial.' (Interview: PHARM_3)

The provision of medicines and the associated post-trial requirements appeared to be an important issue that has been an influential factor in the pharmaceutical industry's decisions to place (or not place) trials in the region to date. The fact that this element was a point raised exclusively by one stakeholder group may indicate a disconnect in expectations regarding responsibilities and requirements between pharmaceutical companies and governments in the region.

6.3.1.2 Follow-up

The cost of drugs was not the only factor that caused concern about post-trial availability. The issue of continued care and follow-up was also raised.

'...research is research. If we continue on supplying drug after the period, who follows up on the patients to make sure that they're not having adverse events, that there are no safety complications as well? Yes, by all means if you've got an oncology subject where they've responded very well to a compound and there's a big risk that their disease will return if you withdraw, then by all means supply for the, for however long that will keep that patient alive...so there are certain therapy areas where it's a responsible thing to do, but in other areas it's not, and the debate for that should be upfront whenever you're setting up the study. You need to have the ethical and regulatory debate prior to the onset of that study.'

(Interview: PHARM_5)

6.3.2 Informed consent

Informed consent is an issue presenting numerous challenges in developing countries due to lower levels of literacy; a lack of familiarity with and, understanding of, the clinical trial process; and cultural differences meaning that the Western informed consent model may not always be an appropriate fit for the region. Obtaining consent in the clinical trial setting can be further complicated by the inclusion or exclusion of certain cultural norms.

Table 7 summarises the responses to the survey questions on informed consent. The results indicate that the respondents generally felt that the Western model of informed consent was appropriate and that revising that process to incorporate cultural nuances that may contravene GCP was not suitable.

| | 1 (Strongly Disagree) | 2 (Disagree) | 3 (Neutral) | 4 (Agree) | 5 (Strongly Agree) | Responses |
|--|--------------------------|---------------------------|---------------------------|--------------|---------------------------|-----------|
| 9. The Western model of informed consent (i.e. consent is required, must only come from the person to be enrolled in the trial, must be freely given etc.) should be applied across all countries in which clinical trials are conducted. | 1 (1%) | 4 (5%) | 2 (3%) | 24 (32%) | 44 (59%) | 75 |
| 10. The way informed consent is collected should be tailored to suit the cultural nuances of the particular region or country where a trial is being conducted, even if this contradicts the requirements of Good Clinical Practice (GCP). | 18 (24%) | 28 (37%) | 8 (11%) | 15 (20%) | 6 (8%) | 75 |
| 11. Informed consent is not handled particularly well in developed countries so it is likely that investigators in developing countries may also struggle. | 4 (5%) | 19 (25%) | 27 (36%) | 23 (31%) | 2 (3%) | 75 |

Table 7: Results of statements 9-11: Informed consent

Interviewees across all of the stakeholder groups raised the issue of informed consent at some point, which highlights its importance in the clinical trial process. Informed consent appeared to be of particular concern to HCPs working in the region. Its significance to that particular stakeholder group was evidenced by the frequency with which it was raised in interviews conducted with those individuals (four out of six HCPs mentioned informed consent, versus four out of nine pharmaceutical respondents). Within the topic of informed consent there were, again, a number of sub-themes.

6.3.2.1 *The doctor-patient relationship*

It was suggested that the doctor-patient relationship in some areas is not the same as in Western countries and thus potentially compromises the process of obtaining informed consent.

'I think the biggest problem that we have is basically that of informed consent, and, um, because these are issues that have been on and on for years, and you'd be surprised that if you ask some people after the trial, they will tell you that don't even know what they've done, and because of the peculiarities of the society, there is so much, you know, in Africa people look at medical doctors as gods, so they're afraid to question them!' (Interview: HCPN_1)

This issue is complicated, as in many cases, the physician is both a healthcare provider and researcher, a situation that is also common in clinical trials in the West.

However, in this particular part of the world, for a number of reasons, the patient is even less likely to challenge his or her physician's recommendation to participate in a clinical trial:

'...most of the time...they are physicians and they are researchers at the same time, which is an ethical problem, so...because in this part of the world, most patients just believe that the doctor knows what is best for them, so when you tell them that "Okay, so I'm doing this study, do you want to join?" they'll tell you, "Ah, doctor, you know what is best for me—I will do it," so again, you're not sure you understand the dynamics in between that kind of relationship.' (Interview: HCPN_1)

This concern was echoed across stakeholder groups, including by several interviewees from the pharmaceutical stakeholder group:

'I would also be concerned...if the doctor in any way, which he can almost not by the sheer invitation to take part, is implying that this is something that's good for them...you know, there needs to be a certain maturity in that relationship that I think could, you know, if that's not there, it kind of undermines the whole informed consent a little bit.' (Interview: PHARM_4)

6.3.2.2 The process of gaining informed consent

Related to the topic of the doctor-patient relationship were concerns about how the process of gaining consent was carried out, and these were specifically related to a lack of explanation from the researchers and a lack of understanding from the participants.

'Most of them don't even understand what they're doing, do you understand? Most researchers just give them a piece of paper to sign that "you have to sign this", and they sign, and even those that you explain to, if you go back to them after two or three weeks, they don't know what you have done.' (Interview: HCPN_1)

'...the importance of the informed consent process and that it's not just a document for participants to sign, but a document for you to ensure that they understand everything that is within the informed consent, it's a process, rather than just a, you know, a mere signature, bribe type of event.' (Interview: HCPN_2)

There were, however, also comments in response to the questionnaire suggesting that the dynamics of the doctor-patient relationship and its relation to the informed consent process were better understood in Sub-Saharan Africa, where they are potentially more of an issue, than in developed countries:

'In my 32 years of clinical research, I have found there is more awareness of and sensitivity to the challenges of true consent and understanding in Africa (by both

local and expat investigators) than is sometimes practised in the first world.'

(Questionnaire: PHARM[30])

6.3.2.3 *Literacy and understanding*

Another issue raised by multiple stakeholders concerned the Western informed consent model and its transferability to regions with lower levels of literacy and formal education, as well as different cultural norms. Some of those interviewed indicated that the issue may not be as simple as the transferring of Western ideals of what comprises true informed consent to patients living in this region, implying that a more robust approach encapsulating cultural nuances and taking literacy into account would need to be incorporated. Additionally, it was suggested that certain allowances be made in the informed consent discussion between doctor and patient that would not necessarily reflect how consent is obtained in the West. This is particularly relevant in cases where factors such as lower levels of literacy and a lack of formal education are a more prevalent issue. These differences in cultural norms and their potential impact on the informed consent process were recognised across the two largest stakeholder groups:

'...the other thing is obviously informed consent, and people are illiterate, people cannot understand eight pages of informed consent, how to transfer Western thinking, especially if it has to be orally delivered, to what people with a very limited education can comprehend, so it's really an informed consent...and then, of course, documentation with people who very often cannot write.'

(Interview: PHARM_9)

'Our population is not like what you might have, may find in the UK. You know, there's a high level of illiteracy, and that has led to low awareness amongst some of the conditions that the people, that the people, uh, suffer here.'

(Interview: HCPG_1)

6.3.2.4 *Cultural differences*

Cultural differences with respect to gaining informed consent were raised in both the

interview and questionnaire responses. In the interviews, these points focused exclusively on gender issues and who provides consent. However, the direct questions within the survey elicited a wider range of responses

Statement 10 asked respondents about the degree to which they agreed with the concept of an informed consent model considering and incorporating the cultural nuances of the particular region or country, even if those norms contradict the requirements of GCP. The majority disagreed (n=28, 37%) or strongly disagreed (n=18, 24%) with that statement. Only 15 (20%) and 6 (8%) respondents agreed or strongly agreed, respectively. A number of the comments suggested that while cultural nuances should be accommodated to a certain degree, GCP should always take precedence.

Strongly disagree:

'It is imperative that all participants provide informed consent. This principle cannot be compromised. It is recognised that cultural nuances may affect how that informed consent is obtained but the principle remains and the standards must not be lowered to account for "nuances"' (Questionnaire: OTHER[1]).

A neutral approach was taken by other respondents, suggesting a degree of compromise:

Neutral:

'I would be uncomfortable with this but it would depend on the category. It would also need ethics approval.' (Questionnaire: PHARM[16])

Those who agreed focused on the need for the participant to understand, however that aim might be achieved:

Agree:

'It needs to be in a manner the patient understands else it is not actually "informed" consent.' (Questionnaire: PHARM[17])

Making allowances for cultural nuances (which many agreed was important) can potentially come at the expense of compromising on one or several of GCP requirements, which most respondents across stakeholder groups suggested was not an acceptable trade-

off. Further exploration of this particular topic would be beyond the scope of this project but is required to ascertain whether it is possible and/or necessary to harmonise informed consent requirements across the globe.

6.3.2.5 *Gender issues*

The topic of gender equality, particularly in relation to acquiring informed consent from females, was of specific concern. In some cultures, males make decisions on behalf of the females in their family, whether the relationship be that of father-daughter, son-mother, or husband-wife. From a Western informed consent perspective, this presents challenges, as it may undermine and compromise the validity of the consent collected for female patients;

‘...how do we get gender equality that we, so that we’re sure that a female subject has actually consented and it was not just her husband or her father who pushed her into a trial?’ (Interview: PHARM_9)

In the questionnaire, 91% of the respondents (n=68) either agreed (n=24, 32%) or strongly agreed (n=44, 59%) with statement 9, which said that the Western model of informed consent (e.g., consent is required, must only come from the person to be enrolled in the trial, and must be freely given) should be used in developing countries,

Strongly agree:

‘Too many risks of patients being forced into trials.’ (Questionnaire: PHARM[4])

However, others held opposing views.

Disagree:

‘This is a 15-year-old question, answered long ago. We know that education level and prevailing culture have to be taken into account to harmonise “western” methodology with in situ feasibility and acceptance.’ (Questionnaire: PHARM[30])

That said, comprises were sometimes by suggested by those supporting the Western approach to informed consent:

‘However, it is required the researcher will apply discretion in typically male-dominated societies and involve husbands in the consent process for women’ (Questionnaire: HCP[2])

There was only one respondent who strongly disagreed with the statement. This respondent agreed that there are several requirements under the Western informed consent model that should be applied in developing countries but suggested that not all of them were appropriate.

Strongly disagree:

‘Cultural difference whether they are SSA [Sub-Saharan Africa], LatAm [Latin America] or Asian, one always needs to consider involving other people in the area. In SSA even the tribal head may need to be involved or a whole village. We definitely cannot impose “IC [informed consent] from the person being treated” if it is not the cultural norm. I agree it should be freely given.’ (Questionnaire: PHARM[29])

Four respondents (5%) disagreed with statement 9 (‘The Western model of informed consent [i.e., consent is required, must only come from the person to be enrolled in the trial, must be freely given, etc.] should be applied across all countries in which clinical trials are conducted’), while the remaining two respondents (3%) were neutral.

Interestingly, most HCPs surveyed agreed with the statement, which was surprising, as it could be assumed that HCPs working within the confines of these nuances may want the

flexibility to incorporate societal norms. The responses to this particular question, however, suggest that those on the ground are supportive of the informed consent process and model in its current (i.e., Western) guise, a result which could partially alleviate the concerns of some of those worried that a completely different consent model may be needed for the region.

6.3.2.6 *Responding to these issues*

The issues related to informed consent were of particular concern to many respondents, given its importance in demonstrating that sound ethical principles have been employed in the conduct of a trial. These challenges, particularly when considered alongside some participants' belief that informed consent represents a demanding enough issue even for experienced researchers in developed countries, put into perspective that informed consent is one of the most essential issues for discussion:

'I don't think we do a good job of actually informing our patients, even in the Western world. You know, US, Central and Eastern Europe. Um, so if we can't do it well with people who are considered to be up to speed with the process, then they're starting off on the back foot!' (Interview: PHARM_2)

Consent was further explored in statement 11, which asked respondents whether they agreed that informed consent is not handled particularly well in developed countries so it is likely that those in developing countries will struggle. Four respondents (5%) strongly disagreed, and 2 respondents (3%) strongly agreed. Moreover, 19 (25%) and 23 (31%) respondents agreed and disagreed, respectively.

Disagreeing with the statement:

'This is too much of a blanket statement—there are more cases than I'd like where it is not handled well but I do not think it is the norm. I do think that developing countries may struggle if dealing with lack of experience and cultural challenges.'
(Questionnaire: PHARM[9])

Neutral comments reflected ambivalence and/or a lack of experience in the area.

'Not sure, but both investigators and patients need to fully comprehend ICF requirements.' (Questionnaire: PHARM[1])

'Have no experience of working in this region so can't agree or disagree'
(Questionnaire: PHARM[23])

Comments from those who agreed with the statement indicated how training can play a role in addressing such concerns:

'However, robust training can help. This was the same situation in eastern EU and now these countries are well-rehearsed in taking consent' (Questionnaire: PHARM[3])

One could argue that the issue of informed consent should be a focus of any discussion around ethics and the behaviour of those involved in clinical trials in this region. Nevertheless, for progress to be made, significant debate will likely be necessary, as the differing opinions indicate that achieving consensus across all stakeholder groups on the most appropriate way to handle the issue in developing countries will otherwise remain difficult.

6.3.3 Ethical responsibility to patients globally

On the topic of the ethical responsibility of the pharmaceutical industry to patients in developing countries, one of the final statements in the questionnaire asked respondents to indicate whether they agreed that pharmaceutical companies do not have an ethical obligation to conduct clinical trials in developing regions. The overall responses indicated that respondents felt that the pharmaceutical industry does have an ethical obligation to involve poorer countries in research. Sixty percent of the respondents either strongly disagreed (n=19, 25%) or disagreed (n=26, 35%) with the statement. A fifth (n=15, 20%) of the respondents were neutral. The remaining 20% of respondents either agreed (16%,

n=12) or strongly agreed (n=3, 4%) with the statement. Comments were left providing the rationale underlying these decisions.

Comments indicating disagreement were related to both a responsibility for conducting trials if marketing drugs in the region, as well as to the belief that regulatory requirements would inevitably change, necessitating trials in Sub-Saharan Africa.

Agree:

'If they are planning to provide or sell the investigational drug in those regions then, provided such trials can be conducted ethically and fairly in those regions, then there probably is an obligation.' (Questionnaire: OTHER[1])

'More and more regulators are asking for global ethnic representation of data in regulatory applications. So pharmaceutical companies will have to go to areas which represent all the populations.' (Questionnaire: PHARM[29])

There were similarities between the comments indicating neutrality and agreement. These remarks were mostly from pharmaceutical industry respondents stressing that companies are businesses and that they should only focus on the development of drugs when commercially appropriate.

Agree:

'They are a business not a public good.' (Questionnaire: PHARM[27])

'Ethical obligation to develop drugs, not regions.' (Questionnaire: PHARM[10])

Neutral:

'I do not think we should be obliged to conduct research there unless it is required to gain approval in a given country. We could apply this statement to performing CTs [clinical trials] in any particular country globally.' (Questionnaire: PHARM[1])

6.4 Unethical behaviour

The results of both the interviews and questionnaires indicate that fears about unethical behaviour play an important role in shaping people's perceptions regarding the appropriateness of clinical trials in Sub-Saharan Africa. During the interviews, concerns about corruption during study set-up, potentially corrupt behaviour by pharmaceutical companies, patient exploitation, and the fear of being perceived as corrupt were raised. These issues were subsequently explored with the questionnaire. The responses to the survey questions on unethical behaviour are summarised in Table 8.

6.4.1 Corruption during study set-up and conduct

Unethical behaviour and potential exploitation were first raised during the interviews:

'...there is an issue of trust and an issue of exploitation or non-exploitation. People are usually really suspicious, you know, but I think you need a lot of public enlightenment, and you need very good policy structure in place which can be enforced, because now, the problem with most of Sub-Saharan Africa...let me use Nigeria, for example, is that you have very good policies, but they're not enforced. So, people come in and do whatever, like the Pfizer trial that took place in Nigeria some years ago that was very scandalous.' (Interview: HCPN_1)

The issue of corruption during study set-up was further explored in the questionnaire. Respondents were asked whether they agreed with a statement suggesting that corruption and fraud were unlikely to impact the conduct of clinical trials in Sub-Saharan Africa. The results indicated that fraud is perceived as a significant potential issue, as 63% (n=47) of the respondents either strongly disagreed or disagreed with the statement. Of the four respondents who agreed (n=3) or strongly agreed (n=1), only one respondent was an HCP based in Sub-Saharan Africa.

| | 1 (Strongly Disagree) | 2 (Disagree) | 3 (Neutral) | 4 (Agree) | 5 (Strongly Agree) | Responses |
|---|--|-------------------------------|------------------------------|----------------------------|-------------------------------------|------------------|
| 12. Corruption and/or fraud are NOT likely to impact the conduct of clinical trials in Sub-Saharan Africa | 15 (20%) | 32 (43%) | 24 (32%) | 3 (4%) | 1 (1%) | 75 |
| 13. Pharmaceutical companies are likely to exploit patients involved in clinical trials in Sub-Saharan Africa. | 13 (17%) | 32 (43%) | 14 (19%) | 10 (13%) | 6 (8%) | 75 |
| 14. Investigators (clinicians) in Sub-Saharan Africa are more likely than those in the West to exploit patients in clinical trials. | 8 (11%) | 21 (28%) | 26 (35%) | 17 (23%) | 2 (3%) | 74 |
| 15. Investigators in Sub-Saharan Africa are more likely than those in the West to falsify data for financial gain. | 7 (10%) | 24 (33%) | 22 (30%) | 17 (23%) | 3 (4%) | 73 |
| 16. Pharmaceutical companies in the West do not always conform to GCP. | 7 (10%) | 24 (33%) | 17 (23%) | 22 (30%) | 3 (4%) | 73 |
| 17. Pharmaceutical companies do not want to engage in research in Sub-Saharan Africa over fears of being considered exploitative. | 2 (3%) | 21 (28%) | 23 (31%) | 26 (35%) | 3 (4%) | 75 |

Table 8: Results of statements 12-17: Ethics and behaviour

Disagree:

‘Unfortunately, some persons are motivated by profit and would aim for profit at any cost. The tobacco industry comes to mind’ (Questionnaire: REG/HCP)

‘Corruption is a universal thing’ (Questionnaire: HCP[2])

Neutral:

‘This hits all walks of life’ (Questionnaire: PHARM[57])

During the interviews, the issue of corruption was particularly stressed by a number of the pharmaceutical industry respondents. It is, however, worth noting that most (seven out of nine) of the respondents in the pharmaceutical group had never worked in the region.

‘...even with aid that’s been given, you hear about it being misappropriated and going to [flips hand] ...and that isn’t going to resonate well with shareholders if you say, you know, “Well we’re giving all of this to Sub-Saharan Africa,” and then, you know, you’ve got to actually track it. It’s not just enough to make a donation, you have to check it’s actually getting to where you think it’s supposed to be getting.’ (Interview: PHARM_4)

This perception held by many who had not worked in the region was, however, corroborated by one pharmaceutical respondent with experience in Sub-Saharan Africa:

‘There is corruption. I’ll be open about that. And it depends on whether you participate in it or not. Whenever I went to a Ministry of Health and they’ve said, “Well, what will you pay us for this?”’ (Interview: PHARM_X⁶)

This same respondent, however, later suggested that the idea of corruption in the region, while real, is exaggerated. The participant stressed that corruption is less prevalent than often portrayed:

⁶ Identifier left out to protect anonymity of respondent due to sensitive nature of comment

'We've got to get over this misconception [cuts self off]...it's a conception and a misconception of corruption in the rest of Africa.' (Interview: PHARM_X⁵)

The universality of corruption and fraud at numerous levels was a sentiment echoing throughout the comments left in response to statement 12 ('Corruption and/or fraud are NOT likely to impact the conduct of clinical trials in Sub-Saharan Africa'). There was a lack of first-hand experience, which highlighted the role of perception and the media's influence via its portrayal of developing countries. The pharmaceutical stakeholder group's general lack of experience of working in this region likely contributed to the content of the responses, with one-third of the respondents (n=24, 32%) indicating neutrality.

There were also comments from those with no experience of working in the region who perceived corruption to be an issue:

Disagree:

'Without first-hand knowledge I cannot say with any certainty but my impression from media representation of the region is that governmental corruption is rife and assuming that to be correct I would assume it could extend to the regulatory environment and healthcare services that might be involved in trials.'

(Questionnaire: PHARM[11])

6.4.2 Unethical behaviour by pharmaceutical companies

The issues raised around unethical behaviour during the interviews were not only related to the conduct of research by HCPs in their role as researchers but also within pharmaceutical companies. Many of the issues related particularly to the levels of transparency and accountability which pharmaceutical companies would be held to if conducting research outside of the more tightly regulated and well-established control of Western regulators and ethics committees. Issues were raised about the ethicality of pharmaceutical companies conducting increased amounts of clinical research in developing countries due to their questionable behaviour in the West.

'Um, basically, I would think that the major pharmaceutical companies in the West are behaviourally very poor...the way they manipulate clinical studies to, uh, profoundly alter the outcome of those medicines to make them much more favourable than they would otherwise be. If they were doing this in third-world countries, they probably would do more of that.' (Interview: PHARM_1).

This particular interviewee's introspective criticism of the pharmaceutical industry was surprising to hear, given his / her level of seniority and experience in the industry. The issue of withholding and/or manipulating study outcomes is a topic requiring more detailed exploration. When the same respondent was probed further about reasons for being so critical of the pharmaceutical industry, they explained that pharmaceutical companies often creates excitement and sensationalise stories that paint them in a favourable light:

'Well, you'll hear the standard bullshit from major pharmaceutical companies, that's for sure.' (Interview: PHARM_1)

Similar comments indicating internal scepticism were heard from other respondents in the same stakeholder group:

'...although I do work in the pharmaceutical industry, I am quite cynical that no successful pharmaceutical companies operate within a capitalist society...where their reason for being is to make a profit, and my personal view is sometimes, um, apparently philanthropic acts that pharmaceutical companies announce are...they're marketing attempts to make them look good, so at the end of the day, you know, there's the potential...you know, the profit might not be there, but the profit is there in intangible assets.' (Interview: PHARM_7)

As a result of the criticisms of the pharmaceutical industry raised during the interviews, the topic of that sector's behaviour in developing countries was covered in statement 13 of the questionnaire. Respondents were asked to indicate whether they agreed that pharmaceutical companies are likely to exploit patients involved in clinical trials in Sub-Saharan Africa. In response to this question, 43% (n=32) of respondents disagreed. Over one-fifth of the respondents either agreed (n=10, 13%) or strongly agreed (n=8, 8%) with

the statement, and the majority of them were HCPs working in the region. This finding represents a perhaps unsurprising but interesting disconnect between the perceptions of pharmaceutical companies and other stakeholder groups.

The case of a trovafloxacin trial in Nigeria by Pfizer was referenced as an example of the pharmaceutical industry's potential to misbehave in developing countries:

Agree:

'There are examples from Nigeria I am sure you are aware of'

(Questionnaire: HCP[3])

Despite there being a degree of accordance with the statement by pharmaceutical respondents, there was no evidence to suggest that any of the pharmaceutical stakeholders indicating a potential for misbehaviour on the part of that sector were aware of specific examples of that happening.

Responses to this statement from pharmaceutical stakeholders demonstrating agreement appeared to be based more on general feelings than on knowledge of previous examples.

Agree:

'I would like to disagree with this—but can't!' (Questionnaire: PHARM[20])

To further explore the topic of unethical behaviour and compliance, a question related to the respondents' perceptions of the pharmaceutical industry's compliance with GCP was included in the questionnaire. This was done in order to assess whether the respondents considered pharmaceutical companies to be largely compliant with GCP in the West, potentially implying that any non-compliance in developing countries was wilful. To that end, statement 16 asked respondents whether they believed that pharmaceutical companies in the West do not always comply with GCP. Approximately one-third (n=24, 33%) of all 73 respondents disagreed with this statement. A further 10% (n=7) strongly disagreed, indicating that many believe that pharmaceutical companies are largely compliant with GCP. Of note (particularly considering the mostly pharmaceutical industry-based sample population) is that over one-fifth (n=17, 23%) of respondents agreed that pharmaceutical

companies do not always comply with GCP in the West. Moreover, a further 4% (n=3), all of whom belonged to the pharmaceutical stakeholder group, strongly agreed with the statement.

Disagree:

'On the whole they do!' (Questionnaire: PHARM[14])

Neutral:

'True, any audit finding is a non-conformance to GCP. But if this question is seeking my thoughts on wilful non-conformance, then I'd be inclined to disagree, these days' (Questionnaire: PHARM[12])

Strongly agree:

'Fact of life, sometimes intentionally, sometimes not' (Questionnaire: PHARM[8])

The interviews also highlighted that developing and selling medicines is a unique business activity, meaning that obligations, and particularly ethical ones, differ significantly from those of other large companies in other industries:

PHARM_6: *'I do think they have an ethical responsibility. I think the pharmaceutical industry is one of a handful of industries where there are ethical considerations as well as business ones that have to be on the table, and that have to be thought of, and that have to be addressed. I think it's very important that the company does have an ethical policy which is clearly laid out and transparent and public, um, so that everybody can see and comment on it, and I think that the investors into the company would want to see that...um, would want to be part of something that...a bigger-picture programme, and not just purely for profit.'*

EE⁷: *'Right. So why do you think this work hasn't been done so much to date then?'*

PHARM_6: *'...maybe because it's white, male-dominated...you know, business-, lawyer-dominated at the top...perhaps it just hasn't got the right blend of people*

⁷ EE refers to the researcher, Efe Egharevba

running these companies...perhaps we should have more ethnic minorities and more women sitting on these boards, and perhaps we'd see a slightly more ethical policy.'

6.4.3 Exploitation of patients

Another issue raised during the interviews was related to the potential for patients to be exploited due to the poor socioeconomic conditions in which many inhabitants of Sub-Saharan Africa live. These conditions potentially make patients more vulnerable, and consequently more susceptible, to coercion into clinical studies, as indicated by one HCP working in the region:

'Again, for Sub-Saharan Africa, why it's particular is because you have a group of vulnerable people... because of the economic problems, I actually put Africans as vulnerable...especially when it comes to research, because most of the people you're going to be doing the research with... they're not the people in the blue-chip companies in their offices, you're going to go to the communities, and these are the people that are poor, that are managing to survive, so any help, in quotes, that they are getting from you, you're not sure if you're inducing them or not.' (Interview: HCPN_1).

This topic was revisited in the questionnaire (statement 14). In response to the statement which suggested that investigators treating patients in developing countries are more likely than their counterparts in the West to exploit patients in clinical trials. In sum, 39% (n=29) of the respondents either strongly disagreed (n=8, 11%,) or disagreed (n=21, 28%). Thirty-five percent of the respondents (n=26) were neutral, while 23% (n=17) and 3% (n=3) agreed and strongly agreed, respectively. The largely neutral response to this question again may allude to a lack of experience working in the region but may also reflect that many respondents did not feel that they had enough knowledge to agree or disagree with this statement. The neutral responses could also be attributed to the participants' attempts to answer in a politically correct manner and lack of comfort with suggesting that an investigator in a developing country would be more likely to exploit patients.

Most HCPs either disagreed or strongly disagreed with this statement. However, it is worth pointing out that certain HCP respondents strongly agreed (n=1) or agreed (n=3) with the statement.

Disagree:

'I think investigators will exploit patients (if given the opportunity) anywhere.'

(Questionnaire: PHARM[32])

Neutral:

'I hope/don't think there would be an intent to do this on a wide basis but societal norms are different and this would be likely to influence some investigators'

(Questionnaire: PHARM[44])

The last comment raises an interesting point around cultural norms and the subjective nature of corruption. This issue is revisited in the Discussion chapter.

6.4.4 Falsification of data for financial gain

A separate but linked topic addressed through the questionnaire explored the potential for investigators to become corrupt in conducting a trial. Statement 15 suggested that investigators in Sub-Saharan Africa were more likely than their Western counterparts to falsify data for financial gain. Of the 73 respondents who answered this question, 24 (33%) disagreed, indicating that many felt that investigators would potentially falsify data. A similar number of respondents (n=22, 30%) were neutral. Twenty-three percent (n=17) agreed, and 4% (n=3) strongly agreed. Comments from those who both agreed and disagreed alluded to there being a likelihood of investigators in Sub-Saharan Africa falsifying data for financial gain but implied that the probability was no greater than for researchers in other parts of the world.

Disagree:

'Not my expertise but fraudulating data is difficult in Africa like anywhere else [sic]' (Questionnaire: PHARM[57])

Agree:

'No more than any other region in the world' (Questionnaire: PHARM[32])

Neutral:

'I think there is more motivation in any developing country to falsify data than developed countries. I don't feel this is Africa specific' (Questionnaire: PHARM[45])

6.4.5 Fear of being perceived as corrupt

The interview responses indicated that it is not only fear of corruption that is an issue for the conduct of research in Sub-Saharan Africa but also the fear of being perceived as acting in an unethical way that has precluded the pharmaceutical industry from conducting research. Consequently, some of the interviewees felt that avoiding working in that part of the world is the way to prevent such potential problems:

'...I know there's been a number of countries who have...very high-profile criticism for having been accused of exploiting, um, populations. Some of this has been well grounded, um, but it has caused a lot of concern about reputation risk about being seen to be exploiting a population who may be considered vulnerable based on their background or education...the reputational risk is so high that it's actually not worth taking.' (Interview: PHARM_4)

'Because you do a study where there may...not be ethical concerns but ethical issues which are addressed...the fear is that they'll just get...be spun out of context, which wouldn't happen in a European or North American or even an Asian environment. And so there's this fear of reputational damage by doing legitimate clinical research in a developing country, such as many of those in Sub-Saharan Africa.' (Interview: PHARM_8)

Responses to questionnaire statement 17, which suggested that pharmaceutical companies do not want to engage in research in Sub-Saharan Africa due to fears of being considered exploitative, raised similar concerns.

Of the 75 respondents, 26 (35%) agreed with the statement. Three of these respondents belonged to the HCP stakeholder group. A further 23 (31%) of participants were neutral. One respondent who was in agreement went as far as to liken (in what may or may not have been a tongue-in-cheek manner) some of the people working to police ethics in the region to the secret police of Nazi Germany:

Agree:

'Agree. Many self-appointed "ethicists" in the region bear more resemblance to the Gestapo than to Ghandi.' (Questionnaire: PHARM[30])

'Big issue. Pharmaceutical companies are not looked at kindly by the public anyway.' (Questionnaire: PHARM[18])

However, other respondents disagreed and pointed to other issues as comprising the road blocks precluding the placement of clinical trials in Sub-Saharan Africa.

Disagree:

'I do not think it is this fear that drives it, but the regulatory expectations, ethics, and reliability of data.' (Questionnaire: PHARM[11])

It became clear through the interviews that much of the effort aimed at bringing clinical research into developing regions will need to focus on gaining the trust of potential patients and assuring them that trials are a necessary part of the development of medicines and that their participation is likely to be a positive experience. This process may take time given the historical evidence of unethical behaviour. Healthcare professionals (who typically have the trust of patients) will be crucial in building that trust:

'So, now, when you tell people that, "Okay, this is essential for your health or for the health of your children," that the drugs we're using now are not working...Once you talk to them and you assure them that their health and safety is taken care of and they will get insurance and nothing that is not "this thing" is going to be done to them, I think a lot of people will...they agree, but again, you need to build trust.' (Interview: HCPN_1)

6.5 Commercial viability and considerations

This section focuses on the commercial and financial issues that were raised throughout this research in connection with the conduct of clinical research in Sub-Saharan Africa.

6.5.1 Pharmaceutical companies are businesses

One of the clearest themes to emerge from the interviews, and particularly—although not exclusively—from those with pharmaceutical representatives—was that pharmaceutical companies are businesses that ultimately exist to generate profit, which drives many of the decisions they make at a corporate level. Africa's perceived lack of commercial attractiveness is an important factor which one could argue has precluded clinical research from being performed in the region to date.

Interviewees from multiple stakeholder groups defended the pharmaceutical industry's stance on generating profit and protecting profit margins as a necessary means of funding further innovation and drug development. Speaking specifically of clinical trials in Africa, one respondent raised the following point:

'At the end of the day, the losses shouldn't be too big, and ideally, there should be some sort of return on investment, even if it's not according to a normal, whatever 10% or 15%, uh, rate [company] or [company] normally expects on investment. But it should not be a dramatic loss, because, I think, this would make development, but also later product delivery, unsustainable.' (Interview: PHARM_9)

The pharmaceutical industry's business position was also discussed in the questionnaire. An equal number of respondents (n=22, 29%) indicated agreement and disagreement with statement 5, which suggested that pharmaceutical companies are businesses whose first priority should be on generating profit. Fifteen (20%) respondents were neutral, while 7 (9%) and 9 (12%) respondents strongly agreed and strongly disagreed, respectively. As was noted during the interviews, many comments responding to this question alluded to the need for pharmaceutical companies to continue to focus on profits to fund future R&D.

Disagree:

'Profit is necessary for continuing R&D, but patients should be the first priority.'
(Questionnaire: PHARM[7]).

Agree:

'But health always demands some social responsibility. It is unethical to have persons die needlessly due to limited access to drugs.' (Questionnaire: REG/HCP)

Strongly agree:

'Get real. We'll get further if public health acknowledges that without profit, there is NO further development of necessary medicines.' (Questionnaire: PHARM[30])

Another point raised in the interviews regarding the importance of pharmaceutical companies' intense focus on profit margins concerned the role of profits in driving innovation, even in areas of unmet medical need:

'Um, so, even if you see what happens with HIV—innovation there was driven through the profit margins in the West, and that's why [company] and [company] and [company] developed drugs' (Interview: PHARM_9)

To explore the perceived profitability (and therefore, appropriateness from a business perspective) of conducting research in this region, questionnaire statement 6 asked respondents whether the Sub-Saharan region is commercially relevant enough to warrant pharmaceutical companies making an effort to conduct research. Almost one-third of the respondents (n=24, 32%) were neutral in regard to Africa's commercial relevance. Several respondents indicated that they did not feel that they had sufficient knowledge to answer the question. Several HCPs pointed at the continent's sizeable population as an obvious factor in Africa's potential profitability.

Neutral:

'Apologies I know nothing about Sub-Saharan Africa's commercial value'
(Questionnaire: PHARM[32])

Agree:

'Although Africa is poor but it has large population to yield the necessary profit [sic]' (Questionnaire: HCP[5])

'There is huge population in developing countries yet to be tapped. Comparable to China' (Questionnaire: HCP[6])

6.5.2 Drug development is expensive

Linked to pharmaceutical companies operating as for-profit organisations is the fact that the cost of drug development is high. Throughout the interviews, prohibitively high drug costs were connected to questions of the appropriateness of conducting trials in this region, as commercial accessibility, should a product be licensed, will be limited to a wealthy few.

High drug costs, particularly for treatments for chronic diseases, was raised on a number of occasions across stakeholder groups in interviews but was best described by an HCP based in Ghana who used the example of a well-known cancer medication;

EE: *'... you were talking about the cost of treatment, um, and the cost being...'*

HCPG_3: *'Oh my God! That is prohibitive (laughs)!'*

EE: *'(Laughs) You say?'*

HCPG_3: *'Very few people can afford it! Even talking about Herceptin. You've heard about Herceptin?'*

EE: *'Yeah, yeah, I've heard about Herceptin.'*

HCPG_3: *'For...yeah, somebody wanted data, and he's like "How many patients can afford it?" and I'm like "Okay, you have about, um, 200, 300...600 patients per year for breast cancer. Out of which 20% are HER 2 positive. That's only 120 patients, out of which less than 1% can afford the drug."'*

The HCPs in the region did, however, recognise the high cost of drug development and the effect that these costs have on the price of treatments.

'Of course we know they're in the market to gain money, so I don't have any grudge against that, and I know it costs them quite a lot of money to develop a product—we're talking of one billion, one to two billion dollars to get a product to the market. Now they need to get their money back for their shareholders and all that, but at the end of the day, they're also doing a very good service for the community, because these are diseases that need a cure, and they are bringing the cure, so I think it's a two-way thing.' (Interview: HCPN_1)

Acknowledging the fact that pharmaceutical organisations must operate as businesses does not, in the opinion of some, absolve the industry of its responsibilities to do more to make their drugs more accessible to patients in poorer countries:

'You know, and it's shameful that many of the most recent treatments that come to market are things that cost ten-, twenty-, thirty-thousand pounds per patient year to treat people. And, of course, that's never gonna happen in poorer populations.' (Interview: PHARM_1)

'You know, we should be looking at how we can change research, how we can change funding, how we can get these patients better access to the compounds that we're privileged to be manufacturing or privileged to be developing.' (Interview: PHARM_5)

The extremely high treatment costs for patients in Sub-Saharan Africa raise questions about the appropriateness of conducting research there. Related to this topic, 24 (32%) respondents agreed with statement 7, which suggested that pharmaceutical companies should not conduct trials in countries where they do not plan on selling their drugs. A further 11 respondents strongly agreed that if a company has no intention of selling a drug in a particular country, it should not conduct research there (statement 7). Forty percent of the respondents (n=30) either strongly disagreed (n=7, 9%) or disagreed (n=23, 31%) with the statement. Nine respondents (12%) were neutral.

Disagree:

‘Even so there may be reasons to involve those countries, e.g., patient population and medical expertise in a particular therapeutic area that can accelerate global development. We must dissolve the prevailing suspicion-based thinking of countries as fragmented units. Many drugs came to Africa based on European or American data. Why not the reverse? The human race is ONE’ (Questionnaire: PHARM[30])

Agree:

‘That is also our corporate policy, however, I believe it is possible that there will be a need for exceptions. And in such cases, long-term compassionate use trials need to be provided instead.’ (Questionnaire: PHARM[41])

Comments suggested that from a commercial perspective, Sub-Saharan Africa’s relevance to clinical trials depends on what value, if any, will be realised by conducting trials in that region. This perspective was not a view that was exclusively voiced by stakeholders in the pharmaceutical group, as one might have expected:

‘If people can’t afford the drugs, I don’t know why they’d do it in Africa’
(Interview: HCPG_2)

Across stakeholder groups, there was an appreciation that pharmaceutical companies must, at the end of the day, generate a profit to keep shareholders content and to fund future research. This need was clear for interviewees across stakeholder groups. For some interviewees, however, the contentious issue appeared to be the pricing of medications, which puts them out of reach of many patients in developing countries. The issue of pricing medicines for developing countries is, again, an important topic that requires further, separate discussion. Although this point is addressed in brief later in this thesis, a full exploration of the associated topics would again be beyond the scope of this thesis.

6.5.3 Sub-Saharan Africa’s commercial relevance

An interesting point raised during interviews was how Africa represents a potential missed commercial opportunity:

'It's a missed...commercial opportunity not to, and I suppose to appeal to privately owned profit-driven companies of moral obligation is likely to be less successful than appealing to kind of the commercial potential or commercial attractiveness. One, in the potential untapped areas of clinical research, and secondly, in the potential markets which will develop and which are developing.' (Interview: PHARM_1)

There were varying opinions about the importance of chronic diseases in the region. In most instances, a participant's stance depended on his or her stakeholder group, with HCPs in the region believing increases in chronic disease to be a significant issue and pharmaceutical respondents primarily emphasising infectious diseases. The relevance of chronic disease in Africa was summarised by one pharmaceutical stakeholder who claimed that the region is commercially negligible:

'Well, it depends from what aspect. Because obviously, at the moment, from a commercial aspect, no, it's not at all important, unless you're really talking a disease that's of significant political influence. Um, HIV or even TB [tuberculosis] to some extent, and some of that...and malaria, clearly is a very real example as well.' (Interview: PHARM_4)

Others highlighted the African market's potential future growth as an indicator of commercial relevance:

'I think companies could benefit, because these markets are growing rapidly at the moment, and that potential is commercially attractive.' (Interview: PHARM_8)

The questionnaire respondents exhibited mixed opinions on statement 8, which suggested that pharmaceutical companies are missing out on a potential commercial opportunity by not doing more work in the region. That said, most either agreed (n=38, 51%) or strongly agreed (n=11, 15%). Six respondents (8%) disagreed with the statement, and no respondents strongly disagreed. Statement 8 was one of only two statements with which no respondents demonstrated strong disagreement.

The questionnaire respondents who agreed with the statement, as well as those who disagreed, indicated that they were not familiar enough with the region's commercial landscape to answer confidently.

Disagree:

'I personally can't see the financial benefit in terms of 'commercial sales' but that is not my area of knowledge.' (Questionnaire: PHARM[17])

Neutral:

'Perhaps agree insofar as naïve populations could be beneficial for development work but less so as regards sales.' (Questionnaire: PHARM[14])

Strongly agree:

'I believe this is true, the treatment naïve populations are huge and as governments become less corrupt the commercial opportunities are in SSA.'
(Questionnaire: PHARM[29])

The commercial relevance of Africa is an important factor in discussions related to the placement of trials in Sub-Saharan Africa. The results of the questionnaire demonstrated this point, as 26 respondents (35%) chose Africa's lack of commercial attractiveness as the number-one barrier to clinical trials in developing countries, as can be seen in Figure 7.

A connected sub-theme to emerge related to how Africa's perceived lack of commercial relevance affects the region's ability to influence the scientific community:

'You know, so it becomes very difficult to, to...they don't make that much money...they don't make that much money from Africa, so they're not really sensitive to what we have to say or...[laughs].' (Interview: HCPG_3)

| | 1 (Strongly Disagree) | 2 (Disagree) | 3 (Neutral) | 4 (Agree) | 5 (Strongly Agree) | Responses |
|--|--------------------------------------|-------------------------|------------------------|----------------------|-------------------------------|------------------|
| 5. Pharmaceutical companies are businesses whose first priority should be to generate a profit. | 7 (9%) | 22 (29%) | 15 (20%) | 22 (29%) | 9 (12%) | 75 |
| 6. Sub-Saharan Africa is commercially attractive enough to warrant considerable efforts by pharmaceutical companies to engage its countries in research. | 2 (3%) | 20 (27%) | 24 (32%) | 21 (28%) | 8 (11%) | 75 |
| 7. If a pharmaceutical company has no intention of ever selling a drug in a country, then it should not perform any clinical trials with that product there. | 7 (9%) | 23 (31%) | 9 (12%) | 24 (32%) | 11 (15%) | 74 |
| 8. Pharmaceutical companies are missing out on a potential commercial opportunity by not doing more clinical trial work in Sub-Saharan Africa. | 0 (0%) | 6 (8%) | 19 (26%) | 38 (51%) | 11 (15%) | 74 |

Table 9: Results of statements 5-8: Commercial considerations

6.6 The global presence of the pharmaceutical industry

As a result of the responses given during interviews regarding the commercial considerations associated with the conduct of clinical trials in developing countries, the questionnaire respondents were asked to think in broader terms about the implications of the pharmaceutical industry's global presence. More specifically, participants were asked about their perceptions of the sector's responsibilities, given its global presence, in the context of conducting clinical trials in Sub-Saharan Africa and developing countries.

6.6.1 Global availability of medicines

Fifty-five respondents (74%) either agreed or strongly agreed that pharmaceutical companies have a responsibility to ensure that developing countries are able to participate in clinical trials, as their products are marketed globally. Only one respondent strongly disagreed with the statement.

Strongly agree:

'Companies should attempt to run trials in developing countries and not shy away due to the difficulties or the lack of knowledge on how trials are run in these countries.' (Questionnaire: PHARM[2])

Strongly disagree:

'Why should companies be exposing subjects to unproven medicine unless there is a strict requirement by that country's regulatory body for local data? I don't know if Sub-Saharan African regulatory bodies require local data—I guess not, hence my response.' (Questionnaire: PHARM[41])

The second statement highlights the pharmaceutical stakeholder group's lack of knowledge about the general regulatory infrastructure. That factor was a trend throughout much of this research and is later discussed in greater detail.

| | 1 (Strongly Disagree) | 2 (Disagree) | 3 (Neutral) | 4 (Agree) | 5 (Strongly Agree) | Responses |
|---|--------------------------------------|-------------------------|------------------------|----------------------|-------------------------------|------------------|
| 1. Pharmaceutical companies provide medicines globally so have a responsibility to involve developing countries in clinical trials. | 1 (1%) | 9 (12%) | 10 (13%) | 23 (31%) | 32 (43%) | 75 |
| 2. Any clinical trial efforts by pharmaceutical companies in Sub-Saharan Africa should focus on infectious diseases rather than chronic diseases. | 11 (15%) | 42 (56%) | 16 (21%) | 6 (8%) | 0 (0.00%) | 75 |
| 3. Pharmaceutical companies should do more to ensure that the products they develop are accessible to those living in developing countries. | 0 (0.00%) | 1 (1%) | 5 (7%) | 23 (31%) | 45 (61%) | 74 |
| 4. Most companies do not think that conducting clinical trials in Sub-Saharan Africa is important. | 4 (5%) | 17 (23%) | 23 (31%) | 27 (36%) | 4 (5%) | 75 |

Table 10: Results of statements 1-4: The global presence of the pharmaceutical industry

6.6.2 Ensuring global accessibility to medicines

Nearly all (n=70, 93%) respondents agreed (31%) or strongly agreed (62%) that pharmaceutical companies need to do more work to ensure that the products that they manufacture are more accessible to those living in developing countries. Five respondents (7%) were neutral, and only one respondent disagreed with the statement. No respondents strongly disagreed. Interestingly, some of the comments made by those who both agreed and disagreed were similar to each other, despite those participants having responded to the question differently. Those who agreed and those who dissented argued the same point, which was that products should be made available based on their relevance to the population in which they are to be tested.

Disagree:

'Depends on product relevance' (Questionnaire: PHARM[30])

Agree:

'Provided it is relevant to the health needs of Sub-Saharan Africa' (Questionnaire: HCP[3])

6.6.3 Importance of conducting trials in Sub-Saharan Africa

When asked if they felt that most companies do not think that conducting clinical trials in Africa is important, most of the participants were either neutral (n=23, 31%) or agreed (36%, n=27). Five percent (n=4) and 23% (n=17) strongly disagreed or disagreed, respectively. Three of the four respondents who strongly agreed and one of the respondents who agreed were HCPs based in the region.

The additional free-text responses indicated how different stakeholders view the industry's perceptions of Africa.

Disagree:

'I am sure companies would be very interested to gain access to naïve populations in the region but may be hesitant as regards regulatory practices and

compliance issues that might damage the value of research conducted. '(Questionnaire: PHARM[11])

Agree:

'Business return currently doesn't support the huge cost and logistical challenges of setting up CT especially pre-marketing in this geography. Government and health service infrastructure needs time to develop and stabilize for anything more than local trials to be considered.'

(Questionnaire: PHARM[44])

Strongly agree:

'Probably they felt Africa is not relevant' (Questionnaire: HCP[5])

6.7 Medical/scientific themes

Naturally, topics related to patient care were raised by interviewees and questionnaire respondents throughout the course of the study. This section addresses the related topics and sub-themes to emerge from both parts of the study.

6.7.1 The pharmaceutical industry's responsibility to patients globally: Understanding interethnic variations in treatment responses

Pharmaceutical companies market and sell their drugs in a number of countries throughout the world. Thus, some interviewees felt that it was critical for research to examine how interethnic variations can affect their efficacy and safety profiles, and for trial populations to reflect all of the populations who will eventually receive a drug:

'Because their drugs are not being sold in their countries alone, and if you're gonna sell drugs in a country that's as diverse as Nigeria or India or China, then both genetically...you cannot just extrapolate data you get in your own country and bring it to those people, so you need to carry out trials in this country to be able to know how safe these drugs are in this population you want to use...' (Interview: HCPN_1)

‘...most of the studies are industry-sponsored and...certain populations are not taken into consideration. So, if the trials are done here, especially if they are products that are metabolised differently depending on the genetic makeup of the individual, then it is good that they have these trials here.’ (Interview: REG_1)

It became clear through discussion that some HCPs in the region felt that a sufficiently significant or robust evidence base is lacking for many of their local treatment practices and that many of their treatment strategies are based exclusively on local clinical experience. One interviewee qualified this point by using an example of a particular drug, the dose and dosing schedule of which he / she had significantly altered based on her observations and previous experience:

HCPG_3: *‘...for example, you have capecitabine. Capecitabine...they know that people from Asia don’t tolerate it that well, they need a lower dose.’*

EE: *‘Uh-huh.’*

HCPG_3: *‘We in Africa know that we cannot tolerate the stipulated dose. We use a lower dose.’*

EE: *‘Uh-huh.’*

HCPG_3: *‘But there are not trials in Africa, so for me, it’s purely just my clinical experience which is level four evidence, you know what I’m trying to say. Now, but if they could do that, then everybody would know that for a drug in an African patient, we use 20% lower, and we still have a good outcome or whatever. And the other thing, we have a drug that is day 1, day 8, and day 21, but Africans cannot take that drug, they can only do day 1 and day 8. I have found that, and I was happy to see trials in South Africa also stating the same thing.’*

EE: *‘Uh-uh.’*

HCPG_3: *‘It’s very difficult to put in the 21st day. But where do we publish this? So, obviously, it’s a genuine, what do you call it, observation?’*

This respondent continued to describe the inability to adequately disseminate these important findings, an issue related to a previously mentioned sub-theme concerning the perceived unimportance of Sub-Saharan Africa to pharmaceutical companies and the associated inability of HCPs to generate interest or publish their results in Western

publications:

'...because there can be some kind of results which doesn't sound like, true...but some of the things, you know, we are academic institutions, so we read something new in a journal, we try it until we realise it doesn't work...there are some things which we've been doing by ourselves because we found out that it works.'

(Interview: HCPG_3)

Healthcare professionals in Sub-Saharan Africa, much like anywhere else, want to ensure that they are giving their patients the most efficacious dose of treatment with the most favourable side-effect profile:

'We want to make sure that the, the, what we're giving to our patients actually do work. So, if it's going to be a post-marketing thing, that should be fine...because, like I said, because that area has not been explored, we don't have evidence to base on some of the things that we do.' (Interview: HCPG_1)

Areas featuring widely known differences in metabolic pathways are a concern, as they have not been explored in any significant detail:

'...I'm involved in a whole bunch of things when you talk about different P450s for example, um, and different body masses and all of these sorts of things changing the way that drugs are handled. So, from a, from a, not a cultural or wealth aspect, but from the genetic background aspect, absolutely. Absolutely. Um, and I'm sure you can dig up lots of examples where you've had a drug go into a certain population and have a different metabolic profile.' (Interview: PHARM_1)

As regards the need to, and responsibility for, running trials in patients from various developing countries, interviewees added a caveat, stressing that these trials should not be conducted exclusively in this region, as doing so would not provide an accurate reflection of the global picture:

'...it gives you a great wealth of, you know, potential patient populations, but also, if they're truly developing...will they fit the criteria? Do they give us a representation of how the drug will be available globally? You can have a small population. I don't think running a study solely in developing countries would be an accurate reflection of the global population.' (Interview: PHARM_2)

Statement 19 of the questionnaire asked those respondents to consider whether pharmaceutical companies have a scientific responsibility to patients in developing regions.

Overall, there was a general agreement that there is an obligation on the part of such firms to ensure, at least from a scientific perspective, that they are running clinical trials in Sub-Saharan Africa and other developing regions. Sixty of the 75 respondents (80%) who answered this question either strongly agreed (n=24, 32%) or agreed (n=36, 48%).

Agree:

'If they are planning to provide or sell the investigational drug in those regions then it probably is responsible to conduct trials there because genetic, hereditary, social and environmental factors can all influence effectiveness of drugs, disease strains and risk factors.' (Questionnaire: OTHER[3])

There was only one respondent who strongly disagreed with the statement. One of the respondents who disagreed with the statement added a caveat to qualify that opposition.

Disagree:

'This answer is assuming adequate race-effect studies are carried out elsewhere.'
(Questionnaire: PHARM[12])

Also highlighted was the West's lack of interest in papers published locally by African HCPs which makes it difficult for them to share their findings and observations with one another and with pharma:

'Because we can't publish. Probably if it's coming from Ghana, the United States will probably just throw the paper away for that matter...there are some things which we've been doing by ourselves, because we found out that it works. Most of the time, it is just an incidental finding, it's just that there is no way of telling that out to other people to even try it out and see whether it works...because there is nobody supporting research in this part of the world.' (Interview: HCPG_3)

6.7.2 Evolution of the disease landscape

As described in the literature review, the disease landscape of Sub-Saharan Africa has evolved and is now characterised by rapidly increasing levels of chronic diseases. This shift was acknowledged by many of the respondents interviewed, with HCPs particularly (but not exclusively) sensitive to these changes:

'Uh, the chronic diseases are becoming very important. Like chronic [indiscernible] hypertension, uh, chronic diabetes mellitus, chronic liver disease are becoming important in the third world.' (Interview: HCPN_3)

'It's like, initially, people used to think that Africa is for infectious diseases, but what we are seeing these days is that the clinical picture is completely different. You see a lot of non-communicable diseases almost overtaking the infectious diseases, so you have a lot of diabetes, a lot of hypertension, of course the consequence is stroke, and of course, we know that this is due to a change in lifestyle.' (Interview: HCPN_1)

'People are starting to live longer. The average age of people living in the West [of Africa] was about 42 years, but it's now increased to round about 48 years.' (Interview: PHARM_3)

The dominant opinion among several respondents was that chronic and infectious disease mortality rates are now equal throughout the Sub-Saharan African region:

'So those who have been subjected to poverty-related diseases as they are growing and malnutrition and all that...is, of course, made worse by the chronic infectious state within the region they've found out that has often resulted in increased risk for non-communicable diseases, so at the moment, from all the literature that is available, there is evidence that Africa is actually labouring under a double burden of disease which is inclusive of both infectious and non, non-communicable diseases.' (Interview: HCPN_1)

Some of the pharmaceutical stakeholders attributed the changing disease landscape to industry-led initiatives aimed at tackling and reducing infectious diseases:

'We're pushing back infectious diseases. There are lots of great initiatives, and there are great...results come out of this in malaria, but also in other diseases, and, uh, the chronic diseases are probably automatically coming to the forefront.' (Interview: PHARM_9).

This decrease in the prevalence of infectious diseases was not a change that any of the HCPs in the region attributed to initiatives associated with pharmaceutical organisations. Moreover, in their eyes, such diseases still represent a very significant area of concern amongst local physicians:

'But infectious diseases are still there and... those chronic and neglected diseases are very important for the researchers.' (Interview: HCPN_3)

'...from my view at the moment, there's still lots of...infectious diseases which are, with the right tools, easy to be treated or prevented, and these are low-hanging fruits in terms of gaining lives, or at least life years, so, you know, I think one should not move the focus too much from infectious diseases, such as malaria, such as TB, but also HIV/AIDS.' (Interview: PHARM_9)

Given that infectious diseases still represent a significant burden for Africa's population, it was suggested that clinical trials on infectious diseases could serve as gateway studies to promote the conduct of trials in the region:

‘And by doing those studies, they’re able to build up, I suppose, the network of expertise within the healthcare professionals but also the kind of, study staff get used to standards that are required for doing pharmacy-sponsored studies.’

(Interview: PHARM_9)

Other interviewees felt that the debate around chronic versus infectious diseases was less important and that what was more critical was for research priorities to focus on the diseases relevant for a particular area:

‘For chronic diseases, they go on a long time, so if there are any studies that are being done in another population to look at...probably not phase III studies, maybe phase IV follow-up for safety, long-term safety, we’d like a lot more of them over here, because over here, we have other compounding factors or comorbidity factors, so we would like for such studies to be done here as well.’ (Interview:

REG_1)

The evolution of the disease landscape and the importance of clinical trials addressing both chronic and infectious diseases were also raised by the questionnaire respondents. The majority of respondents (n=42, 56%) disagreed with statement 2, which suggested that clinical trials should focus on infectious diseases. Eleven (15%) respondents strongly disagreed with that statement, and 16 (21%) were neutral. No respondents strongly agreed with the statement, and only six (8%) agreed that research efforts should concentrate on infectious disease.

Some disagreed that any distinction between the two disease types should be made.

Strongly disagree:

‘The incidence of infectious diseases and diseases of poverty are high in SSA but the increase in urbanisation has led to an increase in NCDs [non-communicable diseases] as well as the lack of treatment for oncologic diseases.’ (Questionnaire:

PHARM[29])

Disagree:

'This is a biased approach—clinical trials should be conducted in all TAs [therapeutic areas] if applicable pt pop [patient population] exists.'

(Questionnaire: PHARM[17])

'Should be addressing all significant medical needs—although perhaps relevant in the event of more localised diseases that will need research in the region specifically.' (Questionnaire: PHARM[11])

Neutral:

'Trials I agree should probably focus more on infectious diseases because the population is readily available. Resources should not necessarily be used to focus on diseases more prevalent in the West as study recruitment can be met elsewhere.'

(Questionnaire: PHARM[12])

There was a reasonable appreciation of the disease landscape and the increased prevalence of non-communicable diseases.

Strongly disagree:

'There is a growing burden on chronic NCDs in Africa. Sub-Saharan Africa has the highest age-standardised prevalence of hypertension and has one of the fastest rates of increase in the number of persons with diabetes.'

(Questionnaire: REG/HCP)

6.7.2.1 *Clinical trial access should be relevant to community needs*

A sub-theme to emerge from the free-text responses, regardless of whether the respondents agreed or disagreed, was that access to clinical trials should be based on relevance to a population, whether chronic or infectious. Arguably, although not explicit in the comments, this also applies to understanding the interethnic variations in treatment response demonstrated by patients from Sub-Saharan Africa.

Strongly disagree:

'All subjects should be allowed access to new medical products.'

(Questionnaire: PHARM[57])

Disagree:

'Depends on whether disease is found in the population. Regardless if chronic or infectious.[sic]' (Questionnaire: PHARM[56])

Neutral:

'It would make sense to include trials on prominent diseases for the population in Sub-Saharan Africa. However, depending on what was being developed, I would not exclude trials in any indication without consideration of the merits of running the study in a particular country.' (Questionnaire: PHARM[53])

6.7.3 Lack of epidemiological data

According to a number of HCPs interviewed, one fundamental issue affecting the direction of Africa's healthcare is a lack of reliable and comprehensive epidemiological data demonstrating the extent to which that region is affected by any particular disease. The problem appears to lie in the scale of existing epidemiological databases, which are capturing information only at the local level but not at the national level:

'Of course, you know that one of our major problems is lack of reliable data...um, you depend a lot on institution data rather than having, you know, a database of national, accumulated...data. That is really lacking.' (Interview: HCPN_1)

The HCPs' lack of confidence in what little epidemiological data does exist appeared to have a number of causes. To a certain extent, the lack of resources dedicated to this type of data collection and to the conduct of epidemiological studies seemed to be responsible. The other challenges were either logistical or cultural:

'...epidemiological data, you have to interview the wife, the husband, and things like this. You have to take some specimens, and it's like, "What are you using them

for? I won't allow you to use my blood. I won't allow you to use my DNA. '''

(Interview: HCPG_3).

Furthermore, the perceived lack of quality in studies and the unreliability of sources can lead to HCPs questioning the outcomes of such research on the seemingly rare occasions that it is conducted:

'Do you know that diabetes, for instance...it's said that one in six people would have diabetes in Nigeria, but if you say that, people look at you and feel that perhaps that is an...understatement you know, an underestimation because it seems that every other person you see has diabetes in Nigeria. ' (Interview: HCPN_2)

The importance of this data was not lost on the HCPs based in the region and was clearly and concisely summarised by a respondent in Nigeria:

'...because you need research in order to be able to plan. So, if you don't have a research to have data, then you cannot plan. ' (Interview: HCPN_1)

| | 1 (Strongly Disagree) | 2 (Disagree) | 3 (Neutral) | 4 (Agree) | 5 (Strongly Agree) | Responses |
|--|--|-------------------------------|------------------------------|----------------------------|---|------------------|
| 19. Pharmaceutical companies do NOT have an ethical obligation to conduct clinical trials in developing regions. | 19 (25%) | 26 (35%) | 15 (20%) | 12 (16%) | 3 (4%) | 75 |
| 20. Pharmaceutical companies have a scientific responsibility to conduct clinical trials in developing regions. | 1 (1%) | 7 (9%) | 7 (9%) | 36 (48%) | 24 (32%) | 75 |

Table 11: Results of statements 19-20: Ethical and scientific responsibilities of global pharmaceutical companies

6.8 Education/training

Another theme that emerged from nearly all stakeholder groups at some point during the interviews was the need for education. The need for such education does not simply apply to a single stakeholder group. Rather, education is necessary in various forms and across the breadth of stakeholders involved in clinical research and healthcare. Such educational initiatives include educating and raising awareness among the general public, educating and training investigators to perform research duties in accordance with internationally accepted standards, and educating pharmaceutical organisations about the capabilities and infrastructure that exist in developing countries.

The respondents indicated that given the low number of clinical trials conducted in Sub-Saharan Africa work is needed to raise awareness of clinical trials, their purpose, and importance among communities in the region. The HCPs in the region clearly made this point:

‘...and as a part of your sensitisation, talk about the burden of the disease...the public-health aspect of the disease and efforts that are being made to educate of the disease burden. I think there are some centres that are doing well, letting people know...because we have data, and they may not have the data...the mortality rate, the morbidity rate, and all this.’ (Interview: HCPG_2)

‘But, I think there needs to be a lot of public enlightenment before...or to prepare them. You understand? Because...there is a bias already, especially following the Trovan trial in Kano. Most people in Nigeria just think that if you say “trial”, they’ll say, “Oh, they’re using you for guinea pigs.” Okay? So, you need to let them realise that this is important, that there is a need to get new drugs...’
(Interview: HCPN_1)

Additionally, respondents indicated that work needs to be done to train investigators in the region to conduct trials at the standard required globally by regulatory bodies, ethics committees, and pharmaceutical companies to protect patients, preserve data integrity, and ensure reasonable quality levels. According to some of the HCPs interviewed, this work has already started in some areas:

'We would rather that since we've developed a pool of investigators who have become GCP compliant. They are trained, as in they should be GCP-compliant, because they've been made through the training to understand that you need to observe best practices in everything you're doing without needing anybody to oversight you... You do it because you know it's the right thing to do, and we've done investigator training for them, we've done health research ethics training for them. So, they have no reason not to understand the importance of being absolutely precise in whatever they're doing and to report exactly what they are doing and not to doctor results and the importance of the informed consent process and that it's not just a document for participants to sign, but a document for you to ensure that they understand everything that is within the informed consent, it's a process, rather than just...a mere signature, bribe type of event. So, they know all this, and they understand all of this...' (Interview: HCPN_2)

The same interviewee later commented on how the focus on training but subsequent lack of opportunity to practice new skills is impacting physicians:

'...one of the frustrations we've been having with training is that we've trained up quite a pool of investigators, and they're all twiddling their thumbs looking for opportunities to practice what they've been trained on, and it's becoming more and more difficult to have people getting trained, because they don't know what they're going to do with the training, so that's why, actively, they're trying to see how Nigeria can participate more in industry-sponsored clinical trials. However, we've started encouraging the investigators to do...investigator-initiated...trials.' (Interview: HCPN_2)

Conversely, however, another interviewee from within the same stakeholder group pointed out the low number of GCP-trained investigators in the region despite current efforts:

'...the lack of GCP-trained investigators, they are not many. Okay, that is a big problem, too, but that can be addressed. Like, we are trying to organise a lot of training for people that are interested all over Nigeria. There is an association I belong to, so we're trying to do that... because if you don't have GCP-qualified investigators, they are bound to do a lot of rubbish, because they don't know what they're doing...' (Interview: HCPN_1)

The last frequently raised theme related to education pertained to the pharmaceutical industry's need for education. Many of the pharmaceutical industry interviewees had never worked in the region, and only one pharmaceutical respondent interviewee claimed to have any significant working knowledge of Sub-Saharan Africa from a clinical trial perspective. In answer to what the region would need to either do or receive to attract more trials, one of the responses typical of the pharmaceutical sector interviewees demonstrated a fundamental lack of knowledge and significant insight regarding the region's needs from a research priority or infrastructural perspective:

'It's awful, really, that I don't, but I don't know enough about that part of the world to know what they see as, what they need to progress, what they need to develop.' (Interview: PHARM_4).

Another interesting issue in relation to education was the suggestion that involvement in clinical trials could potentially help hospitals in the region learn how to use their existing resources more effectively:

'Well, I think putting research into countries which don't normally conduct it is going to have a beneficial effect on helping them to understand how to organise what resource they do have to better effect and to reach a larger proportion of the population, as well as giving an opportunity to provide the population with educational programmes which can be spread by word of mouth, so I think it's going to benefit the community at large.' (Interview: PHARM_6)

Education's key role in changing people's behaviours that could increase their likelihood of suffering from a chronic disease was questioned by one respondent, who used the compelling example of attitudes in the West:

'See, we know a lot about disease in the West. Right? But still people drink, still people smoke, still people are overweight, and willingly so. And yet, they know they have chronic diseases as consequences directly of that, and what I also hear about infectious diseases in Africa makes me think that that is no different at all... You know, the knowledge of a disease activity...doesn't seem to change people's behaviour one little bit. You can see that every day here on the tube. You know people with cold and flu...still come into work...infecting everybody... I'm sure it's exactly the same in the middle classes in Africa. They can see fat Westerners dying of diabetes, and they are quite happy to go the same way and do nothing about it.'
(Interview: PHARM_1)

The questionnaire did not directly deal with the issue of education, although responses highlighted it as a significant barrier to the progress of clinical trials in Sub-Saharan Africa. Statement 18 asked respondents to indicate the top three barriers to industry-sponsored clinical research in Sub-Saharan Africa, and the related comments are summarised in Figure 7 and described in Chapter 7.

6.9 Practical/operational themes

Within the questionnaire n=25 (33%) of respondents chose a lack of adequate infrastructure as the primary barrier to pharmaceutical companies placing clinical trials in sub-Saharan Africa which underscores its importance as an item for discussion in the wider conversation about clinical trials in developing regions.

Many of the practical issues raised by interviewees were related to deficiencies in the operational infrastructure and sufficient regulatory and ethical oversight. However, perceptions of infrastructure levels in the region differed, even between stakeholders within the same group. For example, one pharmaceutical respondent demonstrated an appreciation of the progress made within certain African countries' healthcare

infrastructures, while the comments from others within the same stakeholder group indicated doubts that basic infrastructure was in place in parts of the region:

'But, as we're seeing, the African nations at the moment are undergoing a bit of a renaissance. You know, we're seeing Nigeria as one of the fastest-growing infrastructures in the world....that will eventually trickle down.' (Interview: PHARM_5)

On the other hand, other comments alluded to the presence of very little, if any, infrastructure:

'I do sort of believe that there should be some sort of basic infrastructure...' (Interview: PHARM_8)

It is, however, worth noting that the pharmaceutical respondents who had experience working within Sub-Saharan Africa appeared to have a much clearer understanding of the capability of regulatory oversight in the region:

'Some countries in Sub-Saharan Africa have a very well-developed, and maybe even a too well-developed and too bureaucratic way to look at clinical trials and clinical trial applications, so you lose a lot of time. There it's a little bit like in Europe, prior to European Clinical Trials Directive, where in Germany, it took ages, because they only met every three months, the ethical committee and things like that. Um, so that's one thing, that you don't have an ethical review, because the processes are so chaotic and so long, and, uh, the other thing is that some countries where I have experience...you get your positive opinion within a few days, and I always wondered whether anyone had actually looked at more than the cover letter.' (Interview: PHARM_9)

These deficiencies in infrastructure have played a sizable role in the fact that clinical trials in Sub-Saharan Africa have not been a higher priority on the pharmaceutical industry's agenda:

'...the two biggest issues about why it's not even on the agenda for virtually every other company; firstly, it's the capability within the country, either perceived or actual. And a lot of it is actual, to be honest, with one or two exceptions.'

(Interview: PHARM_8)

'Everybody thinks Africa is a black hole, because they don't take time to see what's actually going on.' (Interview: PHARM_3)

Those based in the region, however, appeared to have a different perception of their region's level of development, with comments suggesting that countries in Sub-Saharan Africa have existing infrastructure and capacity and are well equipped and primed for clinical trial work:

'We have right now about four CROs [clinical research organisations], three of which I know are already functional. Um, we have one clinical trial laboratory. That's a custom-built clinical trial laboratory in the [place] university hospital in [place].' (Interview: HCPN_2)

Where capacity does not exist, some of the interviewees were of the opinion that the pharmaceutical industry should invest in capacity-building to allow countries in the region to participate in research moving forward:

'...if for a particular project, we don't have the capacity, then maybe some of the funds would have to go to building the capacity...but where we have existing capacity to undertake it, maybe then the main funding will be operational and then the appreciative expenses that will have to be incurred.' (Interview: HCPG_1)

Although the questionnaire did not deal directly with the issues of infrastructure and an associated lack thereof, one question invited respondents to rank the largest barriers to clinical trials in order of importance. A lack of adequate infrastructure was highlighted as a significant issue (the second biggest identified barrier), with supplementary comments expanding on its significance for certain respondents:

'If the infrastructure was in place, including sufficient numbers of trained staff, none of the others would be a significant barrier.' (Questionnaire: OTHER[1])

6.10 Biggest barriers and general considerations

As outlined in the previous sub-section, the penultimate survey questionnaire asked respondents to choose the top three issues that they viewed as barriers to placing clinical trials in Sub-Saharan Africa. To that end, they were provided with a list of five previously identified issues. A sixth option allowed the respondents to name any other unlisted items that they saw as barriers. The list of pre-identified barriers was based on the most commonly identified issues during the interviews. The barriers' overall ranks were then determined on the basis of how many stars the respondents had given them, with one star indicating the most important issue, two stars indicating the second most important issue, and so on. In the overall ranking, the most significant barrier was the one that received one star from the highest number of respondents, while the second most significant barrier was the one that the second highest number of participants had assigned one star.

Figure 7 displays this information graphically. The results indicate that the respondents felt that a lack of commercial attractiveness, inadequate infrastructure, and concerns about unethical behaviour were the three top barriers to the conduct of clinical trials in Sub-Saharan Africa.

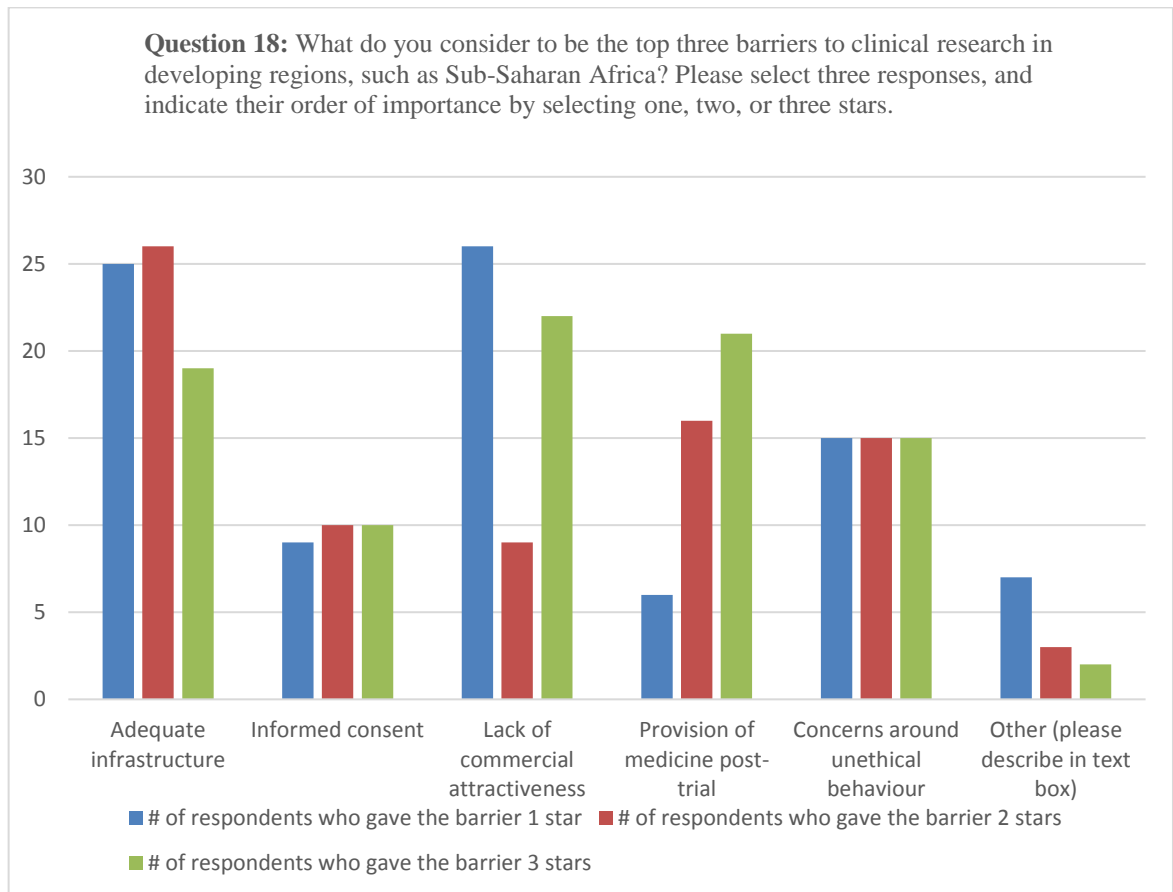


Figure 7: Barriers to clinical trials in Sub-Saharan Africa

Although barriers not mentioned in the questionnaire were described (see Table 12), these all fell under the pre-existing thematic categories that had already been identified during content analysis of the interview transcripts. Of the 14 free-text responses, half referred to local expertise, education, or capacity in some guise. These comments illustrate the importance of providing education and training resources to the region.

| Identifier | Additional barrier | Theme(s) |
|------------|---|--|
| HCP(10) | Lack/shortage of Qualified clinical trials Investigators | Practical (infrastructure) |
| HCP(7) | Reliability of insurance contracts | Practical |
| REG/HCP | Lack of funding and limited research capacity | Practical Commercial |
| PHARM(31) | Lack of clinical research knowledge and/or expertise. Considerable training efforts required. | Education Practical |
| OTHER(1) | If the infrastructure was in place including sufficient numbers of trained staff, none of the others would be a significant barrier. | Practical Education |
| PHARM(31) | Lack of clinical research knowledge and/or expertise. Considerable training efforts required. | Education Practical |
| PHARM(42) | Pharmaceuticals are a business and they have a responsibility to their shareholders primarily. Unless sub-Saharan Africa proves itself to being a viable market then other areas of therapy which reap greater profit will always take priority. The other areas regarding informed consent etc. to provide data with integrity could be facilitated with pharma companies and advising govt's and health boards on how to set up robust, transparent and accountable frameworks. | Commercial Practical (infrastructure) |
| HCP(1) | Capacity of investigators | Education |
| HCP(3) | Adequacy of expertise | Education |
| PHARM(57) | Unknown issues / lack of knowledge | Education |
| PHARM(28) | Corruption will be a huge barrier | Ethics |
| PHARM(41) | People do not know about the risks / benefits of sub-saharan countries. There is not much information about this market readily available to me. | Ethics Commercial |
| PHARM(30) | Monitoring costs (i.e. large distances, costly travel, still very little local expertise that is expensive to employ) | Commercial |
| HCP(9) | Inadequate research funding - 2nd most important | Commercial |
| PHARM(11) | For item 2 I think there could be questions around standard of care and whether or not data obtained in the population in this region could be generalised alongside wider global research populations. | Medical / scientific |

Table 12: Summary of barriers to clinical trials in Sub-Saharan Africa not specifically addressed in the interviews or questionnaire

6.11 Other considerations

The final survey question was a free-text box allowing the respondents to make additional comments on any of the questions or to expand on any of their other thoughts on the topic. The additional comments all related to themes that had already been raised during the study or provide additional feedback and/or recommendation on topics covered within the questionnaire itself. No new themes were identified from the additional comments.

There were a range of comments related to different topics that the questionnaire had addressed. Some respondents left recommendations on how research in developing countries could move forward:

‘I think the most developed and least risky countries should be investigated first and put forward to hold clinical trials. The success and benefits should pave the way for other countries and instil confidence from pharmaceutical companies. It's a long process.’ (Questionnaire: PHARM[18])

‘Perhaps some consideration into how companies can improve their support of medicines provision in the region in ways that are not open to the influence of corruption and can improve healthcare in a more affordable way—even if this acknowledges that maybe optimum treatments may be less available due to the nature of the global commercial market.’ (Questionnaire: PHARM[11])

‘From my perspective, education is the key. If there is understanding, the industry may consider including this region. Next must come political stability (in some countries in the region), the establishment of transparent regulations and a global effort by top-level organisations are what will start to bring about this change.’
(Questionnaire: PHARM[41])

One comment was a plea for objectivity, rather than emotion, to drive decisions on the conduct of research in the region:

'A good questionnaire, but a word of advice, if I may: respondents with too many 1 and 5 "strongly" answers will likely be driven by an imbalance of emotion vs. objectivity. We should not forget that progress can only come from responsible science in harmony with mature ethics, not intimidated by perception terrorists wearing ethical armbands.' (Questionnaire: PHARM[30])

Another respondent suggested reasons why Sub-Saharan Africa is not involved more frequently in industry-sponsored clinical trials:

'I suspect the reason few trials are currently carried out in this region is less to do with prejudice and more to do with convenience. Trials are expensive and often conducted with significant time pressure. It takes time and investment to build up sufficient infrastructure. With payer pressure affecting the pharmaceutical market, profit margins are reduced and it is therefore important to reduce the costs (and risks) associated with clinical development. These factors do not help investment into clinical research infrastructure in developing countries.'
(Questionnaire: PHARM[43])

Other remarks were related to earlier questions on whether pharmaceutical companies have an obligation to conduct research in particular countries or regions:

'As commercial entities I don't believe co [companies] have an obligation to conduct work anywhere in the world and that the potential commercial return will influence where trials are done. I do think society has an obligation to see if treatments/vaccines for diseases unique to different regions can be developed if these indications are sufficiently impactful to local society. If Pharmaceutical Co have any information to indicate that treatments developed for 'Western' countries would behave differently in developing regions, then I do think there is an obligation to explore this so that appropriate information is available to the local prescriber. At present it is quite tough to get non-Caucasian populations involved in CT in developed countries and this is a concern too.' (Questionnaire: PHARM[10])

One HCP suggested that pharmaceutical companies should not view the conduct of research in the region as an obligation but should instead see it as an opportunity:

‘Pharmaceutical companies can legally conduct trials. It should be an opportunity to develop the community where the research was done.’ (Questionnaire: HCP[4])

6.12 Discussion and interpretation of results

The following chapter discusses the data collected through both the interviews and questionnaires in more detail within the context of the study’s objectives and the previously referenced frameworks. The chapter emphasises the ethical, scientific, and commercial benefits of clinical research in Sub-Saharan Africa, as well as the ethical implications of the topics that were raised most frequently, such as informed consent, unethical behaviour, and the post-study provision of medicines.

CHAPTER 7: DISCUSSION

The study identified five categories of themes raised by the interviewees and questionnaire respondents and related to the conduct of industry-sponsored clinical trials in Sub-Saharan Africa. These themes were as follows: (1) ethical, (2) commercial, (3) medical/scientific, (4) educational, and (5) practical.

All five themes are closely related and oftentimes impact one another. The ethical issues largely related to the provision and availability of medicines post-trial, informed consent, and the potential for corruption and fraud on the part of both investigators and pharmaceutical companies operating outside the scope of tightly regulated Western competent authorities and ethics committees. The commercial considerations predominantly centred on the fact that pharmaceutical companies are businesses, many of which have obligations to shareholders, and on the fact that drug development is tremendously expensive. The majority of the profits generated by pharmaceutical companies come from their sales in the West, which is why their focus remains on that part of the world. The medical and scientific issues primarily hinged on the evolution of Sub-Saharan Africa's disease landscape and pharmaceutical companies' responsibility to their global patients to ensure a robust understanding of how their drugs affect patients of different ethnic backgrounds in different parts of the world. The educational issues were mainly related to public awareness regarding clinical trials, as well as to the education of the involved investigators, research staff, and ethics committee members. The final theme consisted of practical issues raised in relation to a lack of infrastructure and oversight.

This chapter summarises the key findings in relation to the previously outlined study objectives. This chapter will also summarise the strengths and limitations of the study design, conduct, and data collection as well as consider what could have been done differently to strengthen the study.

7.1 Study Objective 1: Understanding the benefits of industry-sponsored research for Sub-Saharan Africa

The first objective of this study was to understand the benefits of conducting industry sponsored clinical research in chronic diseases and to understand what collateral benefits this confers to the population and the region.

Ethnic minorities are underrepresented as clinical trial participants, and one potential way of addressing this disparity would be increasing the number of clinical trials conducted in developing regions. Including a greater number of research participants from minority backgrounds is one mechanism through which more clinical trials could be brought to Sub-Saharan Africa. However, ensuring that clinical trials are conducted to the highest ethical standards is paramount, and guidelines specific to the conduct of research in developing countries, such as those proposed by Emanuel et al. (2004), are necessary to protect patients' rights and well-being and to minimise exploitation.

The responses highlighted that clinicians in the region are sensitive to the increasing levels of chronic disease in Sub-Saharan Africa. While the pharmaceutical interviewees were less cognizant of this shift, all appreciated the change in the landscape and understood the potential role of clinical trials in addressing diseases of that nature. Although the potential benefits were described as affecting multiple parties, the responses suggested that patients in the region would most likely be the primary beneficiaries in the short-term.

Understanding who benefits and how they stand to gain is a key step in assessing the appropriateness of research and in minimising the risk for exploitation, particularly when commercial interests must be balanced with medical, scientific, and ethical priorities.

The results of the study are presented within the context of the conceptual framework described in Chapter 1.

7.1.1 Medical/scientific benefits and beneficiaries of clinical research in Sub-Saharan Africa

The results of this study indicated that there are a number of beneficiaries and benefits to the conduct of clinical trials in sub-Saharan Africa. There are medical and scientific benefits to be gained by patients, researchers and by pharma, as will be discussed in the following sections.

7.1.1.1 Understanding interethnic variations in treatment responses

A body of literature indicates that blacks and other minority groups in developed countries are significantly underrepresented in clinical trials, particularly in the United States (Heiat, Gross, & Kruholz, 2002; Ford et al., 2008). For this reason (and potentially others), these variations in response to treatment are still not particularly well understood. It is thought that environmental factors, such as temperature, can affect the physiochemical properties, absorption, distribution, and metabolism of a drug (Ballard, 1974; Burroughs et al., 2002). There are several examples of drugs which have been marketed and subsequently had their label revised to take into consideration differences in effect between different ethnic groups due to variations in pharmacokinetics, pharmacodynamics or the way the medication interacts with drug metabolising enzymes, transporters or pharmacodynamic targets. For example, Tacrolimus for the prevention of organ rejection and warfarin, the commonly used anticoagulant, both have labels that were updated following marketing (Yasuda, Zhang, & Huang, 2008). Variations in treatment efficacy and safety profiles have also been observed with whole drug classes, including beta blockers and antidepressants (Lynch & Price, 2007).

Understanding how medicines impact patients differently benefits a number of stakeholders. To researchers and patients, better insight into interethnic variations in treatment responses results in patients being treated with appropriate medications at the appropriate doses. For healthcare systems and governments, it means that money is not wasted on ineffective or unsafe treatments, or conversely, on effective treatments at unsafe doses. For pharmaceutical companies, a better grasp of where their treatments are inappropriate or require dose modifications can facilitate more ethical and targeted

marketing of drugs to suitable populations. Marketing medications at appropriate dosages for their intended population speaks directly to the principles and benchmarks of ethical research in developing countries as described in the study's conceptual framework. In other words, specifying the beneficiaries of research (in this case, patients of minority background in developing countries) and enhancing the value of research through disseminating knowledge would entail revised labelling and more detailed information on medicines' Summary of Product Characteristics (SmPC).

In the context of the second benchmark described in the conceptual framework (assessing the importance of health problems being investigated and the prospective value to participants), the interviews highlighted a need to better understand the biological differences between black African patients and their white counterparts within the cancer treatment setting. Familiarity with these variations is critical for all drugs with well-characterised metabolic pathways where evidence suggests that interethnic differences may exist, such as drugs that impact the P450 metabolic pathway (McGraw & Waller, 2012). The importance and urgency of understanding these variations in response was clearly illustrated by the comments from a Ghanaian oncologist describing variations in the licensed regimen when using Capetcitabine⁸ for their patients. In that case, a better understanding of these differences in response directly benefits all patients considered for similar treatment regimens across the continent, as that knowledge spares them from the toxicities associated with additional exposure to treatment that is not well tolerated. It also potentially reduces hospital costs, as less medicine is used to treat each patient's disease or side effects. This particular example also illustrates the almost-experimental nature of treating patients with approved medications which may be putting increased pressure on healthcare systems due to additional resources spent on the management of adverse events (as a result of exposure to higher-than-tolerable doses) and/or a lack of efficacy (as result of initial doses at sub-therapeutic levels).

Researchers may benefit from participating in clinical research, irrespective of the location. The benefits of participation were described in the chapter addressing the advantages and

⁸Capecitabine is chemotherapy drug used to treat different cancers, including breast, colon, rectal, stomach, oesophageal and pancreatic cancers (Macmillan Cancer Support, 2016)

disadvantages of clinical trials. Further references to research benefits, mainly in the form of compensation, were provided in the systematic literature review. Additional advantages include access to new treatment modalities, acclimation, the opportunity to learn new skills, and potential publications. In relation to the latter benefit (publications), a topic raised during the interviews was the need for academics from Sub-Saharan Africa to be given a stronger voice amongst researchers in the West and an equal platform from which to disseminate their findings. This need to empower researchers by ensuring that there is a mechanism through which they can share their findings speaks to the benchmark of enhancing the value of research through disseminating knowledge, as described in the conceptual framework.

Further comments made during the interviews suggested that where cultural norms indicate that patients may frequently consult traditional healers, there may also be a need to understand how these treatments may interact with those prescribed by conventional healthcare practitioners. Treatment with traditional healing remedies can in some ways be likened to patients who self-medicate with over-the-counter medications in the West. In the same way that drug-drug interaction studies are performed to better understand potential side effects of medicines taken with common concomitant treatments, one could argue that similar work should be done in developing countries focusing on the most frequently administered traditional healing medications. Understanding how commonly used traditional remedies may interact with marketed drugs is directly linked to the conceptual framework's benchmark requiring that the problems being investigated are of prospective value to study participants.

7.1.1.2. Generating epidemiological data

Another consideration raised during the interviews and also mentioned within the literature regards the lack of epidemiological data in Sub-Saharan Africa. This scarcity of data makes it difficult to accurately determine the levels of chronic disease in the region. In the debate around justifying the need for clinical trials in Sub-Saharan Africa or furthering such research, a 'chicken and egg' paradigm subsequently arises, with a trial needed to generate data but data needed to justify a trial. Although both the interviews and

questionnaire suggested that all stakeholder groups appreciated the rising levels of chronic disease in the region, without the epidemiological data to quantify the extent of the problem, it is difficult to assess future research priorities or accurately quantify any progress. Data are needed to direct efforts to the right place, but conversely, effort is required to generate data. Conducting industry-sponsored trials in this region could help establish, in parallel, databases to more accurately quantify the prevalence of chronic diseases. Those tools would be of particular benefit to pharmaceutical companies, as they would offer insight into market size. Such initiatives would provide an advantage for researchers, governments, and healthcare organisations, as they would facilitate more accurate tracking of the progress made towards tackling these diseases and provide insight into the effectiveness of various interventions.

Although significant investment is required to develop effective databases and registries, pharmaceutical respondents believed that industry should not be responsible for ascertaining levels of disease in any part of the world. Allowing countries to establish their own databases how they see fit is important in ensuring that research efforts do not supplant the existing healthcare system and are instead self-led or collaborative. Such locally initiated efforts should allow pharmaceutical companies to support and facilitate the development of databases using the existing infrastructure and then take advantage of their investment by leveraging the data collected to inform decisions on the placement of future clinical trials.

Establishing national databases is arguably a fundamental step in prioritising healthcare spending and ranking priorities. Moreover, such instruments could also provide pharmaceutical companies with empirical evidence demonstrating the number of potential patients who could be accessed for clinical trials, and that information would clearly benefit pharmaceutical companies. Understanding how many patients are affected by specific diseases would help identify new markets, facilitate access, and contribute to the process of predicting potential revenue for future products.

7.1.1.3 *Closer monitoring from healthcare professionals*

In addition to allowing patients access to medicines that they may not normally receive, clinical trials also allow patients to receive a better standard of care, due to closer follow-up during the trial participation period. Aside from any direct benefit in terms of their own treatment, being part of a research effort to tackle a disease is oftentimes important to patients and adds to their sense of wellbeing. To this end, patients often involve themselves in clinical trials for altruistic reasons, although the proportion of patients motivated by altruism varies significantly across clinical trials and disease types (Tangrea et al., 1992; Braunholtz et al, 2001). Although discussed in the summary of the literature related to the potential benefits of participating in clinical trials, altruism was not cited by many participants in this study, potentially because the drivers for participation in developing countries may be quite different than those seen in the West. It is important to note, however, that evidence of altruistic motives for participants in Sub-Saharan Africa has been described within the previously presented literature review (Zvonareva et al., 2015). The literature also indicated that investigators who participate in research are often more informed and better able to offer their patients newer treatments, highlighting that both patients and researchers are beneficiaries.

7.1.1.4 *Benefits in chronic conditions*

In relation to the benchmark of assessing health problems, the literature reviewed did not specifically speak to what benefit clinical research in chronic diseases could confer to patients in Sub-Saharan Africa. The interviewees did not think that prioritising one type of disease over another was necessary or appropriate. The need for universal access to clinical trials across regions and diseases types was the underlying consensus that emerged from the responses to the question on whether research efforts should focus on infectious or chronic diseases. Overall, the results suggested that it is much less important to focus on granting the region access to clinical trials for a particular type of disease and more essential to increase the region's overall involvement in clinical trials. That perspective maintained that the disease type is a less significant factor than a condition's relevance to the region. Assessments of the importance or relevance of a particular disease to a region

should take place in the country in question to ensure that local decision-making and priority-setting processes are not overruled or ignored. Carrying out such evaluations in the location of interest also guarantees a robust assessment of local health priorities, another key benchmark outlined within the conceptual framework.

7.1.1.5 Summarising scientific/medical benefits

The most important benefit raised was that of better understanding the biological differences between patients in different regions and from different ethnic backgrounds. A number of pharmaceutical respondents noted that while they believed that more trials should be conducted in the region, they also felt that trials should not be run exclusively in developing countries, as the data may not be generalisable to other populations. What many did not acknowledge is that the converse is happening at present. The idea of patients in the West being given medications based purely on data gathered from minority patients in developing countries seemed illogical, yet some pharmaceutical respondents did not appear to take issue with the reverse situation. However, as patients in the West are more frequently the beneficiaries of clinical trials (through post-trial drug availability), this situation is in line with the benchmark in Emanuel et al.'s (2004) framework suggesting that the scientific design of a trial realises social value for the primary beneficiaries.

Comments about HCPs altering approved treatment doses raise concerns about how many patients are potentially unnecessarily treated with sub-therapeutic doses or overdosed with various treatments and consequently needlessly suffer from adverse events that are not expected at approved or marketed doses. The implications of treating patients with sub-therapeutic or poorly tolerated doses stretch beyond the immediate impact on the recipient's health. Poorly tolerated medicines mean extra bed days for patients, thereby occupying resources that could benefit other patients. It also may have an impact on spending at the local and national level. Involving patients from Sub-Saharan Africa, even in the post-marketing setting, would allow for these divergent patient responses at different doses to be captured appropriately. This would, in turn, allow for data to be pooled and for thorough and robust analyses to be conducted to determine whether any interracial variations in marketed treatment doses are required to ensure that product labels reflect the

appropriate dose required for patients of different backgrounds.

As was suggested by the participants, and in line with the social value principle in the conceptual framework, regulatory bodies should enforce a strict requirement for local data from local patients, ensuring that patients directly benefit. However, what should also be considered is the pharmaceutical industry's potential reaction were such regulations to be imposed and enforced. As there is less potential financial reward in the region and a chance that sales may not compensate for any investment (profits from the region are not very large when compared with more developed markets), pharmaceutical companies may simply opt against marketing drugs in those countries. As the previously described benchmarks indicated, creating a paradigm characterised by collaboration and clear mutual benefits for all stakeholders is an important step toward ensuring that trials are not exploitative and that they create social value.

7.1.2 Financial benefits

Commercial considerations and the implications of conducting more research in this region were also frequently cited throughout both parts of the study. Of all the issues raised, regional commercial considerations were the single most important factor informing pharmaceutical companies' decisions to place clinical trials in that country. Data indicated that ultimately, pharmaceutical companies want to know that their efforts will reap a financial reward in the short- or long-term, due to pharma's responsibility to its shareholders. To this end, financial concerns must be taken into consideration in parallel with the development of mechanisms for engaging in research. The need for mutual benefit on the part of both the pharmaceutical industry and the region is positive, as it more closely facilitates the improvement (instead of the replacement) of the existing healthcare system and ensures that responsibility for improving the infrastructure stays at the local level. Additionally, the third benchmark in the conceptual framework related to guaranteeing that product development is an outcome of research (i.e., not conducting research for the sake of making a product available but with a view of learning more about the product) is a potentially problematic yet important balance that must be struck.

The literature reviewed summarised the financial benefits of clinical trials as largely relating to investments in infrastructure and equipment (including the construction of new facilities) and employment creation. However, for the pharmaceutical industry, one key financial benefit is access to a relatively large and untapped population. Entering sub-Saharan Africa before the clinical trial landscape matures (and even after) will allow pharma companies access to a significant number of treatment naïve patients, particularly in chronic diseases, which is a population more difficult to access in developed countries due to the ease with which treatments can be accessed.

The potential commercial benefit to the pharmaceutical industry lies not only in accessing a new patient population comprising a potential market for its drugs, but also in the ability to potentially accelerate timelines and bring drugs to market more quickly. There are a number of papers addressing the lengthy clinical trial timelines that pharmaceutical companies face due to their inability to access patients in the countries where clinical trials are typically placed (Thiers, Sinskey, & Bendt, 2008; Gul & Ali, 2010). These delays in recruitment have a knock-on effect and can lead to significant losses in profit, as companies may struggle to obtain the data that they need to bring products to market quickly or before the competition. Involving developing countries and regions, such as Sub-Saharan Africa, could potentially be a way to more quickly recruit to studies, which could, in turn, facilitate faster product development. Managing the beneficiaries of these potentially accelerated product development timelines is a medical, financial, and ethical challenge, with stakeholders benefitting in different ways but not necessarily equally. Collaborative efforts to facilitate access to medicines are arguably more sustainable and mutually beneficial over the long-term than simply offering free medication.

If pharmaceutical companies are to leverage this sizeable treatment-naïve population to expedite their timelines and increase revenues, a degree of transparency is required. The stakeholders interviewed suggested that if trials are to take place in the region with drugs that will ultimately be marketed in the countries in which they are tested, the pharmaceutical industry may need to ensure some sort of access to the tested treatment following trials. However, the Emanuel et al. (2004) framework makes no reference to the availability of post-trial medicine as being crucial to the conduct of research in developing

countries. To that end, if there are no plans to make a treatment available at study end, but there are considerable other mutual benefits to conducting the trial, this should be apparent. Thus, local ethics committees should consider such factors in the context of the potential longer-term benefits stemming from the pharmaceutical industry's infrastructure investments. In certain instances, it would be appropriate to consider revisiting the pricing models of medicines that should clearly be made available to patients. In other cases, however, it is reasonable to look beyond the accessibility of medicines in isolation to the wider contributions of the industry investment. Any revising of pricing structures will require additional work, including the policing and monitoring of parallel exports (the practice of exporting drugs originally imported to a particular country to another country where they command a higher price) (Wadman & Hutt, 2004).

There was an apparent disconnect between respondents in the pharmaceutical stakeholder group and HCPs regarding the commercial relevance of countries in Sub-Saharan Africa. Although this topic was not covered in the literature review, it was clear in both parts of the study that some stakeholders felt that the region was extremely commercially relevant, whereas others were less convinced. This gap could be due in part to the fact that within the pharmaceutical stakeholder group, there was no real understanding of Sub-Saharan Africa's varied socioeconomic landscape. The lack of knowledge was reflected in the respondents' tendency to describe Africa as though it were a single country. Very few distinguished between the individual countries and their varying levels of socioeconomic development, and when they did, the most frequent reference was to South Africa. As was mentioned earlier in this thesis, the clinical trial landscape in South Africa is more mature than in other parts of the continent. This failure to distinguish or reference the varying levels of development may have been due to the lack of cross-functional representation (i.e., a lack of commercial awareness on the part of R&D staff). Nevertheless, given the seniority of many of the pharmaceutical respondents who participated in the interviews, a greater appreciation for individual countries' commercial differences was expected.

Early decisions in a product's development plan generally require cross-functional input from a number of areas of expertise, including commercial operations (or equivalent). This need should theoretically expose senior R&D personnel to any commercial decisions

associated with countries being considered for clinical trials and subsequent marketing. The lack of commercial awareness from the pharmaceutical respondents may indicate that it is not that Sub-Saharan countries are being considered for trials and then discounted for a lack of commercial attractiveness, but that they are not being discussed or considered at all. Future work regarding the issues that preclude Sub-Saharan Africa's involvement in clinical trials should involve pharmaceutical stakeholders from all functions, and not just those involved in R&D. That greater diversity would help ensure that the commercial benefits to the pharmaceutical industry are equally weighted with the benefits to other stakeholders. That approach speaks directly to the favourable risk-benefit ratio described in the Emanuel et al. (2004) framework. The lack of breadth in the functions represented from within the pharmaceutical industry was a limitation of this study that is discussed later in this chapter.

The general consensus throughout the interviews was that pharmaceutical companies are businesses that exist primarily to make money. The data from the questionnaire exhibited divided opinions as to whether the primary focus of pharmaceutical companies should be on making a profit or on innovating and discovering new treatments. Interestingly, no comments suggested that the two goals need be mutually exclusive. During the interviews, respondents argued that it was imperative for pharmaceutical companies to continue to create profits as a means of incentivising investment from shareholders to, in turn, fund further R&D activities and drive innovation. Innovation is a debatably more abstract benefit to rationalise than other markers of commercial success, such as profit. Innovation in the development of medicines is arguably of benefit to patients everywhere, as it drives understanding of diseases and treatments. Therefore, one could claim that any kind of scientifically robust research conducted anywhere is always of benefit to everyone if it helps identify or refine new or more efficacious treatment modalities. However, if the innovation is only of benefit to patients in the West for the foreseeable future (for accessibility reasons), then the research driving it is not ultimately adhering to the social value benchmarks outlined in the conceptual framework. In such instances, efforts must be made to strike a balance characterised by mutual benefit.

A number of questionnaire respondents indicated that it would not be right to conduct clinical trials in countries in the absence of a plan to market a particular product in that locale. While an initial assessment might suggest that this view would be in line with the benchmarks described in the conceptual framework, it is important to consider the collateral benefits of clinical trials, as described earlier. If the research results in benefits for the investigators, investments in the healthcare infrastructure, and more closely monitored patients, one could argue that it satisfies the benchmark requiring that beneficiaries be specified and that the value of research be enhanced through long-term partnerships, even in the absence of any future plans to market the drug in that particular population. Therefore, the idea that pharmaceutical companies must make their drugs available in the countries in which they are tested is not necessarily valid in light of the other advantages that trials may bring.

From the pharmaceutical industry's perspective, clinical research in any region should be conducted with a view of some sort of eventual financial gain. In the absence of a potential commercial advantage, pharmaceutical companies are likely to struggle to justify carrying out research in chronic diseases in Sub-Saharan Africa and may continue to focus on diseases of political influence, if on anything at all. Of note, the definition of commercial relevance differs across organisations, but this particular finding illustrates that the conduct of research in regions with no financial viability (or prospect thereof) is not compatible with the pharmaceutical industry's business model, given its obligation to focus on creating value for shareholders. It also highlights shareholders in the West as potential beneficiaries of research in Sub-Saharan Africa if pharmaceutical companies can find a way to make it worthwhile commercially.

The results from well-run clinical trials also allow healthcare providers and governments to make strategic financial decisions on what treatment interventions to prioritise (i.e. make more widely available through subsidising or reimbursing). These decisions can save money, as they may preclude investments in ineffective treatments or interventions that are less optimal from a health economics perspective. For developing and developed countries alike, having a pharmaceutical company, as opposed to a government or healthcare institution, pay for a trial subject's treatment also has financial benefits, particularly where

healthcare is socialised. Although this point was raised in the literature review, it did not surface from the interview or questionnaire findings. This could be due to the majority of respondents being from countries where healthcare is socialised; such individuals may therefore not habitually need to consider the cost of their routine healthcare.

Another topic addressed in the literature review but not raised by participants during the study (potentially because of the areas where the interviews and questionnaires were completed) was the potential financial impact of clinical trial participation on families in countries without socialised healthcare. In the United States, for example, where medical treatment is not subsidised to the same degree as it is elsewhere, patients may rely on clinical trials as to access medicines that they cannot afford or that are not covered under their health insurance plans. This point is important to note, as it demonstrates that the access to ‘expensive’ medications potentially afforded by clinical trial participation is not an issue exclusive to patients in poorer countries. Rather, it is equally relevant to those in developed countries due to the generally high cost of medicines globally. Even in countries where healthcare is socialised, clinical trials can provide access to treatments that are not easily accessible for institutions because they have not been deemed appropriate for reimbursement.

The commercial relevance of Africa to the pharmaceutical industry emerged as one of the single largest drivers influencing the placement of trials in the region. There is historical evidence of pharmaceutical companies not being particularly sensitive to the needs of a region until they are economically relevant. Examples include countries and regions such as India, China, and Eastern Europe (which, arguably, did not gain the attention of the industry until their economies became more established) (Platanov, 2003). Africa’s commercial relevance will need to be continuously assessed by pharmaceutical companies before the industry begins to take steps towards redressing any of the other issues raised throughout this research. A balanced perspective considering all of the benefits and potential beneficiaries should be adopted and assessed for appropriateness locally, or at the very least in partnership with local ethics committees and regulatory authorities. The Western model of high treatment costs will not be easily transferrable to Sub-Saharan Africa in the short- to mid-term, and as such, the relevant stakeholders (including

pharmaceutical companies, NGOs, and government organisations) will need to arrive at a mutually beneficial agreement. Together, these stakeholders will need to create a model capable of providing adequate resources to research and the treatment of chronic diseases in Sub-Saharan Africa without sacrificing the pharmaceutical industry's financial viability. Such a model will also need to ensure that all parties benefit.

7.1.3 Practical/operational benefits

During the interviews, the most-cited practical benefit of clinical research was the role that the pharmaceutical industry can play in infrastructure development, capacity-building, and education. The associated benchmark highlighted in the conceptual framework, however, suggests that these efforts should complement or add to the existing infrastructure without replacing it. It was highlighted that endemic issues must be addressed in certain countries for investments to be sustainable and worthwhile. These challenges include issues with providing constant electricity or access to clean water. There are several examples of how foreign investment (outside of the pharmaceutical industry) is helping to develop infrastructure. Examples include the marked presence of Chinese multinational companies and investments in infrastructure, such as roads and railways (Alden & Davies, 2006). A small number of respondents raised the issue of the varying levels of development of the countries in Sub-Saharan Africa. However, as previously mentioned, this point was not frequently mentioned.

It was suggested on several occasions that pharmaceutical companies start with some of the more developed countries that already have the necessary infrastructure before moving on to less-developed countries and cities. This idea is discussed in more detail in the recommendations chapter. It is worth noting that many of the practical issues raised, and even several of the ethical issues, are less relevant when one considers running trials in large cities, as in countries with more urban areas, many of the principal cities are well developed, meaning that they have provisions in place to ensure access to clean water and constant electricity (e.g., generators). Such countries are also home to educated, middle-class populations. South Africa was identified as an anomaly in several of the interviews because of its history, infrastructure, and politics. The active role of South Africa in pharmaceutical industry-sponsored clinical trials over the past decade suggests that it is

possible for countries in the region to be active contributors to clinical research. One of the starting assertions of this research suggested that trials are required to understand interethnic variations in treatment responses. Interestingly, in that context, South Africa's participation in clinical trials is perhaps less relevant than that of other countries, considering its sizeable white population. A Wemos (2013) report summarised the reasons that South Africa stands out as a location selected for clinical trials. While not as inexpensive as India, the population is more genetically diverse and has a high burden of traditional and lifestyle diseases. Furthermore, the majority of the population has limited access to healthcare. Additionally, South Africa has a well-established research infrastructure and numerous experts, making it an optimum site for clinical trials. Another possible explanation for South Africa's involvement in clinical trials is the aforementioned higher percentage of white people as compared to the rest of the countries in Sub-Saharan Africa.

Another practical benefit raised during the interviews noted that industry-sponsored trials contribute to the development of better regulatory and ethical oversight. Comments raised by the interviewees indicated that at present, oversight from both competent authorities and ethics committees is not ideal. In particular, the processes are either not robust enough (there are doubts as to whether studies have been sufficiently reviewed) or so protracted and chaotic as to be prohibitive. This situation draws parallels to what was seen in many European countries prior to the EU Directive which provides guidance and sets out timelines for ethics and competent authority review (Europeans Medicines Agency, 2004). Placing a greater number of pharmaceutical-sponsored clinical trials in the region is likely to improve the existing review and approval processes. That outcome would benefit both pharmaceutical companies and studies initiated by local investigators, NGOs, or charities. More robust ethical reviews, in turn, ensure that the rights and wellbeing of patients are better protected, which is of benefit to trial participants. The implementation of more robust review processes is likely to be a key factor in attracting future clinical trial work in the region. This again raises the 'chicken and egg' paradigm highlighting that more studies are needed to facilitate development processes but that procedures require further development for more studies to take place. The Emanuel et al. (2004) framework calls for public accountability through reviews by non-governmental bodies. However, a significant number of trials need to be reviewed for the knowledge and processes guiding these

appraisals to be comprehensive and trustworthy.

The literature highlighted additional practical benefits associated with the creation of social value through investment. Many of the practical benefits are related to the financial advantages, which highlights the interdependency of benefits and the issues identified. Investing in facilities is important, because the appropriateness of facilities and the quality and availability of equipment are two practical areas of concern that were mentioned throughout this research. For clinical trial results to be reproducible, standardised data collection and reporting across trial sites are imperative. There may be a requirement for specific tools and equipment to be used, and the more sophisticated of such instruments may not typically be available at many sites across Sub-Saharan Africa due to their cost (both the purchase price and maintenance expenses). For many trial sites in the West, pharmaceutical companies reimburse hospitals for procuring the equipment needed as part of the trial. This type of investment could be invaluable in Africa, as it would provide sites with equipment that they may not otherwise be able to afford. Examples from the systematic literature review indicate that the post-trial management of new equipment and additional human resources once the trial site is no longer being paid is a critical issue that should be addressed prospectively before the trial commences.

Earlier chapters discussed how the wider community can also benefit from the construction of facilities, as newer facilities may mean better healthcare standards for those living locally (Fenton et al., 2009). Fenton et al. (2009) also discussed how newer facilities and better equipment are likely to attract talented physicians to the area, which could increase the quality of healthcare in the region. Consideration should be given to the sustainability of such investments, in line with the scientific validity principle described by Emanuel et al. (2004). Issues related to management and transparency in the provision of equipment to sites would need careful monitoring and the implementation of strict guidelines governing how sites use such equipment to conduct research. Such measures would be necessary to prevent problems such as the onwards sale or misuse of equipment.

Many of the practical benefits identified in the literature review aligned with the advantages cited throughout this study, such as the availability of equipment and resources.

At one level, investments in infrastructure could potentially help address the issues that some respondents raised. However, a number of those challenges require investment at the macro-level, as opposed to comparatively smaller local economic investments. For example, ensuring that hospitals have constant electricity (as rolling blackouts in Sub-Saharan Africa are not uncommon) (Mbarika & Mbarika, 2006) and clean water are not issues that clinical research can readily address. Despite these broader challenges, progress can be made within clinical trials. Ensuring constant power is particularly important for clinical trials, as electricity is likely to be needed to power equipment, and not least to maintain adequate storage environments for biological specimens and investigational medicinal products (IMP). To address this issue, pharmaceutical companies could supply generators to guarantee constant power at clinical trial sites. Such an investment would have obvious benefits to hospitals upon the completion of research. Other factors, such as the complex and lengthy processes associated with the import of clinical trial materials and medication, are not uncommon in developing countries that have recently become more involved in clinical trials (e.g., Brazil) and are also likely to be a challenge (Thomson Reuters, 2014). Many times, this is due to bureaucracy and/or requirements for companies to bribe officials to ensure the release of their goods. A further discussion on corruption and unethical behaviour as ethical implications associated with clinical trial conduct follows later in this chapter in the section exploring the ethical implications of conducting clinical trials.

7.1.4 Educational benefits

One of the benchmarks in the conceptual framework described the need for research to facilitate the development of long-term research partnerships. The conduct of clinical research creates the potential for countries (as well as patients and researchers) in Sub-Saharan Africa to benefit from education at numerous levels. Health education interventions aimed at raising awareness of disease have proven valuable in both developed and developing countries, with initiatives that have focused on conditions such as rheumatic fever and cardiovascular diseases (Bach et al., 1996; Zühlke & Engel, 2013).

7.1.4.1 *Education at the community level*

Comments made during the interviews highlighted that when considered alongside Africa's disease landscape, clinical trials have significant potential in helping to raise awareness of diseases. Educating individuals on their condition and treatments options will open a dialogue between trial participants and members of their community, thereby promoting the dispersion of information. That outcome speaks directly to the need to enhance the value of research through the dissemination of knowledge.

The literature reviewed illustrated that industry-sponsored research in the region to date has focused on infectious diseases. This emphasis was also reflected in many of the studies included in the literature review. As highlighted during the interviews, part of the reason for concentrating on the treatment of infectious diseases was that these conditions are the most frequent recipients of publicity. Consequently, many programmes (e.g., educational initiatives and treatment efforts) are in place to tackle diseases such as malaria and HIV, but relatively few programmes have sought to address chronic diseases. In contrast, in the West, large charities focus on chronic diseases, such as heart disease and cancer. The stakeholder interviews also revealed that many of the studies in Sub-Saharan Africa that are not focused on infectious diseases are investigator-initiated. Another potential reason that efforts have historically focused on diseases such as malaria and HIV may be that the public in the West is less interested in fundraising for diseases associated with lifestyle choices than for infectious diseases.

At the community level, clinical trials can help raise awareness of diseases, which could potentially be beneficial in reducing morbidity and mortality, as the earlier detection of many diseases plays a critical role in treatment outcomes. Educating communities about clinical trials is also an extremely important component, particularly given the distrust of pharmaceutical companies harboured by some people in the region following incidences such as the Trovan trial in Kano, Nigeria (Jegede, 2007) and other historical examples of unethical clinical trials in Sub-Saharan Africa (SOMO & Wemos, 2008). The literature review discussed the use of VRs to engage and educate locals on clinical trials, as well as the use of formative research to refine clinical trial protocols to ensure their

appropriateness for the community in question. The use of formative research, while not raised by the participants in this study, is an important component of the Emanuel et al. (2004) framework of collaborative partnership and has links to respecting a community's values, culture, traditions, and social practices. Additionally, formative research also relates (although perhaps indirectly) to a separate benchmark related to involving the community in the process of establishing recruitment procedures and incentives, an activity that falls under the principle of informed consent.

7.1.4.2 *Education of those involved in the conduct of clinical trials*

A greater presence of the pharmaceutical industry and more clinical trials overall could lead to education of local communities about what clinical trials are, what they entail and why they are important. Trials could also help to dispel myths about medical research and misconceptions about what pharmaceutical companies are testing (as well as the reasons they are engaged in testing) and what happens to samples once collected. This is important, because there are common concerns about the theft of blood, trade in body parts, surreptitious birth control, and the deliberate spread of disease in some parts of Sub-Saharan Africa, as was highlighted via the systematic literature review. If trust is to be built with the community, avoiding a patronising attitude towards locals is essential, and consideration should be given towards the use of culturally sensitive methods to dispel misconceptions about what happens during a clinical trial. The uptake of this education is likely to be greater in an environment where clinical trials are happening versus in one where they are not.

Furthermore, a greater pharmaceutical company presence and the conduct of clinical trials could mean education for the professionals involved in that research (e.g., doctors, research nurses, and monitors). Those factors could also foster the collaborative partnership that Emanuel et al. (2004) described as a principle. As research opportunities become more prevalent, locals are more likely to undertake courses of education that allow them to be involved in clinical research as a career. That eventuality speaks to another benchmark, that of facilitating capacity development on the part of researchers and the local community. That could potentially boost the quality of both the research being conducted

and the overall practice of medicine, and provide a better understanding of research to clinicians (again strengthening, and not supplanting, the existing infrastructure and resources) and the general public. Clinical trials could also allow investigators to receive further education about treatment developments in their respective medical fields and to collaborate with, and learn from, investigators at other institutions, thereby fostering long-term research partnerships. Education related to clinical trial conduct will need to be incentivised, not least by situating clinical trials in the region. In the absence of actual trials, researchers would be acquiring knowledge and skills that they would subsequently not have an opportunity to use. Although one could argue that education is never wasted, the counterpoint is that putting training into practice would help reinforce new skills in a more tangible manner than classroom-directed learning.

In addition to the education of investigators and communities, trials may also have a role in educating and training ethics committees and competent authorities, as was discussed in the literature review. Work is clearly required to develop the research oversight infrastructure in many of the countries in the region. Research conducted by the African Malaria Network (AMANET) surveyed 31 ethics committees across Sub-Saharan Africa and identified a need for committee members to receive training on the scientific design of clinical trials, the determination of risks and benefits, and clinical research monitoring (Nyika et al., 2009). Such training could eliminate the need for parallel submissions in which sponsor companies simultaneously submit their protocol to internationally recognised review bodies and the review board in the intended country of research which would empower local communities.

7.1.5 Ethical benefits

It is difficult to separate ethical benefits from scientific, financial, medical, and practical considerations, as they are all linked. Numerous ethical considerations should be taken into account when considering the appropriateness of Sub-Saharan Africa's participation in clinical trials sponsored by industry. Clinical trials can potentially allow patients receive to medicines that they would not otherwise be able to access due to limited availability and prohibitive costs. This factor is arguably as much an ethical benefit as a scientific/medical or financial one. The subjective nature of ethics makes assessing and quantifying the

ethical value or benefit of clinical research a difficult task.

Much of this research can be captured in a single ethical question, namely: Is it right that patients in some parts of the world cannot access the treatments that pharmaceutical companies develop simply because they are poor? If it is not right, the next question regards identifying who is responsible for redressing the issue. While the results of this study do not provide a definitive answer, they do demonstrate that ethics and finance do not sit well together where large corporations are concerned. Further, the questionnaire results also indicated that the respondents did not feel it was right that patients in developing countries should die from diseases when treatments already exist as result of monetary reasons.

Unexpectedly, much of the cynicism and criticism levelled against the industry was internal (i.e., originating from some of the more senior pharmaceutical industry stakeholders), which potentially demonstrates a shift in the thinking of the industry as a whole. Comments made during the interviews suggested an underlying distrust of the industry, even from within that very sector. They also indicated further scepticism around the real intent of pharmaceutical organisations, which do have policies in place promoting the involvement, in some capacity, of developing countries. Several respondents disregarded any work that pharmaceutical companies were performing in developing countries as simply public relations exercises designed to paint the companies in a more favourable light in the public's eyes. Applying the standards outlined by Emanuel et al. (2004) is one method to ensure that regardless of the intent of pharmaceutical companies in engaging countries in the region in research, trials are conducted in an ethical way that is not simply self-serving. If the trials conducted in the region are designed for public relations reasons and the research is carried out according to necessary benchmarks, such activities are arguably not exploitative and are still useful to all stakeholders, as long as they are sustainable.

Comments were made that distinguished the pharmaceutical business model as unique and as therefore entailing a distinctive set of responsibilities to society and the greater good. Although specifics were not given, questionnaire responses pointed toward a belief that

health and healthcare will always demand additional social responsibilities. The pharmaceutical industry is unique from other large businesses, because its primary purpose is to make products to heal those who are ill, rather than to protect those who are not ill from harm.

Governments in some developing countries have taken steps to ensure that subjects who participate in clinical trials within their borders are not unnecessarily exposed to significant risks. For example, until 2005, Indian guidelines had restrictions around a drug's minimum phase of development prior to testing on Indian subjects, and those rules required a 'phase lag'. This meant that drugs needed to be tested in trials one phase behind the current phase at the global level. For example, a drug needed to be in phase III trials in the rest of the world for the Indian Council of Medical Research to allow a phase II trial to be conducted in that country (Bhatt & Lind, 2010). Another example of governments in developing countries taking steps to ensure that research participants are safe and that their wellbeing is protected is that of the Brazilian government. It requires either the study medication or gold-standard treatment to be provided to patients after their participation in a trial is complete for as long as medically necessary (Wang & Ferraz, 2012). While this latter requirement does have significant financial implications for pharmaceutical companies, from an ethical perspective, it guarantees that Brazilian patients who have volunteered to participate in a clinical trial receive the appropriate care and medication post-trial. Brazil's requirement for long-term treatment was raised during the interviews. It was felt that Brazil was a wealthy country capable of supplying medications for its population, instead of relying on trials to do so. This obligation stipulating the long-term provision of medicines is relevant in the context of the conceptual framework, as it would be difficult in such a situation to uphold the benchmark suggesting that the extant healthcare system not be supplanted or to argue that a model in which a company indefinitely assumes a patient's treatment costs is sustainable. While it may at first glance seem appropriate for wealthy pharmaceutical companies to provide access to long-term treatments, the provision of that care cannot be expected to come from pharmaceutical companies. Long-term or routine access to medicines should not be expected to come from commercial organisations, and one could argue that in the case of Brazil, the mechanism through which medicines should be supplied is being replaced which would be inappropriate in the context of the previously referenced benchmark.

7.2 Study Objective 2: Understand the ethical implications associated with research in Sub-Saharan Africa

The second objective of this study was to understand the ethical implications associated with conducting industry-sponsored clinical research in Sub-Saharan Africa. The conceptual framework outlined in Chapter 1 describes the necessity for ethical benchmarks and principles to govern the conduct of clinical trials in developing countries, although it does so at a broad level. The second goal of this study was to understand in precise terms what stakeholders saw as the most pertinent ethical issues in the context of industry-sponsored trials in Sub-Saharan Africa. Of note is the ‘industry-sponsored’ aspect of this study objective, as the ethical implications related to investigator- or NGO-initiated studies are likely to differ according to location (although overlap would be expected). A revised version of the Emanuel et al. (2004) framework specific to industry-sponsored clinical trials is presented later in this chapter. It makes the existing framework more relevant to those trials sponsored and conducted by pharmaceutical companies.

The ethical implications and considerations associated with conducting industry-sponsored clinical research in the region in both chronic and infectious disease areas are numerous. As was discussed in brief earlier, one finding of this study was that many of the stakeholders did not draw any real distinction between the issues or urgency associated with conducting research in chronic diseases versus infectious diseases. No real trends or themes emerged from either part of the study to suggest that the issues raised were more relevant to one disease type than to the other. For this reason, although the original objective was to explore considerations specific to chronic diseases, most of the issues are also applicable for studies on infectious diseases. Across stakeholder groups, the consensus opinion was that if a disease is relevant to a particular region, clinical trials should be conducted in that locale on the condition, regardless of whether it is chronic or infectious. Examples of this stance were evident throughout both the interview and questionnaire responses.

Some respondents across both parts of the study felt that for diseases for which patients can be easily be recruited for trials in the West, patients should be enrolled in the West and

that trials in Africa should not focus on such conditions. However, Africa was felt to be an appropriate location for trials on infectious diseases, such as Ebola or Dengue fever, that predominantly affect those in developing countries. The issues associated with conducting trials in the West on diseases that affect large numbers of patients in developing countries are multifactorial and complex. Some of these questions relate to perceptions of the pharmaceutical industry in developing countries and the industry's fear of being viewed as exploitative. The issue of exploitation is further discussed later in this chapter.

While higher levels of infectious disease in Sub-Saharan Africa may make the region appropriate for conducting clinical trials on those indications, it is important to note that the participants felt that chronic diseases should still remain a priority for research efforts in the region, even if not at the same level as infectious diseases.

7.2.1 Informed consent

One of the most frequently identified barriers to the involvement of Sub-Saharan Africa in clinical trials was informed consent. Emanuel et al. (2004) treated informed consent as its own principle with five associated benchmarks, highlighting its significance within clinical trials. Importantly for this region, where there is significant potential for a patient to be unduly coerced into a clinical trial, informed consent demonstrates that participating subjects have freely and willingly consented and that they understand they are free to withdraw from the trial at any time without their decision impacting the quality of their future care.

As interviewees across the stakeholder groups noted, one issue related to informed consent, particularly in developing countries, is that doctors enjoy a higher social standing than many other professions. As such, the possibility exists that patients are more likely to take actions that they believe that their doctor desires, including joining a clinical trial, and that they are also less likely to challenge their doctors' recommendations, do their own research, and/or seek a second opinion. These latter actions may be more common in Western countries. Patients often believe that their doctors are acting in their best interest, and so if their physician offers them the opportunity to take part in a clinical trial, they are

apt to believe that it represents the best option for them. This means that they are less liable to weigh the advantages and disadvantages of participating in a trial and to make a decision based on their own conclusion. That factor, in turn, gives patients a greater degree of susceptibility to coercion into a clinical trial by investigators keen to recruit clinical trial participants (for a variety of reasons, whether financial or otherwise). Although the issue of higher social standing is also true of HCPs in many Western countries, the situation, as was discussed during the interviews and demonstrated by the literature, is likely to be more evident in developing countries. In Western countries, similar scenarios emerge but are more likely with older or less-educated patients (Robertson, Polonsky, & McQuilken, 2014). Researchers have a responsibility to ensure that vulnerable populations are protected and that a population is chosen to ensure the validity of the research and not simply because it is agreeable.

Although the issue of higher social standing was not specifically raised in the questionnaire responses, comments suggested that the respondents felt it important that patients genuinely understand what consenting to participate in a study entails. This requires a certain level of maturity in the relationship between the investigator and the patient. This context may not be present in Sub-Saharan Africa, as the researcher-research subject relationship paradigm is fairly novel, particularly in chronic diseases that have not historically been the target of research. Physicians embarking on research will need to be mindful that this dynamic (which puts the patient in the role of a research subject) is a recent evolution in the doctor-patient relationship and ensure that the informed consent process takes that factor into consideration.

Issues with disparities in how informed consent is obtained in developing countries versus in the West were also raised during the interviews. In some more rural communities, it may be essential to engage a community or village leader in the research. That individual may need to provide consent on behalf of the village as a whole before its inhabitants can participate in the research. The role of this type of consent and its operationalisation were discussed by Krogstad et al. (2010), who described communal decision-making as common in many rural areas of Sub-Saharan Africa. In these communities, the consent process typically begins with presenting the study to the chief and village council. The

proposal is then discussed with progressively broader audiences: councils of male and female elders, heads of households, other individuals, and parents. Meetings with potential research participants only take place after approval has been granted by these individuals and groups on behalf of the community (Krogstad et al., 2010).

In certain ways, this may introduce issues similar to those described previously regarding the relationship between the investigator and the research participant. For example, if a community leader is approached to have his or her community participate in research and he or she approves that request, the candidates themselves may agree to participate in the research based on this higher-level consent, rather than because of a decision concerning the merits of the research being conducted. Further, they may not understand that the consent provided by the community leader is at one level, and that consent must also be taken from each individual participant. These cultural nuances should be taken into consideration when performing the informed consent process, but all stakeholders involved in clinical research must be aware of their existence. This particular issue touches on numerous benchmarks and requires cultural sensitivity, transparency, and a willingness to deviate from the processes observed in Western countries. Involving or implementing supplementary community and familial consent, where necessary or appropriate, is one of the benchmarks described in relation to the principle of informed consent. There is a much greater effort required on the part of the West to understand and accept the role that these cultural beliefs may play in the conduct of research. As was concluded by Napier et al. (2014) in their *Lancet* report on culture and health: ‘the systematic neglect of culture in health is the single biggest barrier to advancement of the highest attainable standard of health worldwide.’

Incorporating these cultural nuances into the informed consent process was a topic that was explored in greater detail in the questionnaire after the issue was raised by a number of the interviewees. The respondents did not generally agree that cultural factors should be taken into consideration when they do not comply with ICH GCP. These results may have been skewed by large number of respondents who were based in the West and consequently less sensitive to potential cultural differences and their importance in African communities. The results of the questionnaire suggested that GCP must take precedence over cultural norms

in the informed consent process. Further research exploring the attitudes of a larger number of all stakeholders is required to better understand how cultural norms should be integrated into the research process, particularly as regards informed consent. Exploring options for obtaining patients' consent while being sensitive to cultural norms is an important and potentially sensitive issue. Input (and potentially compromise) will be needed from all stakeholders to develop a process that does not compromise patients' rights and also satisfies the requirements of ethics committees and HCPs. These topics are less likely to be an issue when conducting research at large teaching hospitals in major cities, which may be a more appropriate place to begin conducting industry-sponsored research. This recommendation is further discussed in the next chapter.

Further concerns were raised around the 'who' in the consent process were related to gender equality and societal norms in cultures where men make decisions on behalf of females. This arrangement adds another problematic dimension, since consent is not granted by the patient herself, but by her husband or another male family member. In such a situation, proper communication plays a key role in explaining written consent (Dawson & Kass, 2005).

Lower levels of literacy and access to education are issues that are also likely to impact the informed consent process in developing countries. Although levels of literacy in Sub-Saharan Africa are increasing (African Library Project, 2013), the region still lags behind the rest of the world. The issue of obtaining consent from illiterate individuals is not exclusive to this part of the world. In developed countries, there are still concerns around the informed consent process for patients who are unable to read. The best way to address this challenge lies in delivering the information in whatever way is most digestible for patients. In the West, solutions to acquiring these patients' consent include the use of audio-visual materials to ensure that patients understand what participation in the study will entail. That strategy also provides patients with the right of refusal, which is required as part of ICH GCP (Flory & Emmanuel, 2004). Similar locally adapted approaches could potentially be used in Sub-Saharan Africa.

7.2.2 Corruption and unethical behaviour

None of the studies referenced in the literature review raised the topic of corruption on the part of pharmaceutical companies as an issue. This may be due to the fact that only a handful of studies featured respondents who had participated in industry-sponsored trials as either researchers or participants.

Corruption was mentioned in both the interviews and the questionnaire responses and is therefore widely understood to be a significant concern. Many respondents made clear that corruption is not a challenge exclusive to Africa, but rather a risk to which resource-poor countries and those living or working within them are much more likely to be susceptible. Much of the concern around the pharmaceutical industry's behaviour is not without foundation. There are historical cases illustrating how poorly pharma has conducted itself in both minority populations in the West and developing countries in Sub-Saharan Africa and elsewhere. Examples include the surfactant trial in Latin America (Charatan, 2001); the Trovan (trovafloxacin) trial that took place in Kano, Nigeria; and the Boehringer Ingelheim nevirapine HIV trial in Uganda (SOMO & Wemos, 2008). As a result of this negative publicity, HCPs and patients have expressed fears that pharmaceutical companies will use subjects from countries in this region as bodies for collecting data and targets for product marketing without providing due care and attention. The concern around unethical behaviour is not simply that pharmaceutical companies would behave unethically if more industry-sponsored clinical trials were conducted in Sub-Saharan Africa but also that companies would be perceived as exploitative simply by carrying out research in that part of the world. Some respondents suggested that being considered to have behaved unethically is potentially just as damaging as having actually done so. Despite the general lack of experience working in Sub-Saharan Africa, the pharmaceutical stakeholders made remarks related to the prevalence of corruption in Sub-Saharan countries. In most cases, these perceptions of corruption as endemic in the region could not be substantiated through personal experience but were based on opinion and media influence. This point is important, as it speaks to the critical role that perception plays in shaping the views of individual stakeholder groups.

In relation to the pharmaceutical industry's behaviour in the region, most respondents were neutral as to whether pharmaceutical companies would behave poorly if they conducted more research in Sub-Saharan Africa. This neutral response could, however, be an artefact of the sample's skew towards respondents from the pharmaceutical industry. At the time the questionnaire was created, the question about GCP observance was intentionally left vague (i.e., a definition of non-compliance was not given to allow for as broad a spectrum of responses as possible). Although not explicit, the aim of this question was to get a feeling for wilful GCP non-compliance on the part of pharmaceutical companies. However, with the benefit of hindsight, a more specific definition would have made the question clearer and could potentially have changed some responses. At present, the environment is not as closely regulated or as mature in its oversight infrastructure as in countries in the West, and that situation creates a possibility for pharmaceutical companies or individuals within these organisations to exploit the region's inhabitants in several ways, not least in the form of poorly designed trials.

The subjective nature of ethics implies a number of difficult questions, all of which need to be part of prospective cross-stakeholder discussions before trials begin. For instance, companies could inadvertently find themselves being castigated for unethical behaviour simply for setting up a trial in a country where treatment alternatives (other than the intervention to be tested) do not exist. The presence of clear, mutually agreed-upon criteria (similar to Emanuel et al.'s [2004] benchmarks) allowing for assessments of a study's appropriateness may potentially help in determining whether trial designs are acceptable. The availability of medicines post-trial is not the only criterion by which research should be judged when gauging its social value and suitability; even when medicine is not available post-trial, a study may still have significant value. Further consideration needs to be given to situations in which a clinical trial provides the only means of accessing a particular treatment. In particular, questions will need to be asked about what influence or bearing such a situation has on potential subjects' ability to truly and freely provide consent.

There was further concern regarding the possibility of pharmaceutical companies withholding or altering their study results to make them more favourable. To ensure that

research is not exploitative, approving bodies will need to apply pressure to guarantee that results are shared irrespective of outcome and in a way that is understandable and relevant to the population in which the treatment was tested. Comments highlighting the pharmaceutical industry's reticence in sharing trial results were substantiated through searches of clinical trial databases, which indicated a greater number of trials that had been registered and marked as complete than of trials for which results had been posted (National Institute for Health, 2017).

A detailed discussion on the levels of corruption that exist across the various stakeholder groups involved in conducting clinical trials would be beyond the scope of this research. However, tackling the root causes of corruption at all levels will be a key factor in driving forward clinical research in Sub-Saharan Africa (Egharevba & Atkinson, 2016).⁹ The reputations of multinational pharmaceutical companies are often scrutinised to a greater degree than those of multinational companies in other industries, especially when the developing world is involved. Perceived unethical behaviour on the part of pharmaceutical companies has the potential to do substantial reputational damage to those firms. To this end, some companies see the risk of being involved in research in these parts of the world as greater than the potential benefits to their business operations.

The results demonstrated that the respondents were split in terms of their opinions about whether companies were hesitant to conduct trials in the region because of concerns around reputational damage. The findings highlighted fears that the pharmaceutical industry is not viewed favourably by the public in this part of the world and that further research in this region would therefore pose too great a risk for pharmaceutical companies. In particular, the respondents indicated that such research could lead to further damage to a company's reputation, brand, and image which companies invest significant resource into building, maintaining and protecting.

Overall, the results indicated that corruption (perceived or actual) may be a factor contributing to the dearth of trials in Sub-Saharan Africa to date. If corruption is a factor as

⁹See Appendix 19

regards members of IRBs and/or competent authorities, the validity of independent review—another important principle described in Emanuel et al.'s (2004) framework—is undermined. The problems associated with corruption in Africa have been described throughout the literature. Of the 10 most corrupt countries, as defined by the 2014 Transparency Index, 5 are in Africa (Transparency International, 2014). Additionally, according to the Council for Foreign Relations, a 2002 African Union study estimated that corruption cost the continent roughly \$150 billion a year. In comparison, developed countries gave \$22.5 billion in aid to Sub-Saharan Africa in 2008, according to the Organisation for Economic Cooperation and Development (Hanson, 2009). Corruption is thought to be one of the most significant factors that has precluded Africa's growth and development to date (Munyae & Lestedi, 1998; Collier, 2006). Even if the actions deemed corrupt are considered in accordance with cultural or societal norms, where ethics are of such paramount importance, the consequences of unethical behaviour could have serious implications. There will arguably be a need to move slowly and to compromise in some instances. In the absence of a universally accepted definition of what is considered corrupt, it will be important for all relevant stakeholders, as part of a larger discussion to define criteria or benchmarks for what comprises corruption. That discussion will also need to make clear the levels of transparency and accountability required across all stakeholder groups.

Issues such as fraud, non-compliance, and misconduct are frequently reported in developed countries. The self-reporting systems that exist in developed countries, such as the serious breach reporting system in the United Kingdom (a mechanism for organisations to report serious breaches of GCP [Medicine and Healthcare products Regulatory Agency, 2014]) indicate that compliance with GCP can be difficult for investigators of all experience levels and in all countries. Not all breaches that are reported by experienced sites in developed countries are intentional, and if trials are to be run in developing parts of the world, it will be important to remember that this is likely to be the case in those regions as well. As such, it will be essential to ensure that self-reporting mechanisms are available to researchers in this part of the world. However, it will be vital for those investigators to be able to use those systems without the risk of punishment or the fear of being deemed incompetent.

In addition to the potential for pharmaceutical companies to misbehave, equally important is the potential for investigators to unfairly consent patients to participate in a study that is not appropriate for them, compromising the principles of informed consent and respect for recruited participants and study communities. Such a breach could happen for a number of reasons, many of which relate to money. For instance, investigators may try to recruit large numbers of patients into a trial for personal or institutional financial gain. Additionally, pharmaceutical companies often include high-recruiting investigators as authors of peer-reviewed scientific papers, which can lead to increased visibility and potential financial gain through enhanced employment opportunities. Further pressures regarding promotion and tenure, competition amongst investigators, the need for recognition, ego, personality factors, and conflicting personal and professional obligations are all factors that could prompt certain individuals to become involved in fraud or scientific misconduct (Gupta, 2013). All of these drivers of fraudulent behaviour or misconduct are equally relevant for investigators involved in studies in the West. Nevertheless, these factors are arguably likely to be more of an issue in Sub-Saharan Africa and other developing countries.

As part of the wider discussion, it will be important to understand the drivers of intentional fraud and to address these at the most basic levels. Doing so will likely pose a significant challenge for all involved, as the issues relate to systemic and historical matters that go beyond clinical research and that need to be addressed at the macro-level. High levels of transparency around investigator payments and a greater level of accountability should be put into place for investigator sites in countries displaying evidence of high levels of corruption (e.g., as measured by the Transparency Index). Education will be key in preventing both intentional and unintentional misconduct on the part of investigators and hospital site staff, as will be the introduction of policies to ensure adequate penalties (and in the worst cases, debarment) disincentivising such behaviour.

Within governments, regulatory authorities and ethics committees tasked with ensuring only the strictest ethical standards are employed in both the design and conduct of clinical trials may also be involved in unethical behaviour, particularly bribery. This possibility was raised by a pharmaceutical interviewee who alluded to requests from regulatory authority individuals for payments in return for study approvals. In certain ways, this

situation has the potential to be most damaging for patients in the region, as bribes could lead to ethics committees or competent authorities granting approval to trials with poorly conceived or unethical designs and/or could lead to the inadequate regulation of trials. Such behaviour has the potential to affect a considerable number of patients (when country-level approvals are in question) and could create doubts regarding the appropriateness of trial designs in terms of their scientific validity, fair selection of study populations, and ‘independent’ review.

It is important for pharmaceutical companies to maintain the trust of the public. This should not, however, come at the expense of the greater good. The need for education at numerous levels has been a recurring theme interwoven through all parts of this research, and the education of the public in developed countries is another example. It was argued that pharmaceutical companies cannot neglect their global responsibilities out of the fear of reputational damage or the desire to preserve their public image, although there was an appreciation that reputational damage is closely linked to financial consequences and is therefore a sensitive issue. Educating the public in the West about the conduct of research in the region and the safety measures put in place to protect these patients creates a greater sense of transparency. When done correctly, such education could be one way of preventing any reputational damage to individual pharmaceutical companies or the industry as a whole. Efforts aimed at education and public awareness should ideally be implemented proactively, and not as a response to allegations, as so often occurs. More importantly, pharmaceutical companies need to ensure that their clinical trials are ethical and that they complete the proper ethical and regulatory review process. In addition, the industry must make sure that those bodies maintain oversight of the trials in this region. This means that protocols for studies intended for developing countries should take into account the specific ethical issues that could impact their conduct, including the provision of medicines post-trial, comparator drugs and the use of placebo, and reimbursement (Egharevba & Atkinson, 2016).¹⁰ All of these topics are important factors to consider in the design of ethical research for developing countries. However, a detailed discussion of each would be beyond the scope of this thesis.

¹⁰ See Appendix 19.

7.2.3 Provision of medicines post-trial

The provision of medicine post-trial is a significant challenge that has precluded the placement of clinical trials in developing countries for a significant period of time.

Respondents brought up the issue of the availability of medicines post-trial as critical in determining the appropriateness of placing a trial in Sub-Saharan Africa. In raising this point, those participants argued that the results of a clinical trial should benefit patients in the community in which that trial took place after the research is complete, in line with principles described in the conceptual framework. Therefore, the respondents contended that if a drug will not be available to a community following the trial (assuming it is proven to be safe and efficacious), then people in that region should not be involved in the research. This line of reasoning was in agreement with work conducted by Schulz-Baldes et al. (2007) suggesting that it is unethical for study participants in resource-poor settings to assume the risks of research, sometimes for little individual benefit, when patients in wealthier countries are the primary beneficiaries of the results. Participants also agreed with Macklin's (2004) argument that the risk of exploitation is particularly elevated when sponsors or investigators from wealthier countries conduct research in resource-poor settings. Those who agreed indicated that they did not believe it was appropriate to perform clinical trials if a drug will not be commercially available following the trial or if the drug or intervention will be priced in a manner that makes it generally inaccessible to the local community. It is worth clarifying that commercial availability does not necessarily mean that a drug is accessible to the majority of the population, as making a drug available and ensuring affordability are two different matters. The Emanuel et al. (2004) framework contains no explicit requirement for a drug to be made available post-trial, and one could claim that if a trial brings significant investment into infrastructure and other collateral benefits, then guaranteeing post-trial drug availability is less of an issue.

Post-trial access to medicines is multifaceted and requires consideration of a number of topics. The first regards whether the tested drug will be made commercially available in the country where the research is conducted, assuming it is successful in clinical trials. The second issue is that supposing the answer to the aforementioned question is 'yes', the question remains as to who will pay for it. In some clinical trials, a new intervention or

medication is tested against a placebo, and in other cases where an existing treatment is already available, the medication is tested against the existing option (oftentimes referred to as ‘gold standard’). According to some respondents, if neither the investigational treatment nor the active comparator is commercially available in a particular country, then there is no justification for conducting a trial there. However, many also claimed that trials should take place if a disease is relevant to the region, which raises questions about what should be done if a condition is pertinent to a country (and most will be) but the company does not intend to sell the drug in that country because of commercial considerations. In such instances, should a few be granted access through participation in a clinical trial, or should the drug not be available to anybody? The literature raised another related issue, asking whether patients should remain on the active comparator at trial end if it would not normally be available for them to purchase, and if so, how that process should be managed. This is particularly relevant for chronic diseases, which generally have a longer treatment duration, and therefore, higher costs.

The Declaration of Helsinki mandates that in advance of a clinical trial, sponsors, researchers, and host-country governments should make provisions for post-trial access for all participants who still need the intervention being tested if that intervention is found to be beneficial in the study (World Medical Association, 2013). The problem this stipulation poses for many pharmaceutical sponsors is that it introduces a significant financial burden that can in time reduce the cost savings realised by conducting trials in ‘less expensive’ regions. In providing lifelong medications to patients, pharmaceutical companies are committing themselves to costs for which they might remain responsible for long after a patient’s participation in a trial has finished. This continued provision of medicine can be costly, particularly as regards chronic diseases. Such illnesses can last for much longer than infectious diseases and may require daily treatment. In diseases such as cancer with treatments that can often cost thousands of pounds per patient treatment year, the financial implications become even more difficult to justify. As a result, many sponsor companies choose to refer to earlier versions of the Declaration of Helsinki (e.g., the 1989 iteration) that do not include these requirements regarding the provision of medicines to patients post-trial. Companies can make that choice, as there is no legal requirement to reference a specific version of the guidelines (Wolinksi, 2006).

Many respondents who were interviewed referred to the provision of IMP post-trial as a key issue as regards the involvement of developing countries in clinical trials. It was also identified as a barrier that has precluded clinical trial work in the region to date. The respondents left very few comments on how they felt that the issue should be addressed and whether sponsors are the ones responsible for providing medicine after a patient's trial participation had ended. When patients have participated in a clinical trial investigating the effectiveness of an intervention against an infectious disease that is found to be safe and effective, or when a trial has compared a new treatment against an active comparator or placebo, one option is for all participating patients to receive the active comparator for as long as it is effective in controlling their disease. The results of this research suggest that HCPs agree that putting a trial participant on an effective medication (whether the medicine under investigation or the comparator) and subsequently removing that treatment without providing an alternative is not ethical. Emanuel et al.'s (2004) omission of such a key topic is important, as it may suggest that there is not a 'one-size-fits-all' solution that can be applied to this problem. Additionally, further consideration would need to be given to the fact that patients would need to enrol in a clinical trial to receive the drug and to questions of how that could impact their ability to freely provide consent.

The requirement to provide medicine post-trial is less clear-cut for chronic diseases than for infectious diseases. Research and healthcare should not be confused with each other, and some argued that partial responsibility for treating patients should lie with the governments and healthcare systems in these patients' home countries (as noted in the conceptual framework). The issue of providing medicines that would not normally be available to patients following their participation in a trial is even more sensitive. It was suggested that involving countries in more clinical research should not mean pharmaceutical companies bearing the costs of patient care indefinitely, as such an arrangement would potentially run the risk of replacing existing healthcare systems and mechanisms for treatment distribution. It would also make collaborative research in this part of the world unsustainable, as a study's benefits for the healthcare system cannot be expected to continue beyond a reasonable timeframe. As was suggested by interviewees, the decision as to what is reasonable should perhaps not be addressed with a 'one-size-fits-all' approach. Rather, it should be made on a case-by-case basis by taking into consideration the type of disease being treated and the prognosis of treated patients.

Discussions of this approach should include input from all stakeholders concerned to ensure that benchmarks regarding collaborative partnership are mutually agreeable.

Issues related to the availability of medicines and the associated conduct of clinical trials in a particular region have split opinion for some time. In the past, the ethical acceptability of conducting research in poorer countries was primarily framed around how responsive the research was to the health needs and the priorities of the population or community involved. There was also a requirement that a proven intervention be made available to participants and the community after the study, and at reasonable costs (Council for International Organizations of Medical Sciences, 2002). However, as outlined in a paper by Schulz-Baldes et al. (2007) addressing the collateral health benefits of research, these guidelines' primary focus on 'reasonable availability' was criticised as both too narrow and conceptually misleading by an international working group convened in 2001 by the United States National Institute of Health and the University of Malawi (Participants in the 2001 Conference on Ethical Aspects of Research in Developing Countries, 2002). The group proposed a broader framework of 'fair benefits' including not only the medical treatment of participants during the study and the availability of the proven intervention afterwards, but also public-health measures, employment and economic activity, capacity development, and financial rewards. This is an arguably more robust way of analysing the benefits of clinical research that may make assessing the ethical appropriateness of individual trials more straightforward.

7.2.4 The pharmaceutical industry's responsibilities to patients globally

Interview respondents across all stakeholder groups believed that the pharmaceutical industry does have an ethical responsibility to conduct clinical trials in Sub-Saharan Africa. This finding was later confirmed through the responses to the questionnaire. One could argue that the questions regarding whether the pharmaceutical industry has an ethical and scientific responsibility to patients in the region were the two most important survey questions, as many of the other items were related to *how* pharmaceutical companies should conduct trials in the region but not *if* they should do so. In the absence of any obligation or rationale for conducting trials in developing countries, many of the issues identified as part of this work are largely redundant.

Despite the majority of the questionnaire respondents belonging to the pharmaceutical stakeholder group, most believed that pharmaceutical companies have an ethical responsibility to conduct research in poorer countries. Respondents felt that the responsibility to do so is greater when a plan exists to sell the drug in those countries. In support of their position, these participants stated that they felt it is unethical to sell a drug to a population in which it has not been tested in light of the various genetic factors that can influence how a drug is metabolised by patients from different ethnic backgrounds. Exposing patients to medicines that are not well researched and that are therefore poorly understood in patients of a particular genetic make-up was thought to be unethical. This is one example of where ethical and scientific arguments for the conduct of trials in the region meet.

Participants also argued that if companies are planning on making money by selling a drug in a particular region, then it is unethical to market that product without having conducted research in that area. It is possible/probable that the push towards requiring pharmaceutical companies to provide empirical evidence of how their drugs work in different populations will need to come from regulators. At present, many countries in Sub-Saharan Africa are not seen as commercially relevant, and as such, requirements of this nature by governments in that part of the world are likely to have the opposite effect of what is desired. That is, restrictions on selling medicines untested in patients of a particular background are likely, in the short-term, to drive companies away from conducting research in the region, as the expenditures and resources required at this stage to involve patients in Sub-Saharan countries are likely to outweigh the benefits in the short-term. The push for data from various sub-populations will need to come from regulators in more developed countries where there is a greater commercial incentive for pharmaceutical companies to comply with requirements, such as the United States.

Not all of the research participants felt, however, that it is the pharmaceutical industry's responsibility to develop infrastructure in developing countries through conducting clinical trials within their borders. A number of the survey respondents felt that the sector's responsibility lies in the development of medicines, and not regions. Some argued that

government organisations need to take responsibility for ensuring that adequate investment is directed to healthcare and capacity-building to attract research and that responsibility and accountability cannot, and should not, lie with the pharmaceutical industry. There was, however, an appreciation from many respondents that the pharmaceutical industry has a challenging job in terms of balancing its philanthropic responsibilities with the need to generate profit for shareholders.

Although most of the research participants believed that pharmaceutical companies do have an ethical responsibility to involve Sub-Saharan Africa in clinical trials, they felt that such research should only take place in countries with sufficient oversight, expertise, infrastructure, and resources to protect all of the participating trial subjects. Conducting trials in the absence of these key requirements would be unethical and would compromise the safety of potential patients, as well as the validity of any data generated.

7.3 Revised framework for industry-sponsored trials

As this research clearly indicated that pharmaceutical companies have an ethical responsibility to conduct clinical trials in developing regions, a slightly modified version of the Emanuel et al. framework intended specifically for pharmaceutical companies has been developed based on the findings of this study. The framework (presented in Table 13) builds on the principles described by Emanuel et al. but offers slightly modified benchmarks more tailored toward industry-sponsored trials in Sub-Saharan Africa (or other developing countries).

| Principle | Original Benchmark | Revised Benchmark |
|-----------------------------|--|--|
| “Collaborative partnership” | “Develop partnerships with researchers, makers of health policies, and the community” | <i>Develop partnerships with researchers, makers of health policies, regulators, communities, hospitals, and ethics committees</i> |
| | “Involve partners in sharing responsibilities for determining the importance of health problems, assessing the value of research planning, conducting and overseeing research and integrating research into the healthcare system” | <i>Allow partners to take the lead in determining the importance of health problems, assessing the value of research planning, conducting and overseeing research, and integrating research into the healthcare system</i> |
| | “Respect the community's values, culture, traditions, and social practices” | <i>Understand and respect the community's values, culture, traditions, and social practices, and understand where research practices may differ to accommodate these</i> |
| | “Develop the capacity for researchers, makers of health policies, and the community to become full and equal partners in the research enterprise” | NO CHANGE |
| | “Ensure that recruited participants and communities receive benefits from the conduct and results of research” | <i>Solicit guidance from local communities</i> <i>Ensure transparency with regard to what the benefits of research participation are for all concerned</i> <i>Ensure that recruited participants and communities receive benefits from the conduct and results of research through active tracking and accountability measures</i> |
| | “Share fairly financial and other rewards of the research.” | <i>Be explicit and transparent, and share financial gains and other rewards of the research in a fair manner</i> |
| “Social value” | “Specify the beneficiaries of research” | <i>Specify the benefits and beneficiaries of the research across all relevant stakeholder groups</i> |

| Principle | Original Benchmark | Revised Benchmark |
|-----------------------|---|---|
| | “Assess the importance of health problems being investigated and prospective value to participants” | <i>Assess the importance of the health problems being investigated, both commercially and medically</i> <i>Commit to understanding if treatments may require modifications in terms of doses or treatment schedules based on the setting</i> |
| | “Enhance value of research through dissemination of knowledge, product development, long term research partnerships and / or health system improvements” | <i>Enhance the value of research through increasing transparency, facilitating the researcher-led dissemination of knowledge, product development, long-term research partnerships, and/or health-system improvements</i> |
| | “Prevent supplanting the extant health system infrastructure and services” | <i>Empower local healthcare providers, ethics committees, and regulatory authorities, and grant reasonable amounts of autonomy</i> <i>Ensure that efforts are complementary and sustainable without absolving health systems of their duty to their population</i> |
| “Scientific validity” | “Ensure that the scientific design of the research realizes social value for the primary beneficiaries of the research” | <i>Ensure that the scientific design of the research is appropriate and realises social value for the primary beneficiaries of the research</i> |
| | “Ensure that the scientific design realizes the scientific objectives whilst guaranteeing research participants the healthcare interventions to which they are entitled” | NO CHANGE |
| | “Ensure that the research study is feasible within the social, political, and cultural context or with sustainable improvements in the local health-care and physical infrastructure” | <i>Ensure that the research study demonstrates respect and feasibility within the social, political, and cultural context or that it offers sustainable improvements in the local healthcare and physical infrastructure</i> |

| Principle | Original Benchmark | Revised Benchmark |
|--------------------------------------|--|--|
| “Fair selection of study population” | “Select the study population to ensure scientific validity of the research” | <i>Select the study population to ensure the scientific validity of the research, appreciating the local disease landscape and modifying study designs to accommodate these (e.g., medical history, previous exposure to concomitant medications)</i> |
| | “Select the study population to minimize the risks of the research and enhance other principles, especially collaborative partnership and social value” | NO CHANGE |
| | “Identify and protect vulnerable populations” | <i>Identify and protect (without excluding) vulnerable populations</i> <i>Solicit local guidance on appropriate methods of doing so</i> |
| “Favourable risk-benefit ratio” | “Assess the potential risks and benefits of the research to the study population in the context of its health risks” | <i>Assess the potential risks and benefits of the research to the study population in the context of its health risks, and ensure mechanisms are in place to address unavoidable risks</i> |
| | “Assess the risk-benefit ratio of comparing the net risks of the research project with the potential benefits derived from collaborative partnership, social value, and respect for study populations” | <i>Under the guidance of local ethics committees and researchers, assess the risk-benefit ratio of comparing the net risks of the research project with the potential benefits derived from collaborative partnership, social value, and respect for study populations</i> |
| “Independent Review” | “Ensure public accountability through reviews mandated by laws and regulations” | <i>Ensure public accountability through reviews mandated by laws and regulations, including local policymakers, but deferring to globally accepted standards where local regulations do not go far enough in protecting subjects</i> |
| | “Ensure public accountability through transparency and reviews by other international and non-governmental bodies, as appropriate” | <i>Ensure public accountability through transparency and reviews by other international and non-governmental bodies as appropriate, while avoiding taking a paternalistic approach</i> |

| Principle | Original Benchmark | Revised Benchmark |
|---|--|--|
| | “Ensure independence and competence of reviews” | <i>Ensure the independence and competence of reviews across stakeholder groups</i> |
| “Informed consent” | “Involve the community in establishing recruitment procedures and incentives” | <i>Be led by the community in establishing recruitment procedures and incentives that are appropriate to the community engaged</i> |
| | “Disclose information in culturally and linguistically appropriate formats” | <i>Disclose information in culturally and linguistically appropriate formats</i> |
| | “Implement supplementary community and familial consent procedures where culturally appropriate” | <i>Implement supplementary community and familial consent procedures where culturally appropriate. and develop mechanisms for ensuring ongoing consent</i> |
| | “Obtain consent in culturally and linguistically appropriate formats” | NO CHANGE |
| | “Ensure the freedom to refuse or withdraw” | <i>Ensure that the freedom to refuse or withdraw is communicated appropriately in culturally and linguistically understandable ways</i> |
| “Respect for recruited participants and study communities” | “Develop and implement procedures to protect the confidentiality of recruited and enrolled participants” | <i>Develop and implement procedures to protect the confidentiality of recruited and enrolled participants, while considering the potentially insular nature of smaller communities</i> |
| | “Ensure that participants know they can withdraw without penalty” | <i>Ensure that participants are informed that they can withdraw without penalty in ways that are culturally and linguistically appropriate</i> |
| | “Provide enrolled participants with information that arises in the course of the research study” | <i>Provide enrolled participants with information that arises in the course of the research study in culturally and linguistically appropriate ways</i> |

| Principle | Original Benchmark | Revised Benchmark |
|-----------|--|---|
| | “Monitor and develop interventions for medical conditions, including research-related injuries for enrolled participants at least as good as existing local norms” | <i>Monitor and develop interventions for medical conditions, including research-related injuries, for enrolled participants that are at least as good as existing local norms, and better than local norms if considered appropriate to do so locally</i> |
| | “Inform participants and the study community of the results of the research” | <i>Inform participants, the study community, and the wider scientific community about the results of the research in a way that is understandable and that involves and empowers local researchers</i> |

Table 13: Suggested revisions to the Emanuel et al. (2004) framework specific to industry-sponsored clinical trials

7.4 Raising awareness of chronic diseases in Sub-Saharan Africa

It was hoped the one consequence of performing this research and engaging stakeholders from various backgrounds would be greater awareness of the increasing levels of chronic disease in Sub-Saharan Africa.

Across all three parts of the study (i.e., the literature review, interviews, and questionnaire), there was a general appreciation, even from those not based in the region, that chronic diseases are on the rise in Sub-Saharan Africa and many other developing parts of the world. The literature makes clear that levels of chronic diseases in the region are increasing at a worrying rate, although lack of data has meant that the prevalence of chronic diseases is still not well understood in many countries in that area. Although the increase in chronic disease is not isolated to developing countries, it has the potential to have the most significant ramifications for countries in developing regions, many of which have inadequate healthcare systems (due to a lack of funding) and lack the infrastructure and resources necessary to tackle such an epidemic.

The increase in chronic disease levels and the associated implications for the region were best understood by the HCPs and the single regulatory stakeholder, all of whom were based in either Ghana or Nigeria during the interviews. Very few of the stakeholders from the pharmaceutical industry had put much thought into the rising levels of chronic disease in the region but understood how it could be of concern. The pharmaceutical stakeholders who responded to the questionnaire appeared to be more sensitive to the changing disease landscape in the region than those who participated in the interviews. This could simply be due to the larger number of respondents engaged through the questionnaire. It was noted that those stakeholders who were not based in Sub-Saharan Africa knew considerably less about this evolution of the disease landscape as compared to those who were in the region. Although these observations are somewhat anecdotal, they highlight the need for greater awareness regarding this topic. With the benefit of hindsight, it would have been better if understanding the impact of clinical research in chronic disease indications could have been captured and formalised as an objective.

Naturally, other factors could have played a role in the fact that only those comments from

the HCP and regulatory groups demonstrated a familiarity with the disease landscape. For example, the questionnaire was internet-based, meaning that the respondents could perform searches for information on the prevalence of chronic diseases (and other topics) in parallel with questionnaire completion to inform their responses. However, even if that occurred, simply raising the issue of chronic disease levels with participants in both parts of the study created an awareness of the disease landscape, specifically as regards non-communicable diseases. Such knowledge was lacking within the pharmaceutical stakeholder group prior to its participation in this research.

7.5 Strengths and limitations of the study

The following sections discuss the strengths and weaknesses of the study's design, conduct, and data collection process. Moreover, they consider what could have been done differently to strengthen the study.

7.5.1 Strengths

7.5.1.1 Multimethods

The multimethod approach was one of the study's strengths. This approach allowed for a broader set of questions and findings to be investigated than by taking a single qualitative or quantitative approach. The use of non-concurrent research methods allowed for the outcome of one research method to inform the development and implementation of the subsequent one. In practical terms, this approach meant that only those issues that were raised and identified in the interviews the most often were considered and incorporated in the latter part of the study (i.e., the questionnaire). The order and timing of the interview and questionnaire study components allowed for important themes and issues to emerge and inform the survey's development. Had this approach not been taken, the questionnaire would have been driven by the issues identified from the literature review alone. The use of free-text fields within the questionnaire also allowed for the capture and analysis of qualitative responses from those who were not included in the interviews.

7.5.1.2 *Interviews*

The biggest benefit of employing qualitative methods is that they allowed stakeholders to identify what they believed to be the most relevant issues related to the research topic, and to do so in their own words. Given the complexity of the topic and associated issues, the qualitative interviews also facilitated more detailed questioning and gave the participants the opportunity to qualify statements with detailed examples. Additionally, the informal setting in which most of the interviews took place (many interviews were conducted out of working hours while the interviewees were at home) may have been a contributing factor to the participants being more candid and honest in their responses to potentially sensitive questions. Conducting the interviews out of normal working hours also meant that the respondents could not be overheard by colleagues, and additionally, that their co-workers did not know that they were participating in this research study. A more formal setting could potentially have made the participants feel as though they needed to respond in a more formal manner and could have led to less open and honest responses in an attempt to be more politically correct. The semi-structured nature of the interviews also provided a degree of structure and direction to the interviews, without being so prescriptive and inflexible as to preclude the ability to collect a robust set of opinions.

7.5.1.3 *Questionnaire*

Using an online questionnaire meant that surveys could be completed quickly and easily at the convenience of the respondents. The ability to send out a link, as opposed to a hard-copy questionnaire, also allowed for greater uptake of the survey through a snowballing strategy and permitted a larger number of stakeholders to be engaged. The time required to collect and analyse the questionnaire data was less than that needed for the interview-based part of the research. Evaluating the quantitative outputs from this study allowed better understanding the significance of previously raised issues for a larger number of stakeholders within a short period of time. Identifying how a larger number of respondents perceived issues identified as important in certain respects also served to validate earlier findings. Lastly, using software with robust reporting capabilities allowed for the tracking of progress and meant that an analysis of metrics could be performed quickly and easily.

7.5.1.5 *Respondent population*

Although the large representation of the pharmaceutical industry meant that there was potential bias in the overall outcome of the study, it was also a strength, as one could argue that ultimately, decisions on whether industry-sponsored clinical trials will take place in Sub-Saharan Africa will come from this stakeholder group. Stakeholder groups trying to attract industry-sponsored research to the region could use the results of this research to acquire an informed and clear understanding of potential issues, as perceived by those working within the pharmaceutical industry. This knowledge may potentially allow them to be more effective in their efforts to engage pharmaceutical companies in discussions on particularly relevant topics.

7.5.2 Limitations

7.5.2.1 *Interviews*

One of the limitations of the study was the low number of interviews, which were conducted with a restricted group of stakeholders. A higher number of interviews with a more varied group of stakeholders based in the countries of interest might have been achieved either by travelling to those countries (which would have been prohibitively expensive) or recruiting a local interviewer. However, regardless of whether the interviewer came from a drug company, was based in the West, or was local, the possibility would exist of that individual being seen as biased in some way by different groups. Additionally, bias arose from an overrepresentation of pharmaceutical respondents. Consequently, the questionnaire results are largely an assessment of the pharmaceutical industry's attitude toward research in Sub-Saharan Africa.

Another limitation recognised in the research was the way in which certain interviewees, particularly those in the HCP group, were identified. Those candidates were mainly identified through the review of academic journals and snowballing, and as such, all of the HCP interviewees had at least some interest in research. It would have been preferable to have had a mixed sample of HCPs from the region (i.e., those with and without research interests). However, many of the contacted HCPs who were not identified through academic journals or snowballing techniques (e.g., through internet searches) did not

respond to requests to participate in an interview. The outcome of this research may have been different if the HCPs identified in both Ghana and Nigeria did not have an interest or working knowledge of clinical research. Conversely, however, HCPs with no research interests potentially would have been unable to identify the relevant issues due to unfamiliarity with some of the relevant topics. As a result of the sample being biased towards those with an interest in research, it is difficult to ascertain whether this study's results are representative of the general feelings towards research held by most HCPs in the region.

7.5.2.2 *Questionnaire*

Mathers et al. (2007) described one weakness with this type of study as being that questionnaires restrain respondents from expressing their detailed views on issues of concern. This consideration was largely redressed by allowing for free-text comments to accompany responses. The collection of quantitative data, in combination with some qualitative (free-text response) data, meant that there was no further quantitative analysis of the new topics that emerged from the questionnaire. Given that the questionnaire was administered to a larger number of respondents than were interviewed, it could have been interesting to quantitatively assess the new findings that came out of the survey to gain a better understanding of other stakeholders' thoughts on those issues (e.g., a lack of expertise and trained investigators emerged as a significant theme from the questionnaire responses). However, this could have potentially led to multiple iterations of the questionnaire, which could have made the study unfeasible within the given timeline and added to the difficulty of interpreting the results.

One specific limitation of the questionnaire design that was not observed until analysis was that it did not capture the number of years of experience that respondents had in their particular field; instead, it collected the number of years spent in their particular roles. The respondents, particularly those in the pharmaceutical stakeholder group, are likely to have had fewer years of experience in their current role, due to career progression and associated changes in title and/or organisational restructuring, which can occur frequently within large multinational pharmaceutical corporations. With the benefit of hindsight, the questionnaire should have asked the respondents to indicate how long they had been in

their particular industry, instead of asking about the number of years in their current role, as the experience of those in the pharmaceutical stakeholder group may be misleading.

As with the interviews, it would also have been preferable to have had similar numbers of respondents across each stakeholder group to allow for a balanced comparison. The difficulties in engaging HCPs and regulatory stakeholders during the interviews and the higher response rates from those in the pharmaceutical industry suggested the same issues might have been the case for the questionnaire. It was easier to deploy snowball techniques to encourage a greater number of respondents from the pharmaceutical group to complete the questionnaire. Within the pharmaceutical stakeholder group, greater cross-functional representation would have been preferable. Representation of pharmaceutical stakeholders working across functions, including commercial operations, as opposed to the almost exclusively R&D-based group of respondents who completed the questionnaire, may have generated additional insights. For example, greater commercial representation from within pharmaceutical industry may have helped to elucidate more themes around the region's commercial relevance and associated considerations. This would have yielded a more accurate depiction of the commercial factors associated with the conduct of clinical trials in the region. A larger overall number of respondents would also have been beneficial in allowing for a greater degree of confidence in the results. Although a comparatively lower number of respondents from outside of the pharmaceutical industry participated, that again meant that the issues of significance for the pharmaceutical stakeholder group (and specifically those from within R&D) were better understood and documented across various levels of that sector.

Another limitation identified during the analysis of the questionnaire related to the survey question about the post-trial accessibility of medicines. The word 'accessible' was not defined, and therefore, it was not clear how the respondents interpreted it. 'Accessible' can mean either (a) commercially available or (b) financially obtainable for the majority of the population, and these two readings are quite different. The intention was for respondents to define 'available' as both physically available to purchase and financially obtainable. In retrospect, this term should have been explicitly defined, as doing so would have allowed me to ascertain whether the respondents believed that the pharmaceutical industry needs to sell more types of medicines in the region, or to simply sell the currently offered medicines at lower prices.

CHAPTER 8: CONCLUSIONS AND RECOMMENDATIONS

8.1 Conclusions

The first chapter in this thesis outlined a conceptual framework rationalising the role and importance of clinical trials in developing regions, such as Sub-Saharan Africa, against a background of increasing levels of chronic disease and poorly understood interethnic variations in treatment outcomes. Such research should be conducted in accordance with ethical standards appropriate for developing countries, and specifically understanding stakeholder perceptions of industry-sponsored research was the overall objective of this research project.

Neither the studies included in the literature review nor the participants in either part of this research distinguished between chronic and infectious diseases to any significant degree when raising issues. Consequently, the study's emphasis on chronic diseases, while mentioned in places, was not well reflected in the data collected. The issues affecting the conduct of clinical trials in Sub-Saharan Africa were described in general terms, and as such, the rest of the conclusions address those issues broadly, instead of focusing on chronic diseases specifically.

The first objective of this study was to understand the benefits of industry-sponsored clinical research for Sub-Saharan Africa. To address this objective, one key piece of information that needed to be better understood was whether various stakeholders felt that the pharmaceutical industry should be conducting clinical trials in Sub-Saharan Africa in the first place. This study has concluded that overall, the respondents felt that clinical trials remain an important tool in their ability not only to test the efficacy and safety of a particular intervention but also to generate collateral benefits for the region in which the research is conducted.

During the early stages of this project, it became clear that issues and complications related to the conduct of research in Sub-Saharan Africa were secondary to the ‘if’ question (i.e., if pharmaceutical companies should be conducting trials in that region). Although views were divided, the data from both the interviews and questionnaires indicated that the majority of respondents felt that pharmaceutical companies should, in fact, conduct trials in this part of the world. Additionally, the data from the questionnaire demonstrated that the majority of respondents believed that the pharmaceutical industry has both scientific and ethical responsibilities to do so. It is, however, important to note that opinions were diverse, and this conclusion is based on the majority view. In considering this diversity of opinions, it is also worth bearing in mind that the sample’s bias towards pharmaceutical representatives in both the interviews and questionnaires may have impacted the study’s outcome.

The second objective of the study was to better understand the ethical issues associated with the conduct of industry-sponsored research in developing regions, such as Sub-Saharan Africa. These issues are complex, multifaceted, and interlinked in many cases. Most of the issues raised fell into one (or several) of five overarching categories. These categories were:

1. Scientific/medical issues related to biological factors and their impact on treatment outcomes. This category includes issues used in the conceptualisation of this research, such as known genetic variations in metabolic pathways between ethnic groups. Such differences may alter the effects of various treatments, thereby changing outcomes.
2. Ethical issues, including informed consent and the navigation of complex socioeconomic factors with an influence on the relationship between pharmaceutical companies in the West, patients in developing countries, and their treating physicians.
3. Practical issues, which include logistical and operational constraints associated with conducting research in resource-constrained environments.

4. Educational issues related to, among other subjects, patients' knowledge and understanding of clinical trials and researchers' knowledge of appropriate research methods and conduct.
5. Financial issues linked to the commercial rationale for conducting trials, a factor that pharmaceutical companies must consider when deciding whether placing clinical trials in Sub-Saharan Africa is financially viable and worthwhile. The financial issues raised also related to post-trial access to medicines for patients in the region. This factor, in particular, is an example of the interrelatedness of issues, as access to medicines could be considered both an ethical and financial issue.

Clinical trials in developing countries must be sensitive to cultural nuances and allow for study-related processes to take such variables into consideration. Again, this is true only where the principles of ICH GCP are not contravened and so long as potential subjects are not put at any greater risk. Decisions regarding what is culturally acceptable should not be made solely by Western pharmaceutical companies, regulators, and ethics committees. Rather, stakeholders who are familiar with, and sensitive to, these cultural nuances should be included to ensure that the resultant agreements, guidance, or regulations integrate requirements to protect patients, ensure high levels of data quality, and take local cultures into account.

It was also felt that the pharmaceutical industry also has an ethical responsibility to confirm that the drugs that it manufactures are made available to patients globally, and not just to those in Western countries. However, there was an appreciation that ethics and finance do not sit well together, and that for this very reason, discussions around this topic are particularly complex and sensitive.

The majority of participants did not feel as though any one disease type should take precedence over another where the appropriateness of placing clinical trials in Sub-Saharan Africa is concerned. The initial focus of this research was specifically on clinical trials in chronic diseases. However, the respondents did not view a distinction as necessary or appropriate. Although there is significant evidence testifying to the increasing levels of

chronic diseases in Sub-Saharan countries, it was clear that the prevailing sentiment was that pharmaceutical industry-sponsored clinical research should not focus specifically on these disease types alone, but should also emphasise infectious diseases that have historically received much of the attention, both financially and medically. Initial efforts aimed at increasing the number of clinical trials conducted in the region should concentrate on carrying out research across all disease types in accordance with high standards.

Discussions around pharmaceutical industry's decision to place clinical trials in Sub-Saharan Africa predominantly revolve around finance. Unless the pharmaceutical industry stands to financially benefit from carrying out research in the region, that sector will not feel a sense of urgency to increase the region's participation in clinical trials, as the short-term benefits are less attractive. In the absence of any significant incentive for pharmaceutical companies to conduct trials in this part of the world, any substantial increase in Sub-Saharan Africa's footprint on the global clinical trial map appears to be unlikely until the economies in its largest countries are sufficiently well developed. However, increases in government, NGO, private-sector, and charity expenditures on healthcare are likely to gain the attention of the pharmaceutical industry in the future.

8.2 Recommendations

The results of this research support several recommendations for the conduct of industry-sponsored clinical trials in Sub-Saharan Africa.

8.2.1 Strategic placement of clinical trials

In placing clinical trials in Sub-Saharan Africa, pharmaceutical companies should start with countries that are well developed and stable. Pharmaceutical companies should also begin by targeting larger cities with reputable and well-established hospitals, for several reasons:

- a. Targeting larger cities opens a much larger potential patient pool than what would be observed in a more rural environment.

- b. Many of the practical issues associated with trial conduct could be eliminated if that research were conducted in larger cities. For example, challenges regarding importing or transporting drugs and ensuring that patients are able to reach their appointments would likely pose less of a problem (as public transport is more likely to serve large cities). Additionally, larger cities are more likely to have more experienced investigators and support staff to conduct trials and monitors to ensure that studies are conducted to a high standard.
- c. By conducting clinical trials in more developed countries, certain ethical concerns would become less relevant. For example, developed cities have higher levels of literacy, and patients are likely to exhibit greater levels of understanding (for the informed consent process) and to have higher incomes than their rural counterparts, thus reducing (not eliminating) the potential for patients to be coerced for monetary reasons.

8.2.2 Starting with bioequivalence and bridging studies and the establishment of national databases

8.2.2.1 Recommendation: Bridging studies

Pharmaceutical companies should start increasing their footprint in Sub-Saharan Africa through the conduct of well-designed bridging or equivalence studies, particularly in those countries that are research naïve. These studies should begin with marketed products that have been suggested to have a significantly altered efficacy or safety profile in patients of African descent. By doing so:

- a. Research teams in the region would be able to learn clinical research techniques using a drug that is marketed and that should consequently have a robust and well-understood safety profile. This factor would ensure that investigators are prepared for any (serious) adverse events and therefore able to quickly treat their patients upon presentation of symptoms.

- b. Such research would provide greater clarity and add to the knowledge base of data and information related to interethnic differences in response to treatment with specific medications.

8.2.2.2 *Recommendation: Establishment of national databases or registries*

Researchers in Sub-Saharan Africa should develop national databases or registries to quantify the prevalence of diseases in their region in order to assist pharmaceutical companies with assessing feasibility. This data would also allow progress to be tracked and would help justify the inclusion of countries in industry-sponsored clinical trials.

8.2.3 Stakeholder discussions

8.2.3.1 *Stakeholder discussions*

A frank, open, and honest discussion around the issues that have precluded clinical trials from taking place in Sub-Saharan Africa is needed, and it should involve all relevant stakeholders. The conversation must involve leaders from the pharmaceutical industry and should consider the creation of clear, structured clinical trial guidance documents, legislation, and policies on the conduct of industry-sponsored research.

8.2.3.2 *Allowing for autonomy, transparency, and flexibility in current guidelines*

A degree of autonomy needs to be granted to the relevant stakeholders in the region to facilitate decision-making on the appropriateness of trials and procedures. Employing flexible wording in current ethical guidelines governing the conduct of trials in resource-poor environments should be considered to allow scope for various trial designs in different environments and under varying circumstances. Pharmaceutical companies should operate with a greater degree of transparency in these environments to demonstrate an awareness of, and sensitivity to, local issues.

8.2.4 Governments must lead by example

Governments in Africa must lead the way in attracting clinical research from pharmaceutical companies, and they could do so in several ways.

Firstly, governments should oversee the creation of national databases to better quantify the prevalence of diseases, both chronic and infectious. Such data is needed to demonstrate that these countries have the patient populations that pharmaceutical companies require for clinical trials in various disease areas.

Secondly, governments should ensure that reputable local doctors with research interests are encouraged and given access to, and funding for, high-quality training in their area of specialty, clinical research methods, and ICH GCP. This would help foster and nurture a culture of high-quality research in these countries.

Lastly, governments should incentivise clinical research in their respective countries through the granting of concessions in other areas. This process should be encouraged and facilitated through various means, such as ensuring that clinical trial shipments receive priority import processing so that materials are not held up at customs, thereby delaying the initiation of clinical trials.

8.2.5 Revisiting the interpretation of current regulations

Further discussions around the appropriateness of current regulations and their constraints are needed to expand on narrow interpretations of those guidelines for ethical clinical trial conduct. A narrow interpretation of certain current regulations (with respect to, for example, the provision of medicine post-trial) is one factor precluding trials from being placed in Sub-Saharan Africa and requires an approach more sensitive to the specific research environment.

Healthcare professionals in developing countries, as well as regulatory bodies and ethics committees, need to be involved in discussions aimed at establishing, defining, and approving guidelines for international pharmaceutical companies conducting research in

developing countries. These guidelines should outline a clear framework for what constitutes ethical research in resource-poor environments and should be established in a way that does not place unsustainable financial pressure on pharmaceutical companies.

8.2.6 Acknowledging and addressing concerns and perceptions of corruption

There is a need for policymakers and HCPs in Sub-Saharan Africa to acknowledge that many in the West perceive corruption to be a significant risk in developing countries and to behaving accordingly. This may require those in Sub-Saharan Africa to operate with openness, transparency, and honesty beyond what would be expected of their Western counterparts to ensure mutual trust.

8.2.7 Revisiting pricing structures

Pharmaceutical companies need to make greater effort with respect to pricing structures to guarantee that drugs are not prohibitively expensive in Sub-Saharan Africa. This may involve using tiered pricing structures, as well as managing the challenges associated with making drugs available at lower prices in this region, such as parallel imports and counterfeiting.

Appendix 1: Phases of clinical trials

| | |
|------------------|---|
| Phase I | A new drug is tested in a small group of people (oftentimes healthy volunteers) for the first time to evaluate its safety, and tolerability and also to determine a safe dosage range and identify any side effects. |
| Phase II | A drug is tested in a larger group of patients to determine its efficacy and safety. |
| Phase III | The effectiveness of the new drug and, thereby, its value in clinical practice in a much larger group of patients is tested. Comparisons to commonly used treatments can also be made. |
| Phase IV | Post marketing trials. These studies are conducted after the product is licensed in order to gain further information on the drug's effect in various populations and to continue to monitor its side effect profile. |

Appendix 2: JBI QARI Critical Appraisal Checklist for Interpretive & Critical Research

JBI QARI Critical Appraisal Checklist for Interpretive & Critical Research

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

| | Yes | No | Unclear | Not Applicable |
|--|--------------------------|--------------------------|--------------------------|--------------------------|
| 1. Is there congruity between the stated philosophical perspective and the research methodology? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. Is there congruity between the research methodology and the research question or objectives? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 3. Is there congruity between the research methodology and the methods used to collect data? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 4. Is there congruity between the research methodology and the representation and analysis of data? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 5. Is there congruity between the research methodology and the interpretation of results? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 6. Is there a statement locating the researcher culturally or theoretically? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 7. Is the influence of the researcher on the research, and vice- versa, addressed? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 8. Are participants, and their voices, adequately represented? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 9. Is the research ethical according to current criteria or, for recent studies, and is there evidence of ethical approval by an appropriate body? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 10. Do the conclusions drawn in the research report flow from the analysis, or interpretation, of the data? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

Overall appraisal: ☐ Include ☐ Exclude ☐ Seek further info. ☐

Comments (Including reason for exclusion)

Appendix 3: Systematic Qualitative Review Summary Table

| Author | Countries | Disease indication | Industry Sponsored | Stakeholders | Qualitative Method |
|------------------------|--------------------------------|--|--------------------|---|---|
| Akazili et al., 2016 | Ghana | Malaria (paediatric) | No | Parents of participants | Structured interviews |
| Allen et al., 2013 | Tanzania South Africa | HIV Malaria | No | Study participants | In-depth interview |
| Angwenyi et al., 2015 | Ghana Kenya Burkina Faso | Malaria | No | Researchers | In-depth interviews Focus groups |
| Boahen et al., 2013 | Ghana | Not specified. | No. | Community members | In-depth interviews Focus group discussions |
| Buregyeya et al., 2015 | Uganda | Tuberculosis | No. | Participants Parents of participants Community leaders Traditional healers | Focus group discussion Key informant interviews |
| Chantler et al., 2013 | Kenya | Paediatric vaccines (indication not specified) | No. | Village Reporters (VR) Researchers | Focus group discussion Interviews |
| Chatio et al., 2016 | Ghana | Malaria (paediatric) | No. | Parents of study participants | In-depth interviews |
| Corneli et al., 2007 | Malawi | HIV | No. | Community members | Semi-structured interviews Focus group discussions |
| Dial et al., 2014 | Gambia | Malaria | No. | Previous participants | In-depth interviews |

| Author | Countries | Disease indication | Industry Sponsored | Stakeholders | Qualitative Method |
|---------------------------|--------------|---|--------------------|--|--|
| Essack et al., 2009 | South Africa | HIV | No. | Researcher Community Government representatives Ethics committee representatives | In-depth interviews |
| Fairhead et al., 2006 | Gambia | Pneumococcal vaccine | No. | Community members Research participants | Interviews Focus group discussion |
| Gikonyo et al., 2008 | Kenya | Malaria | No. | Researchers Study participants | Interviews Focus group discussion |
| Hill et al., 2008 | Ghana | Nutrition | No. | Study participants | Semi-structured interviews Focus group discussion |
| Kamuya et al., 2013 | Kenya | Not specified. | No. | KEMRI Community Representatives (KCRs) | Interviews |
| Kingori et al., 2010 | Zambia | Paediatric nutrition | No. | Parents of participants Researchers | Interviews Focus group discussions |
| Koen et al., 2013 | South Africa | HIV | No. | Community members | Semi-structured interviews |
| Lairumbi et al., 2012 | Kenya | None specified. | No. | Researchers Community members | In-depth interviews |
| Leach et al., 1999 | Gambia | Meningitis Pneumonia Paediatric DTP (diphtheria, tetanus and pertussis) | No. | Study participants Parents of study participants | Interviews |
| Lihueluka et al., 2013 | Tanzania | Malaria (paediatric) | No. | Parents of participants | Group discussions |

| Author | Countries | Disease indication | Industry Sponsored | Stakeholders | Qualitative Method |
|---------------------------|-----------------|---|--|---|--|
| Magazi et al., 2014 | South Africa | HIV | No. | Study participants | In-depth interviews Ethnographic interviews Focus group discussion |
| Malan & Moodley, 2016 | South Africa | Cancer | No, however participants included those involved in industry-sponsored trials. | Participants | Semi-structured questionnaire |
| Masiye et al., 2008 | Malawi | Malaria (paediatric) | No. | Parents of participants | Focus group discussions |
| Mfutso-Bengo et al., 2008 | Malawi | HIV / AIDS Prevention of pre-term labour | No. | Study participants | Focus group discussion |
| Molyneux et al., 2005 | Kenya | Not specified. | No. | Community members | Group discussions Interviews |
| Molyneux et al., 2013 | Uganda Kenya | Paediatric severe febrile illness and shock | No. | Parents of study participants Researchers | In-depth interviews |
| Moodley et al., 2015 | South Africa | HIV | No, however participants included those involved in industry-sponsored trials. | Researchers Social workers Community advisory board members Patients | Semi-structured interview |
| Ndbele et al., 2014 | Malawi | HIV | No. | Researchers Study participants | In-depth interview Focus group discussion |

| Author | Countries | Disease indication | Industry Sponsored | Stakeholders | Qualitative Method |
|-------------------------|--------------|--------------------|---|--|--|
| Njue et al., 2014 | Kenya | Malaria | No. | Researchers Parents of participants Community members KEMRI Community Representatives (KCRs) | Focus group discussions |
| Nyblade et al., 2011 | Kenya | HIV | No. | Study participants Community advisory board members Previous study volunteers Study staff Community members | Focus group discussion Structured interviews |
| Osamor & Kass, 2012 | Nigeria | Lipid | No. | Study participants | Semi-structured questionnaire |
| Siegfried et al., 2010 | South Africa | None specified. | No, however some respondents have been involved in industry sponsored trials. | Senior decision makers with stake in clinical trials | Key informant interviews |
| Simon et al., 2007 | South Africa | Oncology | No. | Study participants | Semi-structured questionnaire |
| Stadler & Saethre, 2010 | South Africa | HIV | No | Research participants Partners of research participants | In-depth interviews |
| Stadler et al., 2008 | South Africa | HIV | No. | Community members Study participants | Focus group discussion Semi-structured interviews |
| Tarimo et al., 2011 | Tanzania | HIV | No. | Study participants who declined participation | Face to face interview |

| Author | Countries | Disease indication | Industry Sponsored | Stakeholders | Qualitative Method |
|----------------------------|---|---|--|--|---|
| Tarimo et al., 2011 | Tanzania | HIV | No. | Study participants | Focus group discussion |
| Toe et al., 2013 | Burkina Faso | Malaria (paediatric) | No. | Parents of study participants | Semi-structured interviews |
| Van Loon & Lindegger, 2009 | South Africa | Microbiology HIV Intensive care Surgical | No, although pharmaceutical company representatives were involved. | Researchers | Semi-structured interviews |
| Venables & Stadler, 2012 | South Africa | HIV | No. | Partners of study participants | Focus group discussion In-depth interviews |
| Vischer et al., 2016 | Kenya Ghana Burkina Faso Senegal | None specified. | Not specified – interviewees had experience from multiple trials. | Researchers | Interviews |
| Woodsong et al., 2012 | Malawi Zimbabwe | HIV | No. | Study participants Partners of study participants | Semi-structured interviews |
| Zvonareva & Akrong, 2015 | Ghana South Africa | None specified | No. | Community members Previous participants | In-depth interviews |
| Zvonareva et al., 2015 | South Africa | HIV | No. | Participants Previous participants | In-depth interviews |

Appendix 4: PRISMA checklist

| Section/topic | # | Checklist item | Reported in section # |
|---------------------------|---|---|---|
| TITLE | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | Title |
| ABSTRACT | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | N/A – review is part of a wider project for which an abstract exists |
| INTRODUCTION | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 3.1.1 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 3.1.1 |
| METHODS | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | N/A |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 3.2.1 & 3.2.3 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 3.2.2 |

| | | | |
|------------------------------------|----|--|---|
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 3.2.2 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 3.2.3 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 3.2.5 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 3.2.3 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 3.5 – discussed out outcome level. |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 3.2.3 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis. | 3.2.5 |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | N/A |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | N/A |
| RESULTS | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 3.3 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | Appendix 3 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 3.5 |

| | | | |
|-------------------------------|----|--|------------|
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | N/A |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | N/A |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | N/A |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | N/A |
| DISCUSSION | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and s). | 3.4 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 3.5 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 3.6 |
| FUNDING | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | N/A |

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097



University
of Glasgow

Institute of Health
and Wellbeing

Appendix 5: Research Protocol

**Investigating the potential for developing countries to participate
in industry sponsored clinical research into chronic, non-
communicable disease.**

Research Protocol

Efe Egharevba

PhD Candidate

Public Health and Health Policy

Centre for Population and Health Sciences

College of Medicine, Veterinary and Life Sciences

University of Glasgow



Table of Contents

| | |
|---|-----------|
| SECTION ONE: INTRODUCTION | 3 |
| SECTION TWO: AIMS AND OBJECTIVES | 7 |
| SECTION THREE : METHODS | 8 |
| SECTION FOUR: SETTING | 9 |
| SECTION FIVE : POPULATION | 9 |
| SECTION SIX: PROCEDURE | 10 |
| 6.1: STUDY 1 | 10 |
| 6.2: STUDY 1 | 12 |
| SECTION SEVEN: APPENDICES | 14 |



1. Introduction

Historically, pharmaceutical companies have focused their efforts on researching and developing medications for diseases and conditions that affect a wealthy minority of the global population, in an effort, it has been argued, to maximize profits¹¹ The issues that this type of approach creates for less developed countries are two-fold; firstly, this has led to what some have called the 90/10 gap in which only 10 percent of global health research is devoted to conditions that account for 90 per cent of the global disease burden¹². This effectively means that the research which is conducted in an effort to develop medicines has been limited to more affluent countries in the Western world¹³. Secondly, diseases which affect the poorer minority of the global population have not been the focus of much commercial effort because many companies view the expenditure to profit margin for these diseases as not substantial enough to warrant the effort.¹⁴ This has meant that many diseases that affect the greater proportion of the global community have not been researched by pharmaceutical companies who, I would argue, are best placed, through their research and development capacity and expertise to develop such medicines. The combination of these two issues means that most people outside of the Western world have never had access to clinical trials for chronic diseases from which they may be suffering.

¹¹ Macklin, R. 2004. Double Standards in Medical Research in Developing Countries. Cambridge, UK. Cambridge University Press

¹² Drugs for Neglected Diseases Working Group, *Fatal Imbalance: The Crisis in Research and Development for Drugs for Neglected Diseases*, MSF, September 2001

¹³ Borry, P., Schotsmans, P., Dierckx, K. (2005). Developing Countries and Bioethical Research. *New England Journal of Medicine* 353(8), 852-853.

¹⁴ Shah, A. (2000) Pharmaceutical Corporations and Medical Research. Retrieved March 10, 2017, from <http://www.globalissues.org/article/52/pharmaceutical-corporations-and-medical-research2>



1.1 Background

Africa's Evolving Disease Landscape

Sub-Saharan Africa represents a region of the world which is disproportionately affected by disease burden in comparison the rest of the world.¹⁵ With a disproportionate number of people in the region suffering from communicable diseases such as AIDS and HIV¹⁶ and historically inadequate infrastructure and resource to address these diseases¹⁷, the region has been the focus of many charities and health organisations for a substantial period of time. There are, however, a number of changes which are occurring in Africa, both in socioeconomics and in the disease landscape. An increasing proportion of the Sub-Saharan region is now considered middle-class¹⁸ as globalisation and modernisation efforts begin to reach the area. Efforts are being put into modernising the healthcare infrastructure and providing more training and resource to address the neglected diseases which have affected the region for some time¹⁹.

With the change in socioeconomics has also come a shift in the disease types that patients in the region are suffering from. As populations begin to live longer lives due, in part, to interventions and efforts to limit the effects of communicable diseases in the region, people are beginning to suffer from an increasing level of chronic and lifestyle diseases which have historically been associated with those living in the Western world.²⁰ This shift in the disease types presents a problem for the region which is more medically geared toward dealing with communicable

¹⁵ Heyns, C. F., Borman, M. S. Men's Health in Africa Part 2: Non-communicable diseases, malignancies and socio-economic determinants health. *Journal of Men's Health*, 5(2), 127-132.

¹⁶ AVERT. (2011, October 21). Global HIV and aids statistics. Retrieved from HIV & AIDS Statistics from Around the World: <http://www.avert.org/aids-statistics.html>

¹⁷ Poverty and infection in the developing world: Healthcare-related infections and infection control in the tropics. *Journal of Hospital Infection*, Volume 67, Issue 3, November 2007, Pages 217-224 P. Shears

¹⁸ Africa Development Bank, C. E. (2011, October 13). The middle of the pyramid: Dynamics of the middle class in Africa. Retrieved 2011, from <http://www.afdb.org>

¹⁹ World Health Organization. (2005). *Preventing Chronic Disease: A Vital Investment: Who Global Report*. Retrieved 17 December, 2001, from http://www.who.int/chp/chronic_disease_report/en/

²⁰ Heyns, C. F., Borman, M. S. Men's Health in Africa Part 2: Non-communicable diseases, malignancies and socio-economic determinants health. *Journal of Men's Health*, 5(2), 127-132.



diseases. As this shift in disease types evolves over time, it will be necessary for measures to be put in place which facilitate the recognition, understanding, and treatment of chronic diseases in order to prevent epidemic levels of the diseases from occurring in a region which continues to struggle with inadequate healthcare resource and infrastructure.

Industry Sponsored Clinical Research

According to a report by the United States Congressional Budget Office, the pharmaceutical industry is said to spend upwards of \$40 billion annually on research and development²¹ and at any given time more than 30,000 interventional industry-sponsored clinical trials are reported to be on going across the globe.²² It has been argued that participation in clinical trials is of benefit to a clinical trial participant, and the greater community.²³ For example, patients and communities may benefit from closer monitoring of their disease and early access to medicines. The greater community and society may benefit through better understanding of mechanisms of disease and treatment and increased healthcare dedicated resource.²⁴ Despite the fact that there are such a large number of clinical trials conducted every year, statistics show that most of the research is carried out in developed western countries, with subjects in the United States accounting for the majority proportion of the world's clinical trial population despite the fact that the entire United States only accounts for 4.5% of the world's global population.²⁵

²¹ Congressional Budget of the United States – Congressional Budget Office. Research and Development in the Pharmaceutical Industry. October 2006. Accessed 27-Jan-12 from: <http://www.cbo.gov/ftpdocs/76xx/doc7615/10-02-DrugR-D.pdf>

²² National Institute for Health. (2017, January 27). Map of all studies on clinical trials. Retrieved from <https://clinicaltrials.gov/ct2/search/map/click?map.x=419&map.y=237>

²³ Wynder, E. L. (1989). An American health foundation monograph. Coronary artery disease prevention: Cholesterol, a pediatric perspective. Preventative Medicine, 18(3), 323-409.

²⁴ 10 Center for Disease Control and Prevention. (2011). Heart disease facts. Retrieved from <http://www.cdc.gov/heartdisease/facts.htm>

²⁵ 24 Boers, M., Brooks, P., Fries, J. F., Simon, L. S., Strand, V., & Tugwell, P. (2010). A first step to assess harm and benefit in clinical trials in one scale. Journal of Clinical Epidemiology, 63(6), 627-632.

²⁶ US & World Population Clocks. US Census Bureau. <<http://www.census.gov/main/www/popclock.html>>. Accessed 27 July 2011.



The Sub-Saharan region of Africa suffers from a legacy of exclusion from industry sponsored clinical trials despite bearing a large proportion of the global disease burden.² I would argue that the basis of the exclusion of the region has largely been financial as Africa's spend on healthcare is only a fraction of that in the West²⁶ and with profit-seeking pharmaceutical companies driving the research being conducted in chronic diseases, there has been little financial rationale for conducting research in this region. However, with R&D costs increasing, a growing population of middle-class Africans, and money being invested into developing Africa's healthcare infrastructure there may be the potential for a symbiotic relationship to develop. Although literature around Africa's development and R&D's increasing costs exist separately, there does not appear to be a large body of literature which considers the implications that these two considerations could potentially have on the regions participation in research. I would argue that this relationship may potentially be part of the solution to helping pharmaceutical companies contain research and development costs at the same time as helping Sub-Saharan Africa address the growing levels of chronic disease, and lack of expertise, infrastructure and resource which have precluded its participation from the majority of industry sponsored research projects in the past. It is likely that the reason work in this area has been neglected in the past is largely because there has been no financial incentive to conduct such research and also because much of the focus on healthcare in this region has been on tropical and communicable diseases.

There are ethical implications which need to be taken into account when considering the regions participation in clinical trials. These include the potential for exploitation or coercion and the sensitive issues related to the provision of medicine, care and resource after a clinical trial is complete. Most would argue

²⁶ Castro-Leal, F., Dayton, J., Demery, L., Mehra. (2000) Public spending on healthcare in Africa; Do the poor benefit?, K. *Bulletin of the World Health Organisation*, 78(1) 66-72.



that these factors have also played a substantial role in the regions exclusion from the majority of industry-sponsored clinical trials to date.

The major advantages to the regions participation in industry sponsored clinical trials are; provision of additional resource, income for hospitals, additional and potentially better treatment options for patients and training for healthcare professionals both in their area of medical interest, and also in research techniques which they may not receive otherwise. Participating in clinical trials is, of course, not without its disadvantages. These include the potential for the financial compensation healthcare professionals receive for participating in clinical trials to lead to the neglect of routine healthcare responsibilities could be more likely to occur in this region due to its scarcity of resource and inexperience with clinical trials.

The aims of this research are to investigate the potential value as well as ethical implications associated with conducting industry sponsored clinical trials in chronic / non-communicable diseases in this developing region.

2. Aims and Research Questions

2.1. Aim

To understand the ethical implications associated with conducting industry sponsored clinical trials in chronic diseases in Sub-Saharan Africa* and what value / benefit, if any, such research provides to the population in this region and to provide recommendations, upon analysis of data regarding the conduct of industry sponsored clinical research in Sub-Saharan Africa. Through conducting the research, I also aim to raise the profile of the issues related to rising levels of chronic disease in Sub-Saharan Africa amongst various stakeholders.



2.2. Research Question(s):

- Can clinical trials provide a beneficial opportunity to address rising levels of chronic disease in the Sub-Saharan region of Africa without being exploitative?
- Is it possible for the relationship between Western pharmaceutical companies and developing countries in Sub-Saharan countries to be mutually beneficial?
- Do any potential ethical concerns outweigh any potential benefit these countries stand to gain?
- Do pharmaceutical companies have any ethical / social responsibilities with respect to engaging developing nations to;
 1. Encourage / support the development of research infrastructure or to
 2. Develop medicines for conditions which are primarily experienced by the poor?

3. Methods

This study will use mixed methods and will therefore be in two parts. Study one will be qualitative and will use interviews with various stakeholders to get their opinions on, and experiences with, the topics addressed in the research questions. Study two will be both quantitative and qualitative and use questionnaires to quantify and explore the issues raised during the interviews conducted in the first study.



Study 1 – Interviews

The aim of the interviews is to get the opinions and experiences of various stakeholders on the conduct of industry sponsored clinical research in Sub-Saharan Africa through semi-structured interviews. This data will be used to develop the questionnaire used in the second part of the study.

Study 2 - Questionnaires

The aim is to distribute a questionnaire to a wider group of people to collect qualitative and quantitative information based on the responses obtained in the interviews in the first part of the study.

4. Setting

The Sub-Saharan region of Africa was chosen as the best place to conduct this research as of all the developing regions in the world, it appears to be the furthest behind with respect to development of healthcare infrastructure yet suffers disproportionately from disease when compared to the rest of the world.²⁷ Given the size of the region and the varying degrees of development which exist, it was decided that specific countries needed to be identified. Due to their size, economic status, and relative stability at the time the research is planned, Nigeria and Ghana have been chosen as the two countries of focus. If identifying respondents in these countries becomes difficult and further respondents are needed, additional countries in the Sub-Saharan region may be selected. This information will be made available to the ethics committee as soon as possible. Priority will be given to larger cities as there are other practical and ethical issues associated with conducting trials in rural areas of many countries such as decreased levels of literacy, and logistical challenges. I also appreciate that different countries in the region may have their own transient issues (e.g. political instability etc.) which may

²⁷ De Graft Aikins, A., Unwin, N., Agyemang, C., Pascale, A., Campbell, C., & Arhinful, D. (2010). Tackling Africa's chronic disease burden: From the local to the global. *Global Health*, 6(5), 1-7.



change throughout the duration of the research project and could have an influence on the way that various stakeholders view and prioritise different issues. As I currently have existing links with Healthcare Professionals in Nigeria and Ghana, I may be able to develop further links with other stakeholders in this region.

5. Population and sample

The population to be interviewed and complete the questionnaire have been selected with a view of providing the most balanced view / opinion on the issues this research hopes to address. By selecting stakeholders geographically located both inside and outside of the region, a robust contrast and comparison can be performed on the various opinions. These observations will be key for discussion in the content analysis output of the interviews. The stakeholders involved in the interview and questionnaire processes will each fall under one of four broad categories.

1. Policymakers / influencers including; Government representatives, members of international health organisations and charities that work within the countries selected.
2. Local healthcare professionals (HCP's) who have responsibility for patient care.
3. Where they exist, members of any patient advocacy groups (this may include patients and staff). Any patients interviewed or surveyed by questionnaire will not be asked any questions which relate to their disease.
4. Pharmaceutical industry representatives who are involved in the clinical development of medicinal products and placement of clinical trials globally.

Purposive and opportunistic sampling will be used in both parts. Given the assumed geographical location of some of the respondents in both parts of the study, this will be done by a mixture of methods which will include snowballing.



6. Procedure

The study will be formed of 2 parts; interviews (qualitative) and questionnaires (qualitative / quantitative). The interview part of the study will comprise of a series of semi-structured interviews. The quantitative portion of the study (Study 2) will involve surveying various stakeholders through questionnaires.

6.1 Study 1 – Interview

Development of Interview

The interview schedule has been developed from literature reviews and my experience working in this area. Semi-structured interviews will be conducted with 4 different groups of stakeholders to gain subjective insight into the experiences and opinions related to Sub-Saharan Africa's participation in clinical trials. Given the logistical challenges and financial constraints, interviews will either be conducted face to face, where possible, or via telephone where face to face is not feasible. The interviews will be audio-recorded, transcribed before analysis.

The responses to the interview questions will be used to develop a questionnaire which will address the main / recurring themes arising from the interview responses. Interviews will be conducted until saturation, with a minimum of 20 and a maximum of 30. If no clear pattern has emerged having conducted these interviews, then the questions will be re-reviewed and any appropriate changes incorporated before any further interviews are conducted. During the development of the interview, a decision had to be made on whether to focus on the depth of the issues covered, or a wider breadth of issues. It was decided that depth should be the focus of the interview portion of the study as breadth can more easily be covered with the questionnaires to be used in part two.



It is also appreciated that various individuals and groups of stakeholders will have particular areas of interest or areas which are more relevant to them and therefore there is scope for the interview to take a direction which was not expected.

The plan is to conduct 24 interviews in total;

| Stakeholder Group | Number from Nigeria | Number from Ghana | Total |
|--|------------------------|----------------------|-----------|
| Government Representatives | 2 | 2 | 4 |
| Local HCP's | 3 | 3 | 6 |
| Patient Advocacy Group Representatives | 2 | 2 | 4 |
| Pharmaceutical Industry Representatives | --- | --- | 10 |
| Total | | | 24 |

Identification

Identification of individuals to participate in both portions of the study will follow a similar route. Participants will be identified through various means including;

- The use of academic journals to identify HCPs.
- Internet and literature searches will be used to identify potential interviewees within each of the four groups of stakeholders.
- Snowballing will be used to identify potential interviewees within each of the four groups of stakeholders.

Recruitment

Potential interviewees will be contacted via telephone, email or post after being identified and invited to participate in the research. Because of the distances involved, particularly with those based in the Sub-Saharan region, I anticipate the majority of interviews will be carried out by telephone.

Interview Schedule

See Appendix A



Telephone Interviews

The telephone interviews will be arranged via email or post and will be scheduled for a time suitable for both the interviewer, and interviewee. Any costs associated with the telephone interview will be covered by me. If possible, telephone interviews will be recorded – in instances where this is not possible, the interview will be transcribed by hand during the call.

Analysis

Thematic analysis will be performed and the main themes identified will then be used in the questionnaire. Thematic analysis will involve reviewing transcripts of each interview to identify and pull out salient points and creating thematic codes. Once the themes have been created the transcripts will be re-reviewed and recontextualised using the new codes. Each of the themes will then be described and demonstrated through the use of quotes.

6.2 Study 2 – Questionnaires

Questionnaire Development

The questionnaire will be developed based on feedback derived from the interview part of the research and will be predominantly quantitative but will also collect qualitative responses. The responses to the questionnaire will be analysed using thematic analysis. Quantitative data will be analysed using mainly descriptive statistics. The timing of the questionnaires will be largely dependent on when the responses from the interviews have been collated and analysed. Questionnaires will be accessible via the internet as well as in hard copy format. Every effort will be made to cover any postage costs associated with returning the questionnaire, where possible. Checks will be incorporated to ensure that duplicate information is not received from the same respondent when the web-based questionnaire is rolled out. Respondents will be asked to return their



questionnaires by post or submit their completed questionnaire online.

Identification

See identification for Part 1 of the study.

Recruitment

See recruitment for Part 1 of the study.

Questionnaire Procedure

A questionnaire which will allow for the collection of both quantitative and qualitative responses will be administered to a larger sample of the same groups of stakeholders who are interviewed in the first part of the study. Those who complete the questionnaire may also have participated in and contributed to the interview part of the research. Due to the ease of administering questionnaires a substantially larger sample size will be used than completed the interview

| Stakeholder Group | Number from Nigeria | Number from Ghana | Total |
|---|------------------------|----------------------|------------|
| Government Representatives | 5 | 5 | 10 |
| Local HCP's | 25 | 25 | 50 |
| Patient Advocacy Group Representatives | 12 | 12 | 24 |
| Pharmaceutical Industry Representatives | --- | --- | 100 |
| Total | | | 184 |



Questionnaire Schedule

As the content of the questionnaire will be driven by the output of the interview part of the study, the questionnaire will not be generated until the analysis of those responses has been completed. A copy of the questionnaire, once finalised, will be sent to the ethics committee for review.

Analysis

The qualitative section of the questionnaire will be analysed using thematic analysis. The quantitative section of the questionnaire will be analysed using mainly descriptive statistics to link in with the thematic analysis performed on the qualitative section of the interviews conducted in the first part of the study.



Appendix 6: Interview schedule

Investigating the potential for developing countries to participate in industry sponsored clinical research into chronic, non-communicable disease

Research Protocol Interview Schedule

Efe Egharevba

PhD Candidate

Public Health and Health Policy

College of Medicine, Veterinary and Life Sciences

University of Glasgow



Procedures

I will start the interview by thanking participants for taking the time to speak with me. The interview will then begin with an introduction of myself and confirmation that the interviewees are happy to be tape recorded. I will then briefly summarise my professional and academic careers and provide an overview of what the research is about;

Introduction:

'Firstly I would like to thank you for taking the time to speak with me. This interview will be recorded so that it can be transcribed after our discussion, please can you confirm that you're happy to be recorded?'

After confirmation;

'The format of our discussion today will be as follows; before we begin with the formal interview questions, I will tell you a bit more about myself and my professional and academic background and then talk you through the study. I will then collect a bit of information from you after which we can start with the formal interview questions. Please feel free to stop me at any point during our discussion to ask questions and remember that your participation is completely voluntary and you are free to stop participating in the interview at any point.'

My name is Efe Egharevba and I am a [insert year of study] year part-time PhD student at Glasgow University. I'm conducting this research as part of the requirements of my degree in Public Health and therefore have something to gain by completing this project. I have worked in various roles within the pharmaceutical industry for the past 8 / 9 years. At present I am a contract Global Studies Manager at Roche Products Ltd. I have a bachelor's degree in biology from the University of North Texas and a master's degree in clinical research from Cardiff University in Wales.'



I will then find out more about the interviewees by asking them questions about their profession (title / position), their number of years' experience in that position, what country they are based in (if not obvious), and whether or not they have experience with industry sponsored clinical research. This information will be recorded on a form that will be used for all participants and be collected in the same format;

| Name | Title / Position | Number of Years in Current Role | Country |
|------|------------------|------------------------------------|---------|
| | | | |

| | |
|--|-----------------------|
| Experience with industry sponsored clinical research (Y / N): | Y/N – if yes describe |
| Consent: Date: Verbal / Written?: | |
| Additional Comments | |
| Contact Details | |

Next, I will explain the background of my work and what my research interests are and how their responses will be used. They will then be reminded about confidentiality (i.e. that I will not share their information or response with any other



parties) and I will also remind participants that their responses will remain anonymous (i.e. will not be attributable to them specifically);

'As I've worked in clinical research a few years now, this research was born out of an observation that a lot of the clinical trial research work done by the pharmaceutical industry is not carried out in Sub-Saharan Africa despite the fact that chronic disease levels appear to be rising, and that Africa bears a large proportion of the world's disease burden. I would like to understand if there are ethical concerns that exist amongst various stakeholders that have precluded Africa's involvement in clinical trials to date and what those issues, if any, are. I am interested in your personal opinions and experiences, and not those of the institution or company which you work for, although I appreciate there may be some overlap. There are no right or wrong answers to any of my questions. All of the information you provide to me will be completely confidential and will be handled in-line with the University of Glasgow's data handling and retention guidelines and policies. Although your quotes may be used in papers and manuscripts, nothing which can identify you will be used or presented and your quotes will be anonymised. This interview should last no longer than 30 minutes.'

Do you have any questions that you'd like for me to answer before we begin the interview and can you confirm that you are happy to participate in this research?'

After confirmation

'Thank you. We will now begin the interview.'

OR (depending on whether interview is done face to face or over the phone)

'Thank you, please sign this consent form in duplicate as confirmation that you are happy to participate in this research'



For those who are interviewed in person we will then go through the informed consent form which they will sign. For those interviewed over the phone, verbal consent will be recorded.

Interview Structure

The interviews will be semi-structured in nature to allow for respondents to raise issues which may have not been considered during the development of the interview schedule. The list of questions below will be used as a guide / prompt to provide direction for the interview and the exact questions asked may differ between respondents depending on what issues interviewees deem most relevant.

Interview Questions

The interviews will comprise of the 4 research questions which are outlined in the protocol – under each of these questions there will be a series of prompting questions which will be used to encourage respondents to provide more information around particular topics. With each response interviewees will be invited to expand or add additional thoughts.

| Overarching Question | Prompt Questions |
|---|---|
| <i>'Do you think that clinical trials can provide an opportunity to address rising levels of chronic disease in the Sub-Saharan region of Africa without being exploitative?'</i> | <i>'How important is industry sponsored clinical research and does it have a place in Sub-Saharan Africa?'</i> <i>'In the context of Sub-Saharan Africa's disease landscape, how important are chronic diseases? How about Infectious diseases? Do you think the control, research and awareness of one of these disease types is more</i> |



| | |
|--|---|
| | <p><i>important than the other? If so, which one and why?’</i></p> <p><i>‘In your experience or opinion, does research play any role in raising the awareness or controlling the spread of diseases?’</i></p> |
| <p><i>‘Do you think it’s possible for a relationship between Western pharmaceutical companies and developing countries in Sub-Saharan countries to exist?’</i></p> | <p><i>‘Should a relationship exist and if so what kind?’</i></p> <p><i>‘Do you think one party stands to gain more than the other? If so who / how? Can and should this be different? If so, in what way?’</i></p> <p><i>‘Do you think that the relationship can be mutually beneficial?’</i></p> |
| <p><i>‘What do you think that the ethical concerns, if any, are with conducting industry sponsored clinical trials in the Sub-Saharan region of Africa?’</i></p> | <p><i>‘Do you think that there should be any concerns?’</i></p> <p><i>Do you think that they outweigh the potential benefits?’</i></p> <p><i>‘Which of all of the concerns is the biggest and why?’</i></p> |
| <p><i>‘Do you think that pharmaceutical companies have any role to play in Sub-Saharan Africa?’</i></p> | <p><i>‘In your opinion does the pharmaceutical industry have any ethical responsibility to involve poorer countries in clinical research? Why or why not?’</i></p> <p><i>‘What value, if any, do you think the pharmaceutical industry can bring to the region?’</i></p> |



| | |
|--|---|
| | <p><i>'Do you think that this would be welcomed by people in the region? Why or why not?'</i></p> <p><i>'What is the current perception of the pharmaceutical industry in this region?'</i></p> |
|--|---|

Interview End

At the end of the interview, interviewees will be thanked for their participation and given contact details should they want any further information or updates. Contact information will also be taken for participants who would like a copy of the abstract of the final manuscript;

'Thank you again for taking the time to speak with me; I really appreciate your participation in this research. If you would like to contact me for any reason, please do not hesitate to either give me a ring on [insert personal telephone number] or send me an email at t.egharevba.1@research.gla.ac.uk. If you would like a copy of the abstract of the final manuscript, please leave me with either a mailing or email address and I will send one once it has been completed.'



Appendix 7: Questionnaire

Questionnaire

Title of Research: Investigating the potential for developing countries to participate in industry sponsored clinical research in chronic, non-communicable diseases.

Background

My name is Efe Egharevba. I am a doctoral student in the College of Medical, Veterinary, and Life Sciences at the University of Glasgow. I am conducting a research study as part of the requirements of my PhD in Public Health, and I would like to invite you to participate.

This questionnaire is the second part of my research study. The first part involved conducting a series of interviews across a range of stakeholders to understand their thoughts on a number of issues associated with conducting industry-sponsored clinical trials in Sub-Saharan Africa. The aim of this questionnaire is get your views on the topics which were raised in those interviews.

Instruction

Please complete each question before moving onto the next one by either selecting an option which indicates your agreement with the statement (where 1 is strongly disagree and 5 is strongly agree). Please use the free text boxes to add any additional comments. Fields which are mandatory are denoted by a (*).



Text which has been highlighted is guidance text for the ethics committee. This text will not be included in the final online or paper version of the questionnaire.

About you

| | |
|---|---|
| *1. Job title or role | Free response text box in which respondents will be asked to provide a title or role. |
| *2. Number of years in current role | Free response text box to allow respondents to enter number of years in clinical trials. |
| *3. Experience working in clinical trials (Y/N) | Respondents will be asked to select from either the 'Yes' or 'No' radio button on the online questionnaire. |
| **4. If yes to previous question, experience working in Sub-Saharan Africa (Y/N) | Respondents will be asked to select from either the 'Yes' or 'No' radio button on the online questionnaire. |

****Mandatory field if 'Y' box is ticked for Question 3**



Questions 1 – 4

Strongly
Disagree

Agree

Strongly
Agree

***The global presence of pharmaceutical
companies***

Pharmaceutical companies provide

medicines globally so have a responsibility to
involve developing countries in clinical trials.

1 2 3 4 5

Any clinical trial efforts by pharmaceutical
companies in sub-Saharan Africa should
focus on infectious diseases rather than
chronic diseases.

1 2 3 4 5

Pharmaceutical companies should do more to
ensure that the products they develop are
accessible to those living in developing
countries.

1 2 3 4 5

Most companies do not think that conducting
clinical trials in sub-Saharan Africa is
important.

1 2 3 4 5

Any additional comments

Free text box will accompany this option



Questions 5 – 8:

Commercial considerations

Strongly
Disagree

Agree

Strongly
Agree

Pharmaceutical companies are businesses whose **first** priority should be to generate a profit.

1 2 3 4 5

Sub-Saharan Africa is commercially attractive enough to warrant considerable efforts by pharmaceutical companies to engage its countries in research.

1 2 3 4 5

If a pharmaceutical company has no intention of ever selling a drug in a country then it should not perform any clinical trials with that product there.

1 2 3 4 5

Pharmaceutical companies are missing out on a potential commercial opportunity by not doing more clinical trial work in sub-Saharan Africa.

1 2 3 4 5

Any additional comments

Free text box will accompany this option



Questions 9 – 11:

Informed consent

Strongly
Disagree

Agree

Strongly
Agree

The Western model of informed consent (i.e. consent is required, must only come from the person to be enrolled in the trial, must be freely given etc.) should be applied across all countries in which clinical trials are conducted.

1 2 3 4 5

The way informed consent is collected should be tailored to suit the cultural nuances of the particular region or country where a trial is being conducted, even if this contradicts the requirements of Good Clinical Practice (GCP).

1 2 3 4 5

Informed consent is not handled particularly well in developed countries so it is likely that investigators in developing countries may also struggle.

1 2 3 4 5

Any additional comments

Free text box will accompany this option



Questions 12 – 17:

Ethics and behaviour

Strongly
Disagree

Agree

Strongly
Agree

Corruption and / or fraud are NOT likely to impact the conduct of clinical trials in sub-Saharan Africa

1 2 3 4 5

Pharmaceutical companies are likely to exploit patients involved in clinical trials in sub-Saharan Africa.

1 2 3 4 5

Investigators (clinicians) in sub-Saharan Africa are more likely than those in the West to exploit patients in clinical trials.

1 2 3 4 5

Investigators in sub-Saharan Africa are more likely than those in the West to falsify data for financial gain.

1 2 3 4 5

Pharmaceutical companies in the West do not always conform to GCP

1 2 3 4 5

Pharmaceutical companies do not want to engage in research in sub-Saharan Africa over fears of being considered exploitative.

1 2 3 4 5

Any additional comments

Free text box will accompany this option



**Question 17: Barriers to participation in
clinical trials**

What do you consider the top 3 barriers to
clinical research in developing regions such as
sub-Saharan Africa?

Inadequate infrastructure

☐

Informed consent

☐

Lack of commercial
attractiveness

☐

Please select three responses and indicate
their order of importance by entering a 1, 2 or
3 in the box. Please enter a '1' for the most
important and '3' for the least important out of
the three items you select.

Provision of medicine post-trial

☐

Concerns around unethical
behaviour

☐

Please use the text box to expand if you would
like to add additional comments.

Other (please describe).

☐

Free text box will accompany this option.



Question 18 - 19:

Strongly
Disagree

Agree

Strongly
Agree

***Ethical and scientific responsibilities of
global pharmaceutical companies***

Pharmaceutical companies do NOT have an ethical obligation to conduct clinical trials in developing regions.

1

2

3

4

5

Please use the text box to expand if you would like to add additional comments.

Free text box will accompany this question.

Pharmaceutical companies have a scientific responsibility to conduct clinical trials in developing regions.

1

2

3

4

5

Please use the text box to expand if you would like to add additional comments.

Free text box will accompany this question.

Please add any other comments you would like to make on this topic in the text box below.

Free text box will accompany this question.



Appendix 8: Participant letter of invitation (questionnaire)

Research Participant

Letter of Invitation

Title of Research: Investigating the potential for developing countries to participate in industry sponsored clinical research in chronic, non-communicable diseases.

Dear Sir / Madam,

My name is Efe Egharevba. I am a doctoral student in the College of Medical, Veterinary, and Life Sciences Department at the University of Glasgow. I am conducting a research study as part of the requirements of my PhD in Public Health, and I would like to invite you to participate.

Purpose of the Research

The pharmaceutical industry spends billions of dollars in research and development every year conducting clinical trials in a variety of chronic disease indications. Much of this research is conducted in Western countries, with very little industry sponsored research conducted in Sub-Saharan Africa despite the fact that the levels of chronic disease are rising in this region. The purpose of this research is to investigate the ethics of conducting clinical research in Sub-Saharan Africa in chronic diseases by surveying healthcare professionals based Nigeria and Ghana, government representatives as well as pharmaceutical industry representatives based in the West.



This questionnaire is the second part of my research study. The first part involved conducting a series of interviews across the same group of stakeholders to understand their thoughts on a number of issues associated with conducting industry-sponsored clinical trials in Sub-Saharan Africa. The aim of this questionnaire is get your views on the topics which were raised in those interviews. The aim is to administer this interview to approximately 100 people.

What will happen if I decide to participate?

You will be participating in the second phase of this research project. Therefore, if you decide to participate, you will be asked to complete a short questionnaire asking you about your thoughts on a number of topics associated with clinical research in Sub-Saharan Africa. It should take about 20 minutes to complete

Why have I been chosen?

You have been asked to participate in this research because you fall into one of the stakeholder groups mentioned earlier in this information sheet and I would like to better understand your opinions and thoughts on the ethics, appropriateness and usefulness of carrying out pharmaceutical industry sponsored clinical research in developing countries.

Will I benefit from the study?

Although it is unlikely that you will gain any direct benefit from participating in this research, I hope that through raising the importance of addressing the increasing levels of chronic disease amongst the people living in Sub-Saharan region of Africa, others may eventually benefit.

Will my taking part in the study be confidential?

Your participation in this study will be completely confidential. In the event of presentation or publication, your identity will not be revealed the questionnaire will



collect only basic information which will not make you identifiable. All data collected will be handled in accordance with all applicable university data privacy and handling guidelines and will be kept until the research is completed and all final results of the research have been published.

Is my participation voluntary?

Your participation in this study is voluntary. Consent is taken by you completing the questionnaire. If you do not wish to answer a question you may leave it blank.

Who has reviewed this study?

This study has been reviewed and approved by MVLS College Ethics Committee at the University of Glasgow.

What should I do if I have questions?

If you have any study related questions, concerns or comments, you may contact me at any time on 07886 565 978 or my supervisor;

Professor Jacqueline Atkinson

Tel: +44 (0)1413 305 009

Email: jacqueline.atkinson@glasgow.ac.uk

If you have any questions about your rights as a research participant or complaints about how the research is being conducted you may contact;

Professor Richard Mitchell

Head of Public Health

Tel: +44 (0)1413 330 029



University
of Glasgow

Institute of Health and Wellbeing

Email: richard.mitchell@glasgow.ac.uk

Thank you for taking the time to read this letter of invitation.

Kind regards,

Efe Egharevba

PhD Student

Public Health

1 Lilybank Gardens

Glasgow, G12 8RZ

Email: t.egharevba.1@research.gla.ac.uk



Appendix 9: Ethics approvals

16 August 2012

Dear Terry EGHAREVBA

MVLS College Ethics Committee

Project Title: Investigating the potential for developing countries to participate in industry sponsored clinical research into chronic, non-communicable diseases.
Project No: 2012062

The College Ethics Committee has reviewed your application and has agreed that there is no objection on ethical grounds to the proposed study. They are happy therefore to approve the project, subject to the following conditions

- The research should be carried out only on the sites, and/or with the groups defined in the application.
- Any proposed changes in the protocol should be submitted for reassessment, except when it is necessary to change the protocol to eliminate hazard to the subjects or where the change involves only the administrative aspects of the project. The Ethics Committee should be informed of any such changes.
- If the study does not start within three years of the date of this letter, the project should be resubmitted.
- You should submit a short end of study report to the Ethics Committee within 3 months of completion.

Yours sincerely

Professor William Martin
College Ethics Officer

Professor William Martin
Professor of Cardiovascular Pharmacology

R507B Level 5
School of Life Sciences
West Medical Building
Glasgow G12 8QQ Tel: 0141 330 4489
E-mail: William.Martin@glasgow.ac.uk



2 June 2014

Mr Terry Egharevba
Institute of Health & Wellbeing

Dear Mr Egharevba

MVLS College Ethics Committee

Project Title: Investigating the potential for developing countries to participate in industry sponsored clinical research into chronic, non-communicable disease

Project no. 2012062

The College Ethics Committee has reviewed your request dated 31 May 2014 for a minor amendment to the above project and is pleased to grant it. Specifically, you now have permission to conduct the second part of your questionnaire. This permission is subject to the conditions detailed below:

- Project end date: 1 June 2016.
- The research should be carried out only on the sites, and/or with the groups defined in the application.
- Any proposed changes in the protocol should be submitted for reassessment, except when it is necessary to change the protocol to eliminate hazard to the subjects or where the change involves only the administrative aspects of the project. The Ethics Committee should be informed of any such changes.
- You should submit a short end of study report to the Ethics Committee within 3 months of completion.

Yours sincerely

Professor William Martin
College Ethics Officer

2012062Extension.docx

Professor William Martin
Professor of Cardiovascular Pharmacology

R507B Level 5
School of Life Sciences
West Medical Building
Glasgow G12 8QQ Tel: 0141 330 4489
E-mail: William.Martin@glasgow.ac.uk



University
of Glasgow

Institute of Health and Wellbeing

Mr Terry Egharevba
Institute of Health & Wellbeing
1 Lilybank Gardens
Glasgow, G12 8RZ

8 October 2012

Dear Mr Egharevba

MVLS College Ethics Committee

***Project Title:* Investigating the potential for developing countries to participate in industry sponsored clinical research into chronic, non-communicable diseases. Project No: 2012062**

The College Ethics Committee has reviewed your request of 6 October for a minor amendment to your project and has agreed to it. Specifically, you now have permission to conduct your interviews using Skype. This permission is subject to the conditions detailed below:

- The research should be carried out only on the sites, and/or with the groups defined in the application.
- Any proposed changes in the protocol should be submitted for reassessment, except when it is necessary to change the protocol to eliminate hazard to the subjects or where the change involves only the administrative aspects of the project. The Ethics Committee should be informed of any such changes.
- If the study does not start within three years of the date of this letter, the project should be resubmitted.
- You should submit a short end of study report to the Ethics Committee within 3 months of completion.

Yours sincerely

Professor William Martin
College Ethics Officer



University
of Glasgow

Institute of Health and Wellbeing

Appendix 10: Example email to potential participants (interview)


Expertise Requested for PhD Project Investigating Ethics of Clinical Trials in Sub-Saharan Africa

Terry Egharevba

You forwarded this message on 06/03/2013 20:11.

Sent: 06 March 2013 20:11

To: [REDACTED]

Attachments:  Gha_Niq_Letter_of_Invitati~1.doc (57 KB) [Open as Web Page]

Dear Dr [REDACTED]

Apologies for contacting you out of the blue but I came across your name whilst doing some research on health services in Ghana and I thought you might be able to help me.

My name is Efe Egharevba and I'm currently working on a PhD at the University of Glasgow looking into the ethics of conducting industry sponsored clinical trials in non-communicable diseases in sub-Saharan Africa. As part of this research, I'd like to conduct a short telephone interview with you, if you're agreeable.

In the event that you are interested in helping me, I have attached a letter of invitation which outlines the scope of my project. If you are interested in being part of this research, please drop me an email to let me know and I will be in contact to arrange a time to speak that is convenient for you.

Please do not hesitate to contact me with any questions you may have.

I hope to hear from you, in due course.

Best wishes,
Efe Egharevba

Terry 'Efe' Egharevba
PhD Student
University of Glasgow
Institute of Health and Wellbeing

Mob: +44 7886 565 978
Skype: efe.egharevba
Email: tegharevba.1@research.gla.ac.uk



Appendix 11: HCP letter of invitation (interview)

Research Participant

Letter of Invitation

Title of Research: Investigating the potential for developing countries to participate in industry sponsored clinical research in chronic, non-communicable diseases.

Dear Sir / Madam,

My name is Efe Egharevba. I am a doctoral candidate in the College of Medical, Veterinary, and Life Sciences Department at the University of Glasgow. I am conducting a research study as part of the requirements of my PhD in Public Health, and I would like to invite you to participate.

Purpose of the Research

The pharmaceutical company spends billions of dollars in research and development every year conducting clinical trials in a variety of chronic disease indications. Much of this research is conducted in Western countries with very little industry sponsored research conducted in Sub-Saharan Africa, despite the fact that the levels of chronic disease are rising in this region. The purpose of this research is to investigate the ethics of conducting clinical research in Sub-Saharan Africa in chronic diseases by interviewing healthcare professionals, government representatives and members of patient advocacy groups based in either Nigeria or Ghana as well as pharmaceutical industry representatives based in the West. The research will be conducted in two phases. These interviews will form the first phase of that research. The second phase of the research will involve administering questionnaires to a larger number of people. The questionnaires that



your responses are used to help create will be administered to approximately 100 people in the second phase of this study.

What will happen if I decide to participate?

You will be participating in the first phase of this research project. Therefore, if you decide to participate, you will be asked to meet or speak on the telephone with me for an interview that will last approximately 30 minutes during which you will be asked about your thoughts and experiences with pharmaceutical industry sponsored clinical trials in the Sub-Saharan region of Africa. The interview will take place at a mutually convenient time and place (if face to face). The interview will be audio taped to allow for our discussions to be transcribed and analysed after the interview. The tapes will only be reviewed by myself or a representative from an external transcription company who will be bound by a confidentiality agreement.

In addition to being analysed, the responses that you provide will be used to develop a questionnaire which will be administered to a larger number of people during the second phase of this research.

You will not incur any costs for participating in the interview and taking part in the study is your decision. You may also decide not to answer any questions or discuss any topics which you are not comfortable with during the interview.

Why have I been chosen?

You have been asked to participate in this research because you currently work or have worked in in the Sub-Saharan region of Africa and fall into one of the groups of stakeholders who I would like to interview to understand your opinions and thoughts on the ethics, appropriateness and usefulness of carrying out pharmaceutical industry sponsored clinical research in developing countries. The interviews will be carried out with approximately 14 people based in Nigeria and Ghana.



Will I benefit from the study?

Although it is unlikely that you will gain any direct benefit from participating in this research, I hope that through raising the importance of addressing the increasing levels of chronic disease amongst the people living in Sub-Saharan region of Africa, others may eventually benefit.

Will my taking part in the study be confidential?

Your participation in this study will be completely confidential. In the event of presentation or publication, your identity will not be revealed as all identifiers will be removed. The transcripts from your interview will remain confidential and will be handled in accordance with all applicable university data privacy and handling guidelines and will be kept until the research is completed and all final results of the research have been published.

Is my participation voluntary?

Your participation in this study is voluntary. Should you decide that you would like not like to participate in this research during the interview, you are free to withdraw your consent.

Who has reviewed this study?

This study has been reviewed and approved by MVLS College Ethics Committee at the University of Glasgow.

What should I do if I have questions?

If you have any study related questions, concerns or comments, you may contact me at any time on 07886 565 978 or either of my supervisors;

Dr Rebecca Shaw

Tel: +44 (0)1413 305 010

Email: rebecca.shaw@glasgow.ac.uk



University
of Glasgow

Institute of Health and Wellbeing

Professor Jacqueline Atkinson

Tel: +44 (0)1413 305 009

Email: jacqueline.atkinson@glasgow.ac.uk

If you have any questions about your rights as a research participant or complaints about how the research is being conducted you may contact;

Professor Jill Pell

Head of Public Health

Tel: +44 (0)1413 330 029

Email: jill.pell@glasgow.ac.uk

Thank you for taking the time to read this letter of invitation – if are interested in participating, please contact me at the number above or email me at t.egharevba.1@research.gla.ac.uk to discuss further.

Kind regards,

Efe Egharevba

PhD Candidate

Public Health

1 Lilybank Gardens

Glasgow, G12 8RZ

Email: t.egharevba.1@research.gla.ac.uk

Appendix 12: Pharm letter of invitation (interview)

Research Participant

Letter of Invitation

Title of Research: Investigating the potential for developing countries to participate in industry sponsored clinical research in chronic, non-communicable diseases.

Dear Sir / Madam,

My name is Efe Egharevba. I am a doctoral candidate in the College of Medical, Veterinary, and Life Sciences Department at the University of Glasgow. I am conducting a research study as part of the requirements of my PhD in Public Health, and I would like to invite you to participate.

Purpose of the Research

The pharmaceutical company spends billions of dollars in research and development every year conducting clinical trials in a variety of chronic disease indications. Much of this research is conducted in Western countries with very little industry sponsored research conducted in Sub-Saharan Africa, despite the fact that the levels of chronic disease are rising in this region. The purpose of this research is to investigate the ethics of conducting clinical research in Sub-Saharan Africa in chronic diseases by interviewing healthcare professionals, government representatives and members of patient advocacy groups based in either Nigeria or Ghana as well as pharmaceutical industry representatives based in the West. The research will be conducted in two phases. These interviews will form the first



phase of that research. The second phase of the research will involve administering questionnaires to a larger number of people. The questionnaires that your responses are used to help create will be administered to approximately 100 people in the second phase of this study.

What will happen if I decide to participate?

You will be participating in the first phase of this research project. Therefore, if you decide to participate, you will be asked to meet or speak on the telephone with me for an interview that will last approximately 30 minutes during which you will be asked about your thoughts and experiences with pharmaceutical industry sponsored clinical trials in the Sub-Saharan region of Africa. The interview will take place at a mutually convenient time and place (if face to face). The interview will be audio taped to allow for our discussions to be transcribed and analysed after the interview. The tapes will only be reviewed by myself or a representative from an external transcription company who will be bound by a confidentiality agreement.

In addition to being analysed, the responses that you provide will be used to develop a questionnaire which will be administered to a larger number of people during the second phase of this research.

You will not incur any costs for participating in the interview and taking part in the study is your decision. You may also decide not to answer any questions or discuss any topics which you are not comfortable with during the interview.

Why have I been chosen?

You have been asked to participate in this research because you hold a relevant position within the pharmaceutical industry and I would, therefore, like to interview you to understand your opinions and thoughts on the ethics, appropriateness and usefulness of carrying out pharmaceutical industry sponsored clinical research in



developing countries. The interviews will be carried out with approximately 10 pharmaceutical representatives based in the EU and US.

Will I benefit from the study?

Although it is unlikely that you will gain any direct benefit from participating in this research, I hope that through raising the importance of addressing the increasing levels of chronic disease amongst the people living in Sub-Saharan region of Africa, others may eventually benefit.

Will my taking part in the study be confidential?

Your participation in this study will be completely confidential. In the event of presentation or publication, your identity will not be revealed as all identifiers will be removed. The transcripts from your interview will remain confidential and will be handled in accordance with all applicable university data privacy and handling guidelines and will be kept until the research is completed and all final results of the research have been published.

Is my participation voluntary?

Your participation in this study is voluntary. Should you decide that you would like not like to participate in this research during the interview, you are free to withdraw your consent.

Who has reviewed this study?

This study has been reviewed and approved by the MVLS College Ethics committee at the University of Glasgow.

What should I do if I have questions?

If you have any study related questions, concerns or comments, you may contact me at any time on 07886 565 978 or either of my supervisors;



University
of Glasgow

Institute of Health and Wellbeing

Dr Rebecca Shaw

Tel: +44 (0)1413 305 010

Email: rebecca.shaw@glasgow.ac.uk

Professor Jacqueline Atkinson

Tel: +44 (0)1413 305 009

Email: jacqueline.atkinson@glasgow.ac.uk

If you have any questions about your rights as a research participant or complaints about how the research is being conducted you may contact;

Professor Jill Pell

Head of Public Health

Tel: +44 (0)1413 330 029

Email: jill.pell@glasgow.ac.uk

Thank you for taking the time to read this letter of invitation – if are interested in participating, please contact me at the number above or email me at t.egharevba.1@research.gla.ac.uk to discuss further.

Kind regards,

Efe Egharevba
PhD Candidate
Public Health
1 Lilybank Gardens
Glasgow, G12 8RZ
Email: t.egharevba.1@research.gla.ac.uk

Appendix 13: Example email sent to Study 2 (questionnaire) participants

Expertise Requested for PhD Project Investigating Ethics of Clinical Trials in Sub-Saharan Africa

Terry Egharevba

You forwarded this message on 28/06/2014 13:37.

Sent: 28 June 2014 13:28

To: [REDACTED]

Attachments:  Letter of Invitation - Que~1.doc (55 KB) [Open as Web Page]

Dear Dr [REDACTED],

Apologies for contacting you but my name is Efe Egharevba and I am currently a part-time PhD student at the University of Glasgow and I came across your name during my literature review. I'm currently undertaking research looking at the ethics associated with conducting pharmaceutical company sponsored clinical trials in chronic diseases in sub-Saharan Africa. I came across your name during my literature review.

As part of this research I have created a short online questionnaire and am soliciting the expertise of health care professionals in the region as well as pharma professionals globally in order to gain some insight into the opinions on a number of issues associated with conducting clinical trials in sub-Saharan Africa. I would be extremely grateful if you could take a few minutes to access and complete the questionnaire which can be found at the following link;
<http://freeonlinesurveys.com/app/rendersurvey.asp?sid=2nso98va928ya90494176&refer=www%2Efacebook%2Ecom>

If you could complete the questionnaire by the 5th July, I would be extremely grateful.

I have attached a letter of invitation which will provide you with a bit more background information on the study's aims and objectives.

If you have any questions on anything at all, please do not hesitate to contact me. If you have any colleagues who you think would be interested in contributing to this research, please feel free to forward the link onto them as well.

Thank you again for your help.

Best wishes,
Efe

Terry 'Efe' Egharevba
PhD Student
University of Glasgow
Institute of Health and Wellbeing

Appendix 14: Codes generated from thematic analysis of transcripts

The provision of medicine post-trial is one of the most frequent ethical concerns raised by stakeholders in multiple groups. This is not an issue exclusive to the Sub-Saharan region of Africa, but is of particular concerns in this region due to the countries socioeconomic climate.

Codes: Ethical

| | |
|---|---|
| Availability of gold standard treatment | Provision of medicine after the trial is a contentious issue if the drug wouldn't be accessible to patients normally |
| Availability of medicines after a trial | Provision of medicine post trial is off putting for companies conducting oncology trials |
| Provision of medicine post trial | Ethical concerns - the biggest is provision of medicines after the trial |
| Provision of medicine after the completion of a trial is a universal issue, not one specific to SS Africa | There are instances of trials where patients are given trial drug then compassionate use after a trial despite the fact the drug would be far too expensive to be provided normally in that country |
| Provision of medicine after the trial | Pharma companies should not run trials in a region if the intention is not to make the drug available at the end of the research |
| Provision of medicine after the trial hasn't put pharma companies off in the past | Availability of gold standard treatment |
| Provision of medicine after the trial is a big issue for conducting trials in SS Africa and some countries won't conduct trials where there is no provision of trial medication or gold standard alternative post trial | Declaration of Helsinki |

Informed consent is an issue that has numerous challenges associated with it in developing countries due to lower levels of literacy, lack of understanding of the clinical trial process and cultural differences which mean that the western informed consent process may not necessarily fit the region.

Codes: Ethical

| | |
|---|--|
| Ethical concerns - gender issues and consent | Informed consent is one of the biggest ethical challenge associated with conducting clinical trials in SS Africa (Nodes) |
| Ethical concerns - informed consent | Informed consent is the biggest ethical challenge associated with conducting clinical trials in SS Africa |
| Ethical concerns - patients understanding of clinical trial process | |
| Illiteracy | Informed consent isn't done particularly well in developed countries so developing countries could struggle |
| Informed consent | |
| Informed consent - lack of understanding | Issues outside of ICF and GCP trained investigators can be handled and overcome |
| Informed consent - minors | The biggest ethical concern is informed consent |

The legacy of pharma companies in some countries, both developed and developing, is contentious. The potential for patients and / or HCPs to be exploited is greater in developing countries because of socioeconomic conditions which exist in these regions. Sub-Saharan Africa also has a legacy of corruption and fraud at numerous levels and there is concern that this could affect both investigators and / or pharma companies (and potentially ethical and regulatory bodies).

Codes: Ethical

| | |
|--|---|
| Coercion | Ethics - there is a concern that ethical issues might be taken out of context because of the population the drug is being investigated in |
| Corruption | Exploitation - is a difficult concept to get away because those who aren't familiar with trials may even label things we do in the west as exploitative |
| Corruption - Clinical trials in SS Africa could lead to corruption (Nodes) | Falsification of data is an issue in Ghana |
| Corruption - Clinical trials in SS Africa could lead to corruption | Fraud |
| Corruption - Clinical trials in SS Africa could lead to corruption (Nodes) | Government organisations in the western world ineffectively try to police the behaviour of pharmaceutical companies |
| Corruption - transparency index | Patients in SS Africa may know about some of the unethical things that pharmaceutical companies have done in the past |
| Corruption in SS Africa is a misconception | |
| Ethical concerns - fair market value and payment to investigators to SS Africa | Patients in SS Africa would be used simply as bodies in clinical research |
| Ethics - fear of reputational damage | |
| The lack of heterogeneity (sex, race) in pharma company board rooms may be contributing to the lack of emphasis on ensuring developing countries are involved in clinical research | Pharma companies ethical responsibility |
| Pharma companies in the west manipulate data in order to affect the outcomes of trial results | Pharma companies have cleaned up their act in SS Africa |
| Pharma companies have done unethical things in the past | Pharma companies still have questionable ethics in West, let alone the developing world |
| Pharma companies have historically not had a good record in developing countries with respect to informed consent and treatments for chronic disease | Pharma companies work in a tough paradigm but those turning profit should look at giving to lesser developed countries in some way |
| Pharma companies like to think they're ethical but whether or not there is an ethical obligation to involve poorer countries in research is a tough one | Trust |
| Pharma companies should apply the same, if not more stringent ethical guidelines on trials conducted in SS Africa | Finance - Accountability of payments to investigators |
| Pharma companies sometimes try and run clinical trials in SS Africa that wouldn't pass ethical review in the Western world | In SS Africa some people take part in trials with expensive drugs just to gain availability |
| Pharma companies have to be careful that they're not perceived to be bribing | In the right sort of studies, issues such as corruption can be overcome |
| Pharma companies are not perceived well in developed countries | Many Africans are vulnerable because of their financial situation which raises ethical concerns such as coercion |
| Pharma companies don't want to engage in research in the region over fears of being perceived as exploitative | Patients in SS Africa should not be paid for participation in clinical trials |
| Pharma companies in the west have poor behaviour | SS Africa is getting more and more investment from international banks which is having a positive effect on corruption. |

Pharmaceutical companies are businesses that ultimately exist to generate profit. This single fact dictates many of the decisions they make. Africa's lack of commercial attractiveness is an important factor which has precluded clinical research being performed in region to date.

Codes: Commercial

| | |
|--|--|
| Chronic diseases aren't researched in SS Africa because pharma companies won't make a profit | Pharma companies exist to make a profit |
| Developing medicines for poorer countries presents issues for pricing | Pharma companies focus on developing treatment for chronic diseases because they are longer term treatments and therefore provide a better ROI |
| Industry sponsored research in SS Africa has little commercial importance except for diseases of political influence such as HIV | Opening up of drug libraries to academics and interested parties may benefit the SS region of Africa |
| Not involving poorer countries in clinical research is a missed commercial opportunity | Pharma companies gain sales and market increases by having a larger presence in SS Africa |
| People in the west favour expensive monoclonal antibodies over affordable medicines | |
| Pharma companies are concerned about their Return on Investment (ROI) | HIV drug development and research was driven through the profit margins in the west and probably would not have been prioritised were it not for the potential profit companies stood to gain |
| Pharma companies are only in Africa for the money | |
| Pharma companies could benefit from running trials in SS Africa because of the potential commercial attractiveness | Some of the things inherent in the way SS Africa does business are fundamentally at odds with the way pharma companies are encouraged to do business in the West |
| Pharma companies don't focus on infectious diseases because they're not financially lucrative | Pharma companies need some sort of return on investment (if even if not the classic margins) in order to make their contribution to research in developing countries sustainable |
| Pharma companies don't make much money in Africa and are therefore not sensitive about what HCPs in the region have to say | Pharma companies need to earn profit and recover investment |
| Pharma companies should be conducting clinical trials in SS Africa because of the economic growth and the potential market share that the region represents | Pharma companies focus on developing treatment for chronic diseases because they are longer term treatments and therefore provide a better ROI |
| Pharma companies work in a tough paradigm but those turning profit should look at giving to lesser developed countries in some way | Pharma companies work in a tough paradigm but those turning profit should look at giving to lesser developed countries in some way |
| Pharma is interested in making money | Pharma is interested in making money |
| Philanthropic acts by pharma are sometimes a way to create profit through intangible assets | Philanthropic acts by pharma are sometimes a way to create profit through intangible assets |
| The lack of drivers for pharma companies to conduct research in SS Africa combined with the actual cost of doing the studies detracts from the motivation pharma companies feel to conduct trials in that region | The lack of drivers for pharma companies to conduct research in SS Africa combined with the actual cost of doing the studies detracts from the motivation pharma companies feel to conduct trials in that region |
| The population of SS Africa will soon be 1 billion people and pharma companies are missing out on potential revenue by not doing more work in the region | There is a widespread need for cheap medicines but those who potentially have them in their drug libraries not interested in developing them because of limited potential for profit |

The cost of drug development is high which leads to drug companies charging high prices for products produced. The costs of these medicines in sub-Saharan Africa are prohibitively high and cast doubt on the appropriateness of conducting trials in this region as accessibility will be limited to a wealthy few.

Codes: Commercial

| | |
|---|--|
| Changes need to be made around the patent system to encourage drug companies to charge less for their medicines | Affordability of medication - if people can't afford the medicines being tested pharma companies won't do research in SS Africa |
| Pharma companies need to do more to make their drugs accessible to poorer patients | Changes need to be made around the patent system to encourage drug companies to charge less for their medicines |
| Recent treatments are too expensive and inaccessible to poorer patient populations | Cost of drugs is prohibitively high in SS Africa |
| Socioeconomic changes in region | Drugs are expensive to produce |
| The trend of high cost medicines is a short term one because payers cannot afford them long term | Industry sponsored research in SS Africa has little commercial importance except for diseases of political influence such as HIV |

Pharmaceutical companies have a responsibility to research the differences in response to treatment for patients based in different parts of the world to ensure both safety, and efficacy of products made available globally.

Codes: Medical / Scientific

| | |
|--|--|
| Biological differences between different racial groups | If a trial is positive in one country in Africa, other countries in Africa will use the drug too |
| Biological differences between races | SS African patients may not necessarily fit all of the criteria if they are from truly developing countries |
| Concomitant use of traditional medicines is akin to patients self-medicating with OTC drugs from their pharmacy | Running a trial solely in Africa would not give an accurate reflection of the global picture |
| Differences in treatment doses necessitated by biological differences in response to treatment often come about through clinical experience and not through data from trials | Safety data should be collected from patients in Africa |
| Evidence based medicine forms the basis of medical practice | SS Africa does not have a significant evidence base for a lot of its current treatment practices |
| Increased focus on personalised healthcare should create more opportunities for SS Africa to be involved in research | SS Africa tend to have to prescribe based on what is approved in the Western world |
| Pharma companies sell their drugs to a diverse group of people so studies should be done everywhere. | Research, in order to be useful, must be reproducible and well-controlled in order for them to be worthwhile |

Due to changing socioeconomic conditions in the region, the disease landscape of sub-Saharan Africa has changed such there are rising levels of chronic diseases. This, however, should not take focus away from existing priorities which include the prevention and treatment of infectious diseases.

Codes: Medical / Scientific

| | |
|---|---|
| Africa has a double burden of disease | HIV drug development and research was driven through the profit margins in the west and probably would not have been prioritised were it not for the potential profit companies stood to gain |
| Prevailing opinion is that infectious disease mortality is the same as infectious disease | HIV remains a serious problem for SS Africa |
| Chronic and infectious disease are just as important as each other to research | Infant mortality may be of larger concern than focussing on chronic or infectious disease |
| Chronic disease is a significant health problem in SSA | Tuberculosis |
| chronic diseases are increasing in prevalence in SS Africa | Infectious disease - people tend to focus on these because they're obvious without considering what treating these diseases may mean for chronic disease down the line |
| Chronic diseases are naturally coming into the research spotlight through the tackling of infectious diseases | Infectious diseases are low hanging fruit in terms of gaining life years and therefore should remain the research priority in SS Africa |
| Chronic diseases aren't often considered for clinical trials in SS Africa | |
| Clinical trials can raise awareness and control the spread of disease | Infectious diseases could be a hook for clinical research into SS Africa because of their higher prevalence and |
| Data suggests that the average age of people living in West Africa is increasing | It's difficult to say whether or not infectious disease has research priority over chronic disease in SS Africa |
| Historically research in SS Africa has focussed on infectious diseases | Infectious diseases still are still a significant problem for sub-Saharan Africa |
| HIV - SS Africa receive 'crumbs from the table' with respect to first world medicines to treat the disease | Infectious diseases studies could be a way of getting staff used to the standards they will need to be working to in order to attract more useful research |
| Monitoring of infectious disease trials in dangerous regions presents an operational challenge | Infectious diseases, when not treated, lead to chronic diseases |
| Most of the research in Ghana is in infectious disease. | Prevalence of non-communicable disease in SS Africa |
| Most trials done in SS Africa are in infectious disease as this gets the most publicity and disease levels are more documented | Research outside of infectious disease is usually investigator led |
| No good programs exist to tackle chronic diseases | There is a need for safe and effective medicines for chronic diseases in sub-Saharan Africa |
| Pharma companies shouldn't focus on infectious diseases versus chronic, they should look at what is important to a particular community | Transition from infectious disease to chronic disease |

Much of the problem of prioritising research efforts in sub-Saharan Africa come from the lack of epidemiological data for the region. A lot of work is needed to be able to quantify the extent of the problems before efforts can be made to tackle them.

Codes: Medical / Scientific

| | |
|---|--|
| Epidemiological research | Evidence based medicine forms the basis of medical practice |
| Epidemiological research is necessary to quantify prevalence | Major problem for SSA is lack of reliable epidemiological data |
| Epidemiological studies are difficult to run in SS Africa because of cultural barriers | Registries |
| Epidemiological studies show there is a big problem with non-communicable diseases in SS Africa | |

Deficiencies in infrastructure and ethical & regulatory review framework and processes, whether perceived or actual, have precluded pharma companies from placing clinical trials in the sub-Saharan region of Africa. These deficiencies (if / where they exist) need to either be redressed or where deficiencies are only perceived, capabilities need to be communicated to pharma companies to attract more research. Further research being conducted in the region will contribute and develop existing infrastructure further.

Codes: Practical / operational

| | |
|--|---|
| Africa is undergoing a renaissance with rapidly growing infrastructure | Regulatory - Africa is trying to develop a harmonised legislation for clinical trials in SS Africa |
| As healthcare systems develop and get better they will begin to attract more trials. | |
| Countries in SS Africa should ensure that regulatory and ethical framework is in place in order to maintain high standards of research potentially involving external countries who already have the appropriate infrastructure in place | Regulatory - holes in regulations are being addressed with assistance from established countries |
| Developing countries are very willing to participate in trials. Those with infrastructure generally provide results. | SS Africa should ensure that infrastructure is put in place then high quality successful studies should be conducted in order to demonstrate their ability in clinical trials] |
| Equipment | Regulatory - oversight is very important |
| In order to improve the clinical research capabilities of SS Africa then one should target disease areas where existing infrastructure is already supportive e.g. infectious diseases | SS African can attract more research to the region by focussing on their infrastructure |
| Infrastructure | Regulatory - regulation is new to SS Africa |
| Limited capabilities (perceived or actual) have precluded more clinical trial work being done in SS Africa to date | |
| Pharma company resource can help develop the region | Regulatory - regulatory organisations require racial diversity within their clinical trials |
| Pharma presence brings infrastructure, investment and education | Regulatory review |
| Practical issues - constant electricity | Regulatory review - can lead to delays for some studies which may deter pharma from conducting studies in the region |
| Record keeping | Sites in Africa lie dormant after large scale infectious disease trials are completed |
| SS African countries need to put into place basic infrastructure to facilitate conduct of research | Some countries in Europe are still not actively involved in clinical trials because they lack the appropriate equipment and healthcare systems |
| The Chinese are putting in infrastructure which is helping the SS region of Africa develop | Some countries in SS Africa have well developed systems for reviewing clinical trial applications. These systems can often be extremely bureaucratic. Some have systems which don't seem robust at all. |
| The reasons (3) more work isn't being done in SS Africa is; infrastructure, cost, and reputational risk of being seen as exploitative. | Some countries in SS Africa have well developed systems for reviewing clinical trial applications. These systems can often be extremely bureaucratic. Some have systems which don't seem robust at all. |
| There are academic units of excellence in which research could be conducted spread throughout Africa | There are challenges associated with the shipping and storage of medicine to SS Africa |
| There are varying levels of development between countries in the SS Africa region. Pharma companies should start research in more developed countries before moving to those lesser developed. | Transporting of drug from the West to SS Africa can be difficult |
| Capacity building | Tribal wars |
| Larger presence of the pharma industry would bring collateral benefits such as education, information and jobs | Learnings from the industrial revolution in the West should be applied to those living SS Africa who are beginning to live in close confinement in urban environments |
| | South Africa is getting more work because of better facilities |
| Pharma companies could add value to the SS region of Africa | South Africa is an anomaly in Africa because of its history, infrastructure and politics |
| | People do not look hard enough at Africa's potential to be involved in clinical trials |

Education at multiple levels is key to driving the increase of clinical research in sub-Saharan Africa. This includes education of the public, education of pharma, and education of healthcare professionals in the region.

Codes: Education

| | |
|---|---|
| Education - investigator training | Investigators in Nigeria have been trained in research methods but have no research to do |
| Education has more of a role to play in spreading awareness of disease than research | Unfamiliarity with SS Africa |
| Education is necessary before implementing a trial | Issues outside of ICF and GCP trained investigators can be handled and overcome |
| Pharma companies could provide health care education and work with charitable organisations | Many patients in SS Africa probably don't know a lot about the pharmaceutical industry |
| Training | Work needs to be done to dispel myths and misbeliefs about participation in clinical trials |
| Public enlightenment | Misconceptions about clinical trials |
| Campaigning and disease awareness is getting better in the US and Australia | |

Appendix 15: Analysis and interpretation of categories and themes generated from transcript analysis.

Mind Map of ethical theme with codes and sub-codes.

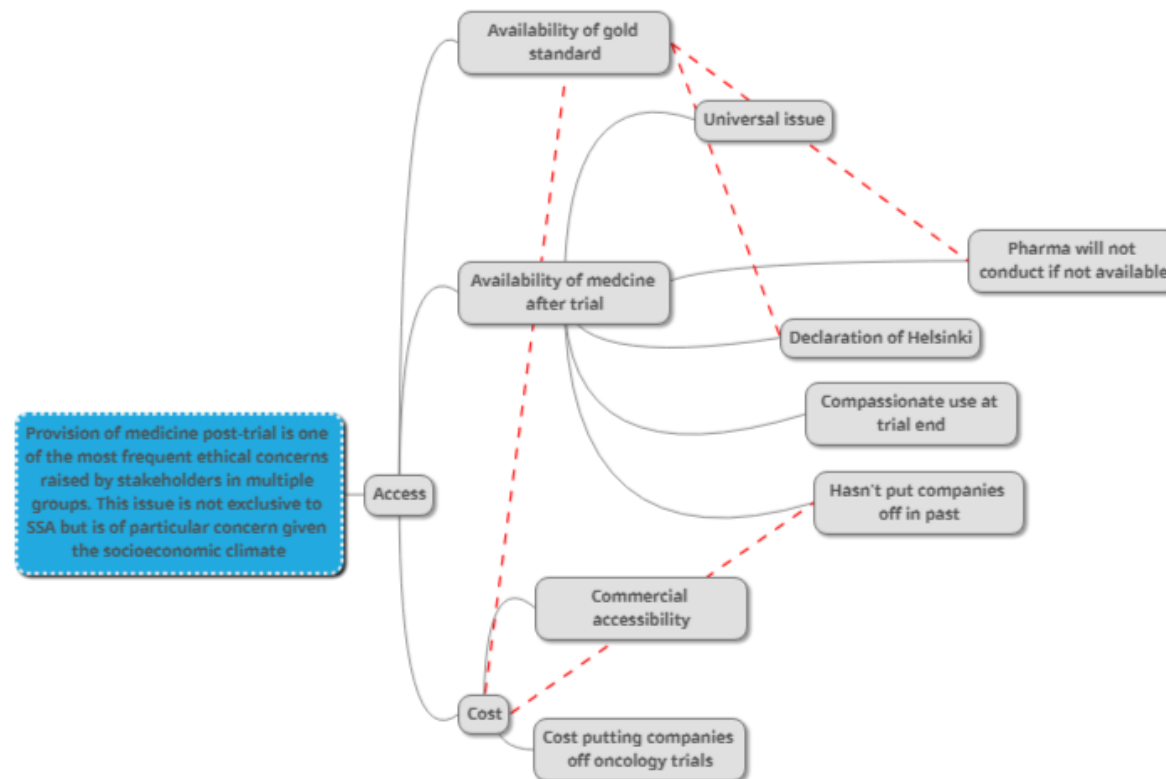


Figure 8: Analysis and interpretation of theme related to post-trial provision of medicine to trial participants

Mind map of ethical theme with codes and sub-codes

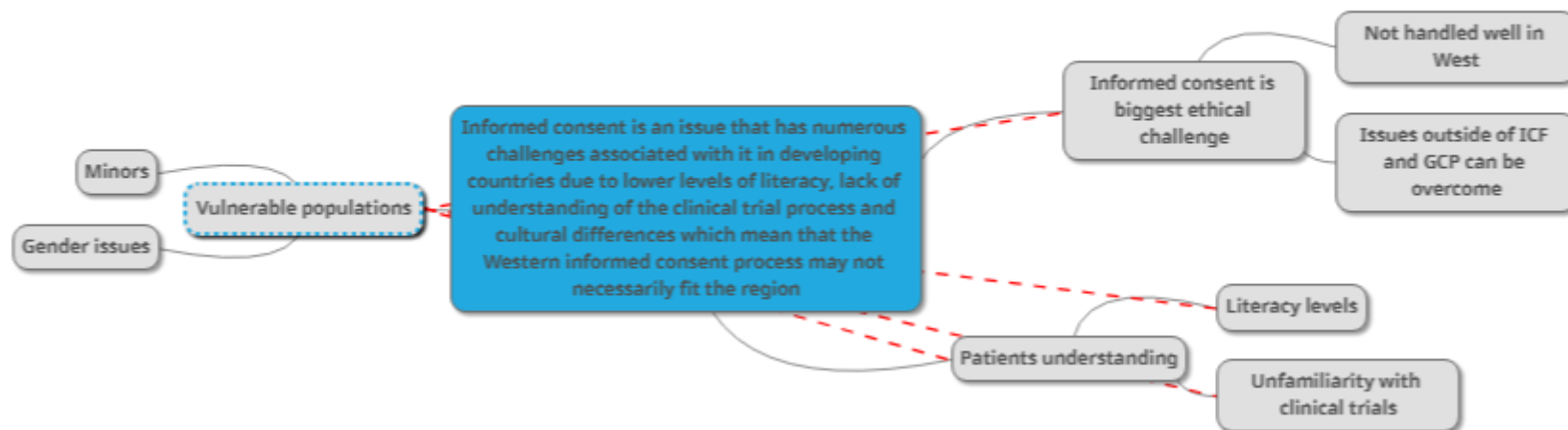


Figure 9: Analysis and interpretation of theme related to informed consent

Mind Map of ethical theme with codes and sub-codes

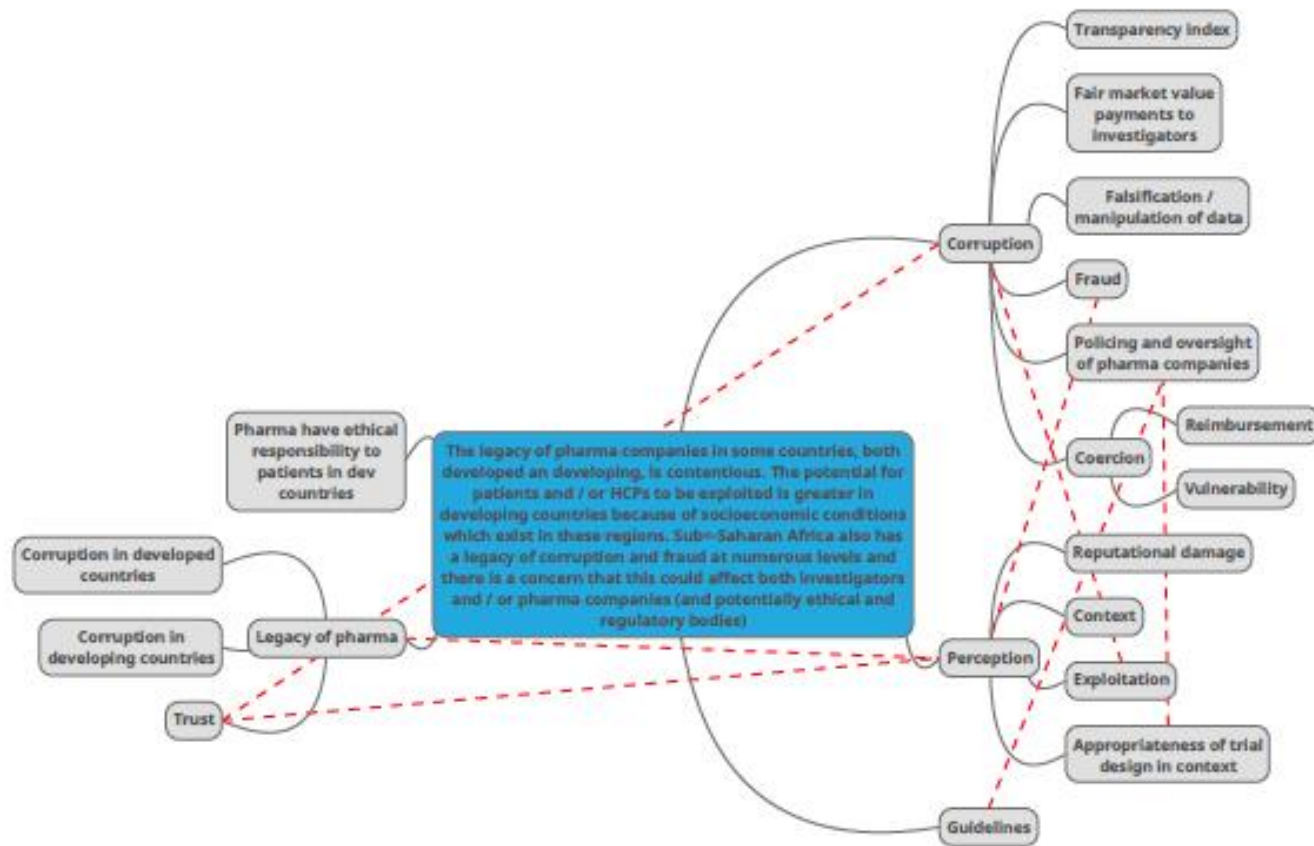


Figure 10: Analysis and interpretation of theme related to the legacy of pharmaceutical companies in Sub-Saharan Africa.

Mind Map of commercial themes with codes and sub-codes

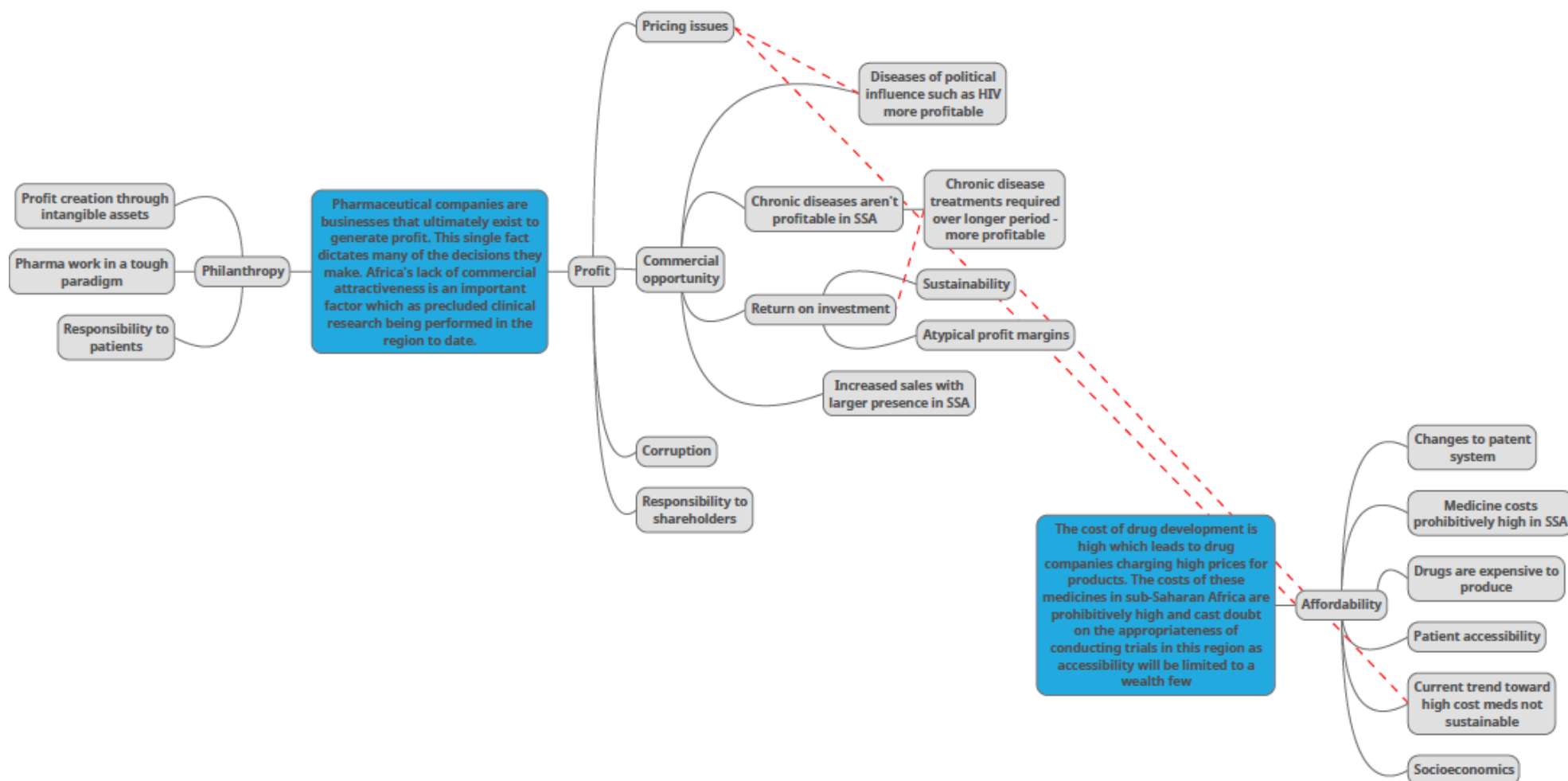


Figure 11: Interpretation and analysis of codes related to pharmaceutical companies' drive for profits, the high cost of treatments and their interrelatedness. .

Mind Map of scientific / medical theme with codes and sub-codes

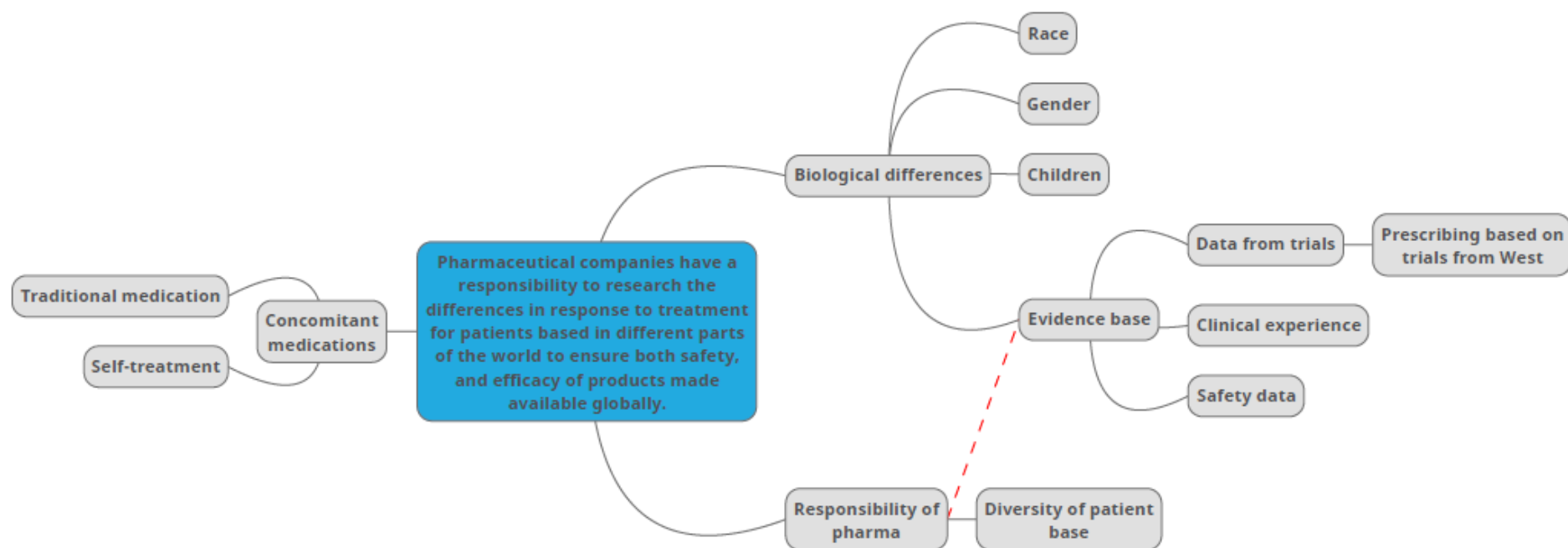


Figure 12: Analysis and interpretation of themes related to pharma's responsibility to research differences in treatment outcomes in different ethnic groups. .

Mind Map of scientific / medical theme with codes and sub-codes

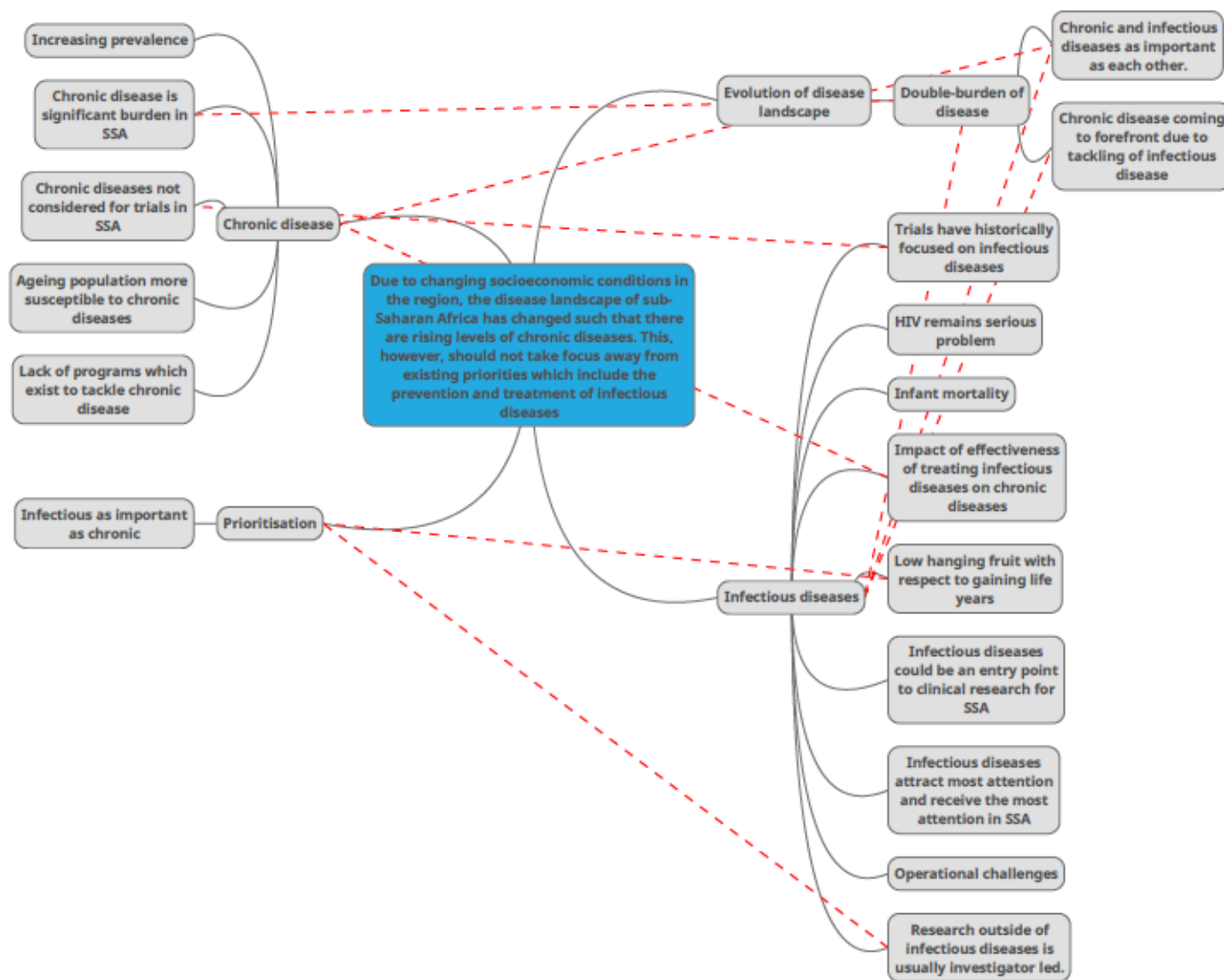


Figure 13: Analysis and interpretation of theme related to Sub-Saharan Africa's changing landscape.

Mind Map of scientific / medical theme with codes and sub-codes

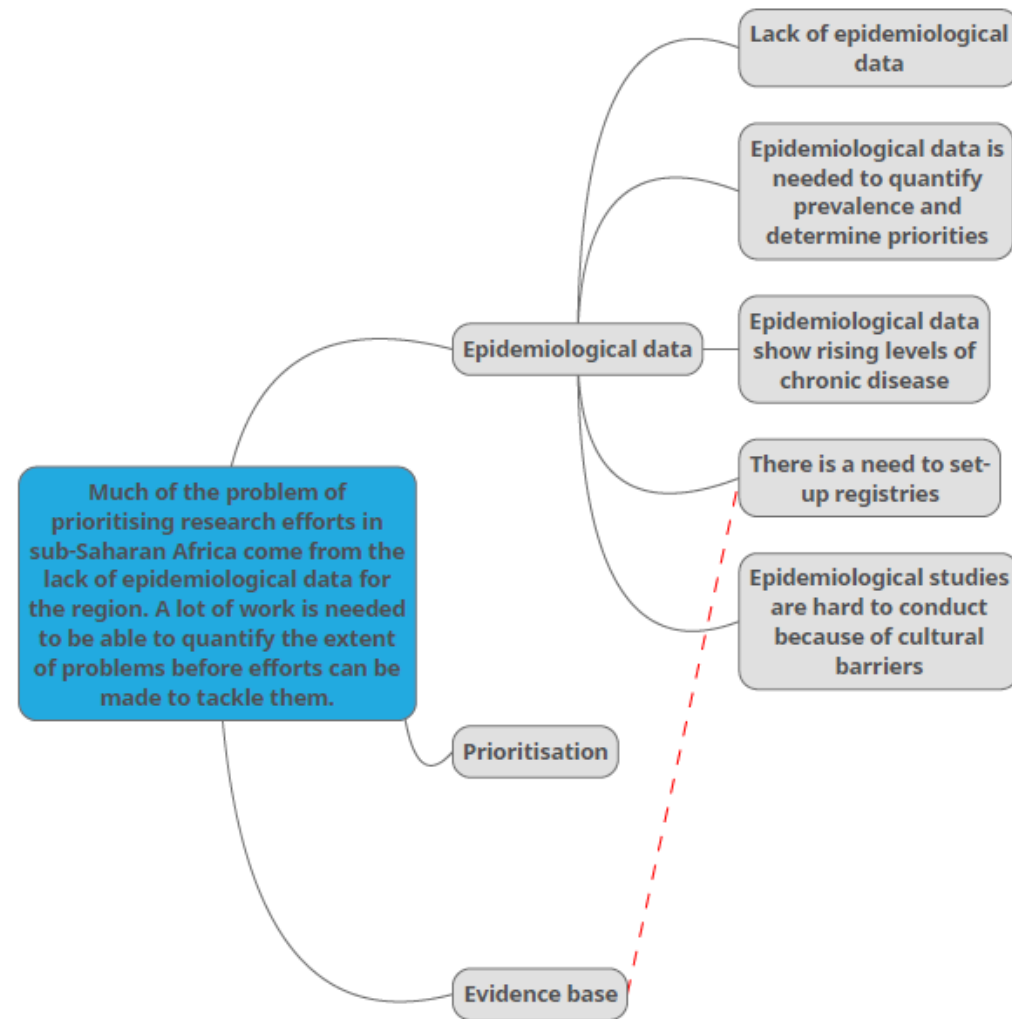


Figure 14: Analysis and interpretation of themes related to lack of epidemiological data

Mind Map of practical / operational theme with codes and sub-codes

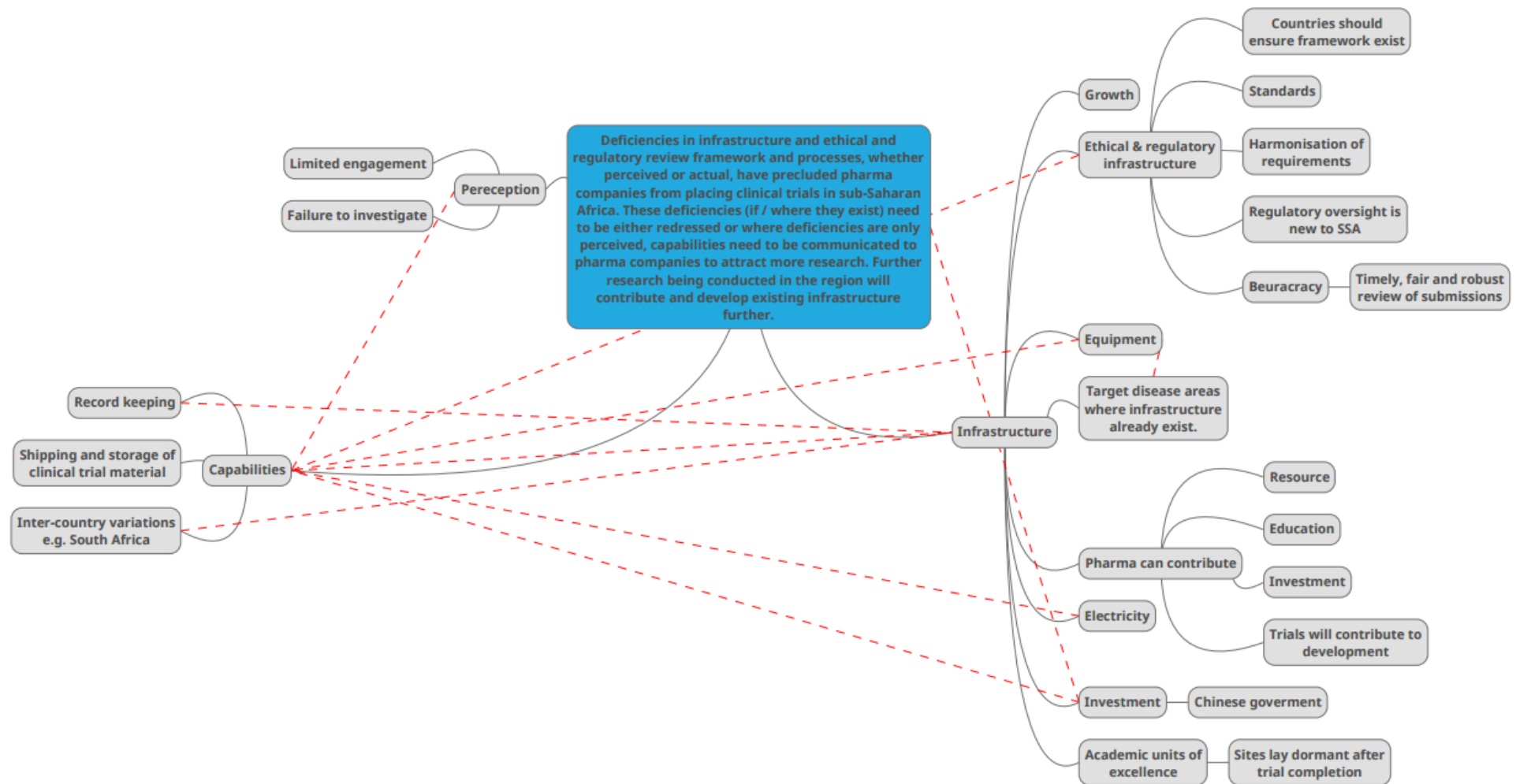


Figure 15: Analysis and interpretation of themes related to deficiencies in infrastructure

Mind Map of educational theme with codes and sub-codes

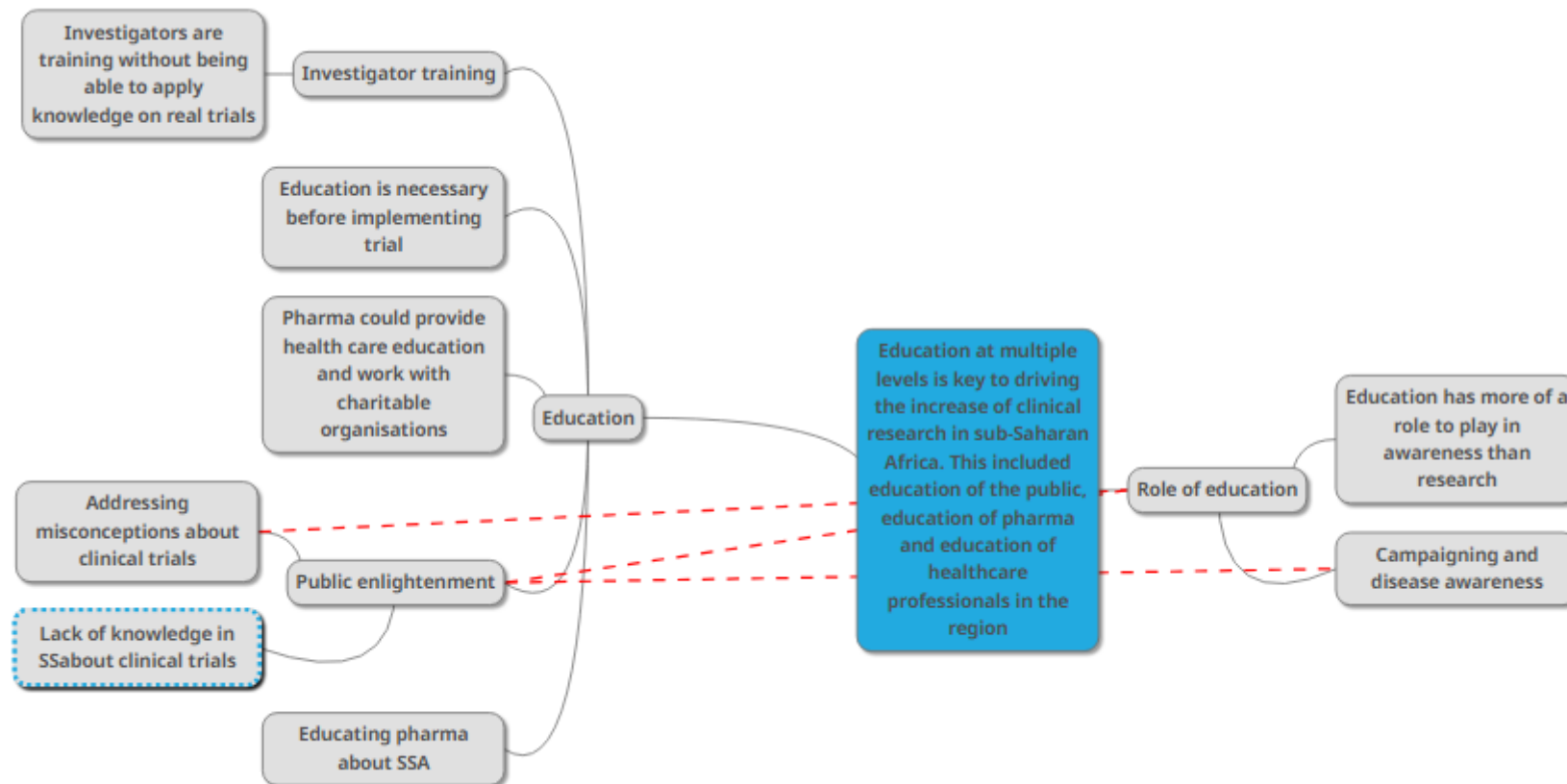


Figure 16: Analysis and interpretation of the themes related to education

Appendix 16: List of Respondents who participated in Study 1 (Interviews)

| Unique Identifier | Role | Years in Current Role | Clinical Trial Experience? | Method of Interview | Location |
|-------------------|--|-----------------------|-----------------------------|---------------------|--------------|
| HCPN_1 | Physician / Clinical Pharmacologist | 10+ | Yes – as Research Physician | Skype | Nigeria |
| HCPN_2 | Radiologist | 30+ | Yes – as Research Physician | Telephone | Nigeria |
| HCPN_3 | Surgeon | 15+ | No | Telephone | Nigeria |
| HCPG_1 | Radiographer | 20+ | Yes | Telephone | Ghana |
| HCPG_2 | Research Fellow | 15+ | Yes | Telephone | Ghana |
| HCPG_3 | Clinical Oncologist | 15+ | Yes | Telephone | Ghana |
| REG_1 | Food & Drugs Board | 10+ | Yes – Regulatory | Telephone | Ghana |
| PHARM_1 | CEO Strategy & Business Development | 20+ | Yes – Pharma | Face to face | UK |
| PHARM_2 | Operational Leader [Pharmaceutical Company] | 10+ | Yes – Pharma | Face to face | UK |
| PHARM_3 | Non-executive Chairman, [Clinical Research Organisation] | 20+ | Yes – Pharma | Skype | South Africa |
| PHARM_4 | Operational Leader, [Pharmaceutical Company] | 20+ | Yes – Pharma | Face to face | UK |
| PHARMA_5 | Executive Director, Operations, [Pharmaceutical Company] | 5+ | Yes – Pharma | Face to face | UK |
| PHARMA_6 | Medical Research Manager, [Pharmaceutical Company] | 15+ | Yes – Pharma | Telephone | UK |
| PHARMA_7 | Interim Clinical Director, [Pharmaceutical Company] | 15+ | Yes – Pharma | Telephone | UK |
| PHARMA_8 | Medical Director, [Pharmaceutical Company] | 20+ | Yes – Pharma | Telephone | UK |
| PHARMA_9 | Head of Translational Medicine, [Non-Profit Foundation] | 15+ | Yes – Pharma | Telephone | Switzerland |

Appendix 17: List of respondents who participated in Study 2 (Questionnaire)

This information was taken directly from an output from the online software and so all information captured is as entered. The last column relates to the stakeholder group each respondent falls under as identified by myself, and was not self-reported.

| Job title or role?* | Number of years in current role?* | Experience working in Clinical Trials?* | If yes to previous question, experience working in sub-Saharan Africa? | Corresponding stakeholder group / Identifier* ** |
|---|--|--|---|---|
| Director, Clinical Science | 6 | Yes | No | PHARM(1) |
| Study Manger | 4 | Yes | No | PHARM(2) |
| Study Manger | 4 | Yes | No | PHARM(3) |
| Senior Clinical Study Manager | 10 | Yes | No | PHARM(4) |
| Clinical Trial Manager | 4 | Yes | No | PHARM(5) |
| Clinical Project Manager | 2 | Yes | No | PHARM(6) |
| Clinical Pharmacovigilance Operations Manager | 0-1 | Yes | No | PHARM(7) |
| Global Studies Manager | 3 | Yes | No | PHARM(8) |
| Clinical Research LOC Support Manager | 1 | Yes | No | PHARM(9) |
| Study Manager | 7 | Yes | No | PHARM(10) |
| Lead Clinical Study Manager | 2 | Yes | Yes | PHARM(11) |
| Clinical Study Manager | 11 | Yes | No | PHARM(12) |
| Global Study Manager | 2 | Yes | No | PHARM(13) |
| Clinical Operations Manager | 5.5 | Yes | No | PHARM(14) |
| Clinical Research Associate | 3 | Yes | No | PHARM(15) |

| Job title or role?* | Number of years in current role?* | Experience working in Clinical Trials?* | If yes to previous question, experience working in sub-Saharan Africa? | Corresponding stakeholder group / Identifier* ** |
|--|--|--|---|---|
| Clinical Site Management Oversight | 1 | Yes | No | PHARM(16) |
| Global Studies Leader | 2.5 years | Yes | Yes | PHARM(17) |
| Global Studies Manager | 5 | Yes | No | PHARM(18) |
| Country Study Manager | Two | Yes | No | PHARM(19) |
| Medical Manager | 1 | Yes | No | PHARM(20) |
| Clinical Research Associate | 8 | Yes | No | PHARM(21) |
| Global Studies Manager | 3 | Yes | Yes | PHARM(22) |
| Global Studies Manager | 3.5 years | Yes | No | PHARM(23) |
| Clinical PV Operations | 2.5 years | Yes | No | PHARM(24) |
| Global Studies Manager | 10 | Yes | No | PHARM(25) |
| Clinical Operations Manager | 3 | Yes | No | PHARM(26) |
| Scientific Director | 0.5 | Yes | Yes | PHARM(27) |
| Senior Associate, GSM | 1 | Yes | No | PHARM(28) |
| Chairman | 6 | Yes | Yes | PHARM(29) |
| Managing Director of African CRO | 14 | Yes | Yes | PHARM(30) |
| Clinical Studies Manager | 15 | Yes | No | PHARM(31) |
| Clinical Programme Manager | 1 | Yes | No | PHARM(32) |
| Medical Director | 4 | Yes | No | PHARM(33) |
| Clinical Study Manager | 8 | No | | PHARM(34) |
| Study Manager | 8 | Yes | No | PHARM(35) |
| Clinical Study Manager | 2 | Yes | No | PHARM(36) |
| Associate Director Clinical Operations | 2 | Yes | No | PHARM(37) |

| Job title or role?* | Number of years in current role?* | Experience working in Clinical Trials?* | If yes to previous question, experience working in sub-Saharan Africa? | Corresponding stakeholder group / Identifier* ** |
|---|--|--|---|---|
| Programme Manager | 3 | Yes | Yes | PHARM(38) |
| Associate Director, Clinical Operations | Of | Yes | No | PHARM(39) |
| Associate Director, Clinical Study Management | 2 years | Yes | No | PHARM(40) |
| Sr Manager, Clinical Operations | 1.5 | Yes | No | PHARM(41) |
| CRA | 4 | Yes | No | PHARM(42) |
| Clinical Study Manager | 3 | Yes | No | PHARM(43) |
| Operations Program Lead | 10 | Yes | No | PHARM(44) |
| Global Studies Manager | 2.5 | Yes | No | PHARM(45) |
| Clinical Research Associate | 3 | Yes | No | PHARM(46) |
| Clinical Research Associate | 8 | Yes | No | PHARM(47) |
| Clinical Study Manager | <1 | Yes | No | PHARM(48) |
| Clinical Trial Manager | 4 | Yes | No | PHARM(49) |
| Study Management | 2 | Yes | No | PHARM(50) |
| Associate director | 1 | Yes | No | PHARM(51) |
| Study Management Associate | 1.5 | Yes | No | PHARM(52) |
| Associate Director, Clinical Operations Lead | <1 | Yes | No | PHARM(53) |
| Clinical Study manager | 6 | Yes | No | PHARM(54) |
| AD - Clinical Study Management | less than 1 | Yes | No | PHARM(55) |
| Study Manager | 6 | Yes | No | PHARM(56) |
| Clinical Research Director | 8 | Yes | No | PHARM(57) |

| Job title or role?* | Number of years in current role?* | Experience working in Clinical Trials?* | If yes to previous question, experience working in sub-Saharan Africa? | Corresponding stakeholder group / Identifier* ** |
|---|--|--|---|---|
| CEO | 6 | Yes | No | PHARM(58) |
| Physician/Lecturer in Clinical Pharmacology/Therapeutics | 7 | Yes | Yes | HCP(1) |
| Professor / Consultant Surgeon | 22 years | No | No | HCP(2) |
| Medical Officer/ Doctoral Student | 11 years as a medical officer | Yes | Yes | HCP(3) |
| Dr | 14 | Yes | Yes | HCP(4) |
| Consultant surgeon | 16yrs | No | No | HCP(5) |
| Consultant Physician / Nephrologist / Professor of Medicine | 20 | Yes | Yes | HCP(6) |
| Professor | 3 | Yes | Yes | HCP(7) |
| Teaching cardiologist and researcher | more than 10 | Yes | Yes | HCP(8) |
| Consultant | 10 years | Yes | Yes | HCP(9) |
| Medical consultant | 10 | Yes | Yes | HCP(10) |
| Clinician, Researcher, Teacher | 16 | Yes | Yes | HCP(11) |
| Technical Advisor on Non-Communicable Diseases | 2 | No | No | REG / HCP |
| Technical Advisor | 4 | Yes | Yes | REG |
| Investment Director | 0.5 | Yes | Yes | OTHER(1) |
| Managing Consultant | 2 | Yes | No | OTHER(2) |
| Lawyer | 2 | Yes | No | OTHER(3) |

*indicates question was mandatory / ** indicates information was not self-reported



Appendix 18: Consent form (interviews)

Consent form

Title of Research: Investigating the potential for developing countries to participate in industry sponsored clinical research into chronic, non-communicable disease

Please Initial Box

I confirm that I have read and understand the letter of invitation for the above research study and have had the opportunity to ask questions.

☐

I understand that my participation is voluntary and that I am free to withdraw or to omit answering any particular question, without providing a reason at any time.

☐

I agree to take part in the above study.

☐

I agree to the interview being audio recorded

☐

I agree to the use of anonymised quotes in publications

☐

| | | |
|------------------------------|---------------|--------------------|
| _____ Name of Participant | _____ Date | _____ Signature |
| _____ Name of Researcher | _____ Date | _____ Signature |

Researcher: Efe Egharevba, PhD Student, Public Health, 1 Lilybank Gardens, Glasgow 8RZ. t.egharevba.1@research.gla.ac.uk

Appendix 19: Published article

Contemporary Clinical Trials Communications 3 (2016) 102–110



Contents lists available at ScienceDirect

Contemporary Clinical Trials Communications

journal homepage: www.elsevier.com/locate/conctc



The role of corruption and unethical behaviour in precluding the placement of industry sponsored clinical trials in sub-Saharan Africa: Stakeholder views

Efe Egharevba^{*}, Jacqueline Atkinson

Glasgow University, Institute of Health & Wellbeing, 1 Lilybank Gardens, Glasgow, G12 8RZ, United Kingdom

ARTICLE INFO

Article history:

Received 27 December 2015

Received in revised form

23 April 2016

Accepted 26 April 2016

Available online 30 April 2016

Keywords:

Clinical trials

Ethics

Sub-Saharan Africa

Corruption

Pharmaceutical

ABSTRACT

Clinical trials still represent the gold standard in testing the safety and efficacy of new and existing treatments. However, developing regions including sub-Saharan Africa remain underrepresented in pharmaceutical industry sponsored trials for a number of reasons including fear of corruption and unethical behaviour. This fear exists both on the part of pharmaceutical companies, and investigators carrying out research in the region. The objective of this research was to understand the ethical considerations associated with the conduct of pharmaceutical industry sponsored clinical trials in sub-Saharan Africa.

Corruption was identified as a significant issue by a number of stakeholders who participated in semi-structured interviews and completed questionnaires. Additionally, fear of being perceived as corrupt or unethical even when conducting ethically sound research was raised as a concern. Thus corruption, whether actual or perceived, is one of a number of issues which have precluded the placement of a greater number of pharmaceutical sponsored clinical trials in this region.

More discussion around corruption with all relevant stakeholders is required in order for progress to be made and to enable greater involvement of sub-Saharan African countries in the conduct of industry sponsored clinical trials.

© 2016 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Background

1.1. Introduction

Clinical trials are the mainstay in new drug development processes, as well as for product license extensions for existing therapies [1]. Despite the fact that developing countries are usually under-represented in research due to a lack of commercial viability and trained researchers, Africa is emerging as an important destination for clinical trials [2]. Sub-Saharan Africa has largely been excluded from industry sponsored clinical trials for a number of reasons. Whilst many of these reasons are related to commercial and practical concerns, there are also a number of ethical issues which have precluded the placement of industry sponsored research in this region to date. These issues include concerns around the appropriate mechanisms for delivering informed

consent, fear of being considered exploitative particularly with the conduct of randomised placebo-controlled studies, as well as other considerations around continued access to medicines once the trials are complete [3,4].

The use of placebo in clinical trials is an arguably contentious benefit of conducting research in developing countries. On one side placebo-controlled trials are easier to implement in developing countries due to less availability of standard of care treatments and a greater number of treatment naïve patients and thus the ability to produce less ambiguous data which might reduce the time it takes to approve a new drug [5]. However, there are obvious ethical concerns with conducting studies in developing countries which would not be approved in developed countries and it could be argued that the conduct of such research would only be appropriate if reduced timelines to drug availability would be relevant for participating subjects. This is an important point to consider as there are a number of examples of drugs which have not been marketed in the developing countries in which they were tested. Limaye et al. assessed the relationship between the number of clinical trials conducted and the number of new drug approvals

^{*} Corresponding author.

E-mail address: efe.egharevba@googlemail.com (E. Egharevba).

<http://dx.doi.org/10.1016/j.conctc.2016.04.009>

2451-8654/© 2016 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

(NDAs) issued in India and South Africa and described a gap between the number of studies conducted and marketed availability of these new drugs in these two developing countries. The study concluded that of trials conducted with sites in India and South Africa, approximately 40% and 60% respectively led to a market authorisation in the EU or US without an approval in India or South Africa [6]. Homedes & Ugalde discuss similar issues in Latin American countries where sponsor organisations have conducted pivotal clinical trials and either failed to subsequently market the drug in that country or have marketed the drug at a prohibitively high cost, precluding access to treatment for many patients in that country [7].

Another significant concern on the part of pharmaceutical companies, however, is that of corruption. The African Development Bank estimate that corruption costs the continent of Africa around \$148 billion per year [8]. In comparison, developed countries gave \$22.5 billion in aid to sub-Saharan Africa in the year 2008 [9]. These concerns around corruption and the associated implications for patient safety, data integrity, and the industry's reputation have all played some role in preventing pharmaceutical companies from placing more clinical trial work in the region, despite Africa's strengthening healthcare systems and growing economies. There are equally, however, concerns around corrupt or unethical industry practices on the part of healthcare professionals based in the region. These concerns are particularly relevant for countries where there are historical cases of pharmaceutical corruption. For example, in Nigeria where the impact of the meningococcal meningitis outbreak and subsequent trial of trovafloxacin by Pfizer [10] in 1996 during which 11 children died and many more were left disabled after receiving the experimental treatment trovafloxacin (Trovan) received much attention [11]. More recent examples of unethical behaviour in the conduct of clinical trials in developing countries include that of a trial which ran from 1997 to 2003 in Uganda sponsored by Boehringer Ingelheim who were testing nevirapine for the treatment of HIV. During this trial investigators failed to obtain patients' consent regarding changes in the experimental design and administered incorrect doses of the drug [12]. More recently the DART trial conducted in Uganda, Zimbabwe and the Ivory Coast which compared structured treatment interruption (STI) with continuous therapy (CT) in patients receiving anti-retroviral therapy for the treatment of HIV highlighted unethical behaviour wherein patients who were on the STI arm of the trial were not switched back to the CT arm of the trial, despite the Data Safety Monitoring Board (DSMB) finding that treatment interruption was associated with a higher risk of disease [12].

Clinical trials can potentially play an important role in helping to contribute to the development of a country's healthcare system in a number of ways including raising research standards, exposing physicians to new diagnosis and treatment modalities and bringing health improvements as well as badly needed investment [13]. Angwenyi and colleagues describe the benefits of investment from clinical trials in studies that were conducted in Ghana, Kenya and Burkina Faso, summarising how all three countries benefited from upgrades and renovations to the physical infrastructure, additional medical supplies and medical equipment [14]. It is also important, however, to note that despite the potential collateral benefits of clinical trials, the benefit of faster access to drugs may not always be relevant as a recent paper by Hay et al. reported that only 10.4% of drugs entering into phase I clinical trials are approved by the US Food & Drug Association [15]. However, in order for sub-Saharan Africa to increase its footprint in the clinical trial space, the topic of corruption, whether actual or perceived, and its associated impact on data quality, patient safety and pharmaceutical engagement in the region needs to be further explored, understood

and addressed. Whilst corruption represents just one of a number of challenges related to conducting trials in the region, it represents arguably one of the most significant and therefore needs to be addressed before other more practical topics can be discussed.

1.2. Objectives

This is part of a larger study of stakeholders' views on the benefit, if any, to the population and the ethical implications of conducting industry sponsored clinical research in the sub-Saharan region of Africa.

This article presents those research findings which are associated specifically with corruption and unethical behaviour.

2. Methods

The study involved two parts. Since there is little research on views of stakeholders interviews were conducted to explore issues. These were then used to develop a questionnaire.

2.1. Choice of countries

For the interviews Nigeria and Ghana were chosen as the two sub-Saharan countries from which health care professionals would be contacted due to their size, economic status, and relative stability at the time the research was planned. Existing links to health care professionals also existed. Pharma respondents were in Europe (UK & Switzerland) and South Africa. For the questionnaire study the countries targeted for pharma respondents were the UK, US, and Switzerland however through snowballing questionnaires from pharma were also completed in France and Spain. For the healthcare professional group the countries in Africa were expanded to include were expanded to include South Africa however through snowballing respondents from Uganda, Egypt, and Liberia also completed the questionnaire.

2.2. Chronic versus infectious

The reasons chronic diseases were chosen are twofold; firstly, there is evidence within the literature which illustrates increasing levels of chronic disease in the region [15,16]. Secondly, infectious disease rates are higher in developing countries (and therefore unbalanced when compared to the disease profile of Western countries). In order to compare the issues related specifically to the conduct of trials in a like for like manner, focusing on chronic disease allows comparison of patients in both the developed and developing world.

2.3. Identifying stakeholders

Two groups of stakeholders were involved; industry professionals and health care professionals in the relevant countries. Stakeholders were identified from a variety of sources including literature reviews and internet searches. For healthcare professionals this was largely done through academic journal review contributions. No specific journals were targeted however search efforts focused on contributors to articles related to clinical trials conducted in patients in Ghana and Nigeria. Healthcare advocacy and government websites were used to identify potential government respondents. Some stakeholders from the pharmaceutical group were identified through existing professional links as well as via snowballing techniques. Although not specifically targeted, snowballing also led to the inclusion of a Non-Government Organisation (NGO) respondent with experience in clinical trials.

For the interviews, senior pharmaceutical representatives

(Associate Director level or above) were targeted as they were felt to be most influential on the direction of their respective organisations and therefore have greater influence on the direction of the industry as a whole.

For the questionnaire, respondents from the same group of stakeholders were contacted, although the requirement for pharma respondents to be senior was relaxed. This criterion was relaxed as it was felt that senior staff members were more likely to influence the direction of their respective companies and therefore have a greater influence on the direction of the industry as a whole. As the issues which senior pharmaceutical representatives believed to be most relevant had already been elucidated during the interviews, the aim of the questionnaire was to explore those themes in greater detail. Additionally, relaxing the criterion allowed for a greater number of respondents from various functional areas to be identified and approached.

2.4. Interviews

A semi-structured interview was developed based on issues raised in academic papers, industry press and past informal conversations with colleagues. It was piloted with a few industry colleagues.

2.4.1. Contacting stakeholders

Potential interviewees were contacted by email with a copy of the Research Participant Letter of Invitation which outlined the study in more detail and explained what would be required in the event they chose to participate in the study.

2.4.2. Interview conduct

Due to the distances involved semi-structured interviews were conducted either by telephone, Skype, or face to face and recorded using a Dictaphone. Each interviewee was informed that their responses would be recorded and transcribed and asked to provide informed consent before recording began. Interviewees were questioned about the ethical issues that they associated with the conduct of clinical trials in sub-Saharan Africa. All interviews were conducted in English.

A copy of the interview schedule can be found in [Appendix 1](#).

2.5. Questionnaires

A questionnaire was developed created using the thematic outputs from the interviews, resulting in 21 questions. It was piloted with several pharmaceutical industry colleagues and minor amendments were made following feedback. Changes were mostly typographical and grammatical. Some changes were required additional language to be added for clarity. The questionnaire could be reached online and was hosted by Survey Monkey.

A copy of the questionnaire can be found in [Appendix II](#).

2.5.1. Contacting stakeholders

Potential respondents were contacted by email. The email contained a short outline of the study and included an ethics approved plain language statement which contained more detailed background information as well as information related to what would be required if they decided to participate in the study. The email also contained a direct link to the questionnaire.

Consent was taken as implied by the return of the questionnaire.

2.6. Analysis

2.6.1. Interviews

The data from the audio recordings were analysed using

thematic analysis facilitated by the use of a qualitative data analysis (QDA) computer software package, Nvivo[®]. The resulting codes were sorted into themes. In some instances codes fell into multiple theme categories. Using the codes that fell under each of the initially identified overarching categories, a number of more detailed themes were derived. The initial coding was performed by EE and then reviewed by JA and a colleague. There were no discrepancies identified. Only the themes related to corruption are considered in this paper.

2.6.2. Questionnaires

Outputs from the survey software were transferred into Nvivo[®] and thematic analysis was performed on any free response comments which were submitted alongside questions. Basic calculations were performed on the numeric outputs of each question for the purpose of descriptive statistics.

2.7. Ethical approval

Ethical approval for the study was given by University of Glasgow College of Medical, Veterinary and Life Sciences Research Ethics Committee.

3. Results

Only results relating to corruption and/or unethical behaviour are presented here.

3.1. Interviews

3.1.1. Respondents

Ninety-eight emails were sent out to various stakeholders from whom twenty-two responses (22%) were received. After further contact sixteen (16%) interviews were conducted. A breakdown of the number of planned and actual interviewees can be found in [Table 1](#). High level information of each respondent can be found in [Table 2](#).

Most of the interviewees fell into one of two groups; Health Care Professionals based in Ghana or Nigeria, or pharmaceutical professionals. Only one government respondent was involved in the interviews.

3.1.1.1. Pharma respondents. At the time of interview, all respondents in the pharma stakeholder group worked at manager level or above and had roles in the research and development arm of their respective organisation. Most ($n = 8$ or 89%) held a position equivalent to Associate Director or above. One respondent, whilst currently not working for a pharmaceutical organisation, had done so previously and at the time of interview was working for an NGO which manages and develops a research and development portfolio and was therefore deemed suitable for interviewing.

3.1.1.2. HCP respondents. Five out of the six respondents (83%) falling under this stakeholder category were physicians. The one respondent who was not a physician was a patient facing member of clinic staff (i.e. a member of staff who is not a medic but still has direct interaction with patients). This persons responsibilities were to perform basic tasks associated with collecting patient samples for research trial participants. All were based in either Ghana or Nigeria.

3.1.1.3. Government/policy maker respondents. Despite contacting six individuals within this particular stakeholder group, only one responded and was interviewed. The interviewee was based in Ghana and was working for the country's Food and Drugs Board.

Table 1
Number of planned and actual interviewees.

| Stakeholder group | Number from Nigeria (planned) | Number from Nigeria (Actual) | Number from Ghana (planned) | Number from Ghana (Actual) | Total (planned) | Total (Actual) |
|---|-------------------------------|------------------------------|-----------------------------|----------------------------|-----------------|----------------|
| Government representatives | 2 | 0 | 2 | 1 | 4 | 1 |
| Local HCPs | 3 | 3 | 3 | 3 | 6 | 6 |
| Patient advocacy group representatives | 2 | 0 | 2 | 0 | 4 | 0 |
| Pharmaceutical industry representatives | — | — | — | — | 10 | 9 |
| Total | | | | | 24 | 16 |

Table 2
High level overview of interview participants.

| Unique identifier | Role | Years in current role | Clinical trial experience? | Method of interview | Location |
|-------------------|--|-----------------------|-----------------------------|---------------------|--------------|
| HCPN_1 | Physician/Clinical Pharmacologist | 10+ | Yes – as Research Physician | Skype | Nigeria |
| HCPN_2 | Radiologist | 30+ | Yes – as Research Physician | Telephone | Nigeria |
| HCPN_3 | Surgeon | 15+ | No | Telephone | Nigeria |
| HCPG_1 | Radiographer | 20+ | Yes | Telephone | Ghana |
| HCPG_2 | Research Fellow | 15+ | Yes | Telephone | Ghana |
| HCPG_3 | Clinical Oncologist | 15+ | Yes | Telephone | Ghana |
| REG_1 | Food & Drugs Board | 10+ | Yes – Regulatory | Telephone | Ghana |
| PHARM_1 | CEO Strategy & Business Development | 20+ | Yes – Pharma | Face to face | UK |
| PHARM_2 | Operational Leader [Pharmaceutical Company] | 10+ | Yes – Pharma | Face to face | UK |
| PHARM_3 | Non-executive Chairman, [Clinical Research Organisation] | 20+ | Yes – Pharma | Skype | South Africa |
| PHARM_4 | Operational Leader, [Pharmaceutical Company] | 20+ | Yes – Pharma | Face to face | UK |
| PHARM_5 | Executive Director, Operations, [Pharmaceutical Company] | 5+ | Yes – Pharma | Face to face | UK |
| PHARM_6 | Medical Research Manager, [Pharmaceutical Company] | 15+ | Yes – Pharma | Telephone | UK |
| PHARM_7 | Interim Clinical Director, [Pharmaceutical Company] | 15+ | Yes – Pharma | Telephone | UK |
| PHARM_8 | Medical Director, [Pharmaceutical Company] | 20+ | Yes – Pharma | Telephone | UK |
| PHARM_9 | Head of Translational Medicine, [Non-Profit Foundation] | 15+ | Yes – Pharma | Telephone | Switzerland |

3.1.2. Themes

Corruption was identified as a significant barrier to the conduct of clinical trials in sub-Saharan Africa across stakeholder groups. The types of corruption that stakeholders were concerned about differed based on which stakeholder group the interviewee fell into.

3.1.2.1. Perception of corruption. Pharmaceutical industry stakeholder members were concerned about not just the corruption which could occur during the set-up and conduct of the trial but also held fears around perception – in particular being perceived as corrupt and/or exploitive even when conducting ethically sound research.

I know there's been a number of countries who have ... very high profile criticism for having been accused of exploiting populations. Some of this has been well grounded but it has caused a lot of concern about reputation risk about being seen to be exploiting a population who may be considered vulnerable based on their background or education. And the reputational risk is so high that it's actually not worth taking." (PHARM_8)

"Because you do a study where there may ... not be ethical concerns but ethical issues which are addressed ... the fear is that they'll just get ... be spun out of context which wouldn't happen in a European or North American or even an Asian environment. And so there's this fear of reputational damage by doing legitimate clinical research in a developing country such as many of those in sub-Saharan Africa." (PHARM_8)

During a number of interviews, pharmaceutical stakeholders (i.e. those working in the pharmaceutical industry) raised the issue of whether or not the idea of significantly higher levels of corruption in sub-Saharan Africa is a perception or a reality. A

pharmaceutical industry respondent who was actually based in sub-Saharan Africa substantiated the claims from other pharmaceutical stakeholders around corruption but argued that it is for the individuals involved to decide whether or not to participate in it, describing it as being exaggerated in some instances.

"There is corruption. I'll be open about that. And it depends on whether you participate in it or not. Whenever I went to a Ministry of Health and they've said; 'well what will you pay us for this? [...]' We've got to get over this misconception ... it's a conception and a misconception of corruption in the rest of Africa." (PHARM_X¹)

3.1.2.2. Responsibility of pharmaceutical companies. The complexity of issues around corruption became evident when discussions progressed onto the topic of the structure of pharmaceutical companies. Publicly traded companies have a responsibility to shareholders and the importance of ensuring their buy-in to any efforts to engage countries perceived as corrupt was a topic which was raised through the interviews as well. The amount of resource required to track the flow of equipment and investigational product was also a topic that was raised. This is relevant particularly when considering the earlier referenced transparency index metrics, an objective measure of corruption, for the countries who were represented by those involved in these interviews [9].

"... you know and you hear, you know, even with aid that's been given you hear about it being misappropriated and going to ... and that isn't going to resonate well with shareholders if you

¹ Identifier left out to protect anonymity of respondent due to sensitive nature of comment.

say, you know; 'well we're giving all of this to sub-Saharan Africa and then, you know, you've got to actually track it. It's not just enough to make a donation, you have to check it's actually getting to where you think it's supposed to be getting and stuff like that.' (PHARM_4)

Concerns of corruption were not just directed toward those who are involved in the region. Several pharmaceutical interviewees were critical of the industry and raised issues around the potential for pharmaceutical companies to behave in a corrupt way if working outside the more closely regulated confines of the West's regulatory and ethical oversight;

"... basically I would think that the major pharmaceutical companies in the West are behaviourally very poor. They are extremely cynical in the way that they conduct studies in the West, in the way they publish data in the West, and do not publish data where they withhold data. The way they manipulate clinical studies to profoundly alter the outcome of those medicines to make them much more favourable than they would otherwise be. If they were doing this in third world countries, they probably would do more of that." (PHARM_1).

"... although I do work in the pharmaceutical industry, I am quite cynical that no successful pharmaceutical companies operate within a capitalist society where they're out to make, you know ... where their reason for being is to make a profit and my personal view is sometimes apparently philanthropic acts that pharmaceutical companies announce are really attempts to you know, they're marketing attempts to make them look good so at the end of the day you know there's the potential ... you know the profit might not be there but the profit's there in intangible assets". (PHARM_7)

3.1.2.3. Historical corruption. Health care professionals were focussed on the troubling history of clinical trials in developing countries. There are high profile historical examples of pharmaceutical companies behaving inappropriately in developing countries. Just as some pharmaceutical representatives had concerns that stakeholders involved in the trial process in sub-Saharan Africa may not behave ethically, healthcare professionals in the region also had their own concerns about potential corruption on the part of pharmaceutical companies. These fears around the legacy of corruption in Africa and its potential consequences on the conduct of ethically sound clinical research in the region suggest that trust is a mutual concern and will be an important factor if countries in sub-Saharan Africa are to participate in more industry sponsored research;

... there is an issue of trust and an issue of exploitation or non-exploitation. People are usually really suspicious you know but I think you need a lot of public enlightenment and you need very good policy structure in place which can be enforced because now the problem with most of sub-Saharan Africa ... Nigeria, let me use Nigeria for example is that you have very good policies but they're not enforced. So people come in and do whatever, like the Pfizer trial that took place in Nigeria some years ago that was very scandalous. (HCPN_1)

"Most people in Nigeria just think that if you say 'trial', they'll say 'oh they're using you for guinea pigs' OK?" (HCPN_1)

3.1.2.4. Unethical behaviour of healthcare professionals. There was

recognition on the part of the healthcare professionals based in the region that they were perceived by some externally as corrupt. Comments suggested that some of the training groups operating in the region have started to include discussions around transparency and corruption as part of the training provided to further educate potential researchers.

"... so they have no reason not to understand the importance of being absolutely precise in whatever they're doing and to report exactly what they are doing and not to doctor results and the importance of the informed consent process and that it's not just a document for participants to sign, but a document for you to ensure that they understand everything that is within the informed consent, it's a process, rather than just a, you know, a mere signature, bribe type of event. So they know all this and they understand all of this ..." (HCPN_2)

Healthcare professionals based in the region also expressed concern regarding the potential for healthcare professionals to coerce potential trial subjects into a study which may not be right for them. The socioeconomic conditions which exist in many parts of this region make subjects more susceptible to being unduly coerced and potentially impact a potential subject's ability to make an informed decision in the presence of an insistent investigator. Investigators may stand to benefit from enrolling as many patients as possible into clinical trials for a number of reasons, for example for financial gain or professional notoriety etc.

"Again for sub-Saharan Africa why it's particular is because you have a group of vulnerable people and when I mean vulnerable people I'm not thinking about children or women or pregnant women alone or disabled or prisoners, I'm thinking of ... because of the economic problems I actually put Africans as vulnerable and especially when it comes to research because most of the people you're going to be doing the research with ... the clinical research, the clinical trials, they're not the people in the blue chip companies in their offices, you're going to go to the communities and these are the people that are poor, that are managing to survive so any help, in quotes, that they are getting from you, you're not sure if you're inducing them or not." (HCPN_1).

This susceptibility to coercion is also made worse by the dynamics of the physician: patient relationship in this part of the world where doctors enjoy a higher social standing and are therefore less likely to be challenged by their patients.

"... because in this part of the world most patients just believe that the doctor knows what is best for them so when you tell them that; 'OK, so I'm doing this study, do you want to join?' they'll tell you 'Ah, doctor, you know what is best for me – I will do it!'" (HCPN_1).

Transparency and open dialogue from investigators is one way through which this behaviour can be countered and trust can be built with patients in the region, particularly following incidents such as the trovafloxacin (Trovan) trial which increased the levels of distrust.

So, now, when you tell people that OK, this is essential for your health or for the health of your children. That the drugs we're using now are not working. You need to get new drugs and this is the only way you can find out so I think you just need to talk to people. Once you talk to them and you assure them that their health and safety is taken care of and they will get insurance and

nothing is not 'this thing' is going to be done to them I think a lot of people will ... because I've done trials, like I told you with my boss before and you see most times once you talk to them, they agree. They agree, but again you need to build trust." (HCPN_2)

The topic of corruption and unethical behaviour is a complex one. The results from the interviews evidenced mutual suspicion and concern on the part of both pharmaceutical companies in the West and healthcare professionals based in Ghana and Nigeria. The concerns around corruption appear to be genuine although potentially exaggerated, however historical examples on the part of the pharmaceutical companies such as the Pfizer Trovan incident in Kano, Nigeria are still recent enough to cause concern for some of those treating patients in sub-Saharan Africa.

3.2. Questionnaire

3.2.1. Respondents

Two-hundred and thirty-seven emails were sent out to potential respondents and seventy-five questionnaires were eventually completed (32%).

Of the 75 respondents, the largest percentage, 77% (n = 58) were from the pharmaceutical industry followed by 15% (n = 11) from healthcare professionals and 4% (n = 3) were from a group which was labelled other but included; a Lawyer, Investment Director and a Managing Consultant. The regulatory group comprised only a small percentage of those surveyed (1%, n = 1).

3.2.2. Themes

Five questions were related to corruption and unethical behaviour and are presented here. The quantitative responses for these questions are given in Table 3. Each question gave respondents the opportunity to comment, those relevant to the theme of corruption are presented as they were entered (verbatim).

3.2.2.1. Corruption and/or fraud are NOT likely to impact the conduct of clinical trials in sub-Saharan Africa. The first question related to corruption asked respondents to indicate whether they agreed with a statement which suggested that corruption and fraud were unlikely to impact the conduct of clinical trials in sub-Saharan Africa. The results indicate that fraud is perceived to be a significant potential issue as (63%, n = 47) either strongly disagreed or disagreed. Of the four respondents who agreed (n = 3) or strongly agreed (n = 1), only one respondent was an HCP based in sub-Saharan Africa.

Disagree;

"Unfortunately, some persons are motivated by profit and would aim for profit at any cost. The tobacco industry comes to mind" (REG/HCP)

"Corruption is a universal thing" (HCP(2))

Neutral;

"The (sic) hits all walks of life" (PHARM(57))

The universality of corruption and fraud at numerous levels was a sentiment which was echoed throughout the supplementary comments. Many respondents lacked experience working in the region, however the role of the media in shaping the perception of those in the West was also evident.

Disagree;

"Without firsthand (sic) knowledge I cannot say with any certainty but my impression from media representation of the region is that governmental corruption is rife and assuming that to be correct I would assume it could extend to the regulatory environment and healthcare services that might be involved in trials." (PHARM(11))

3.2.2.2. Pharmaceutical companies are likely to exploit patients involved in clinical trials in sub-Saharan Africa. In response to this question 43% (n = 32) of respondents disagreed. Over a fifth of respondents either agreed (13%, n = 10) or strongly agreed (8%, n = 6) with the statement, the majority being HCPs working in the region. This finding represents an arguably unsurprising disconnect between the perceptions of the pharmaceutical industry between stakeholder groups. Comments left in response to this question point quite clearly to the Pfizer trovafloxacin (Trovan) trial as the biggest example in recent history;

Agree;

"there are examples from Nigeria I am sure you are aware of" (HCP(3))

There were also some respondents from the pharmaceutical stakeholder group who believe that pharmaceutical companies are likely to take advantage of clinical trial subjects in developing countries. This echoed some of the comments made during the interview part of study.

Table 3
Responses to questionnaire questions related to corruption and unethical behaviour.

| | 1 (strongly disagree) | 2 (disagree) | 3 (neutral) | 4 (agree) | 5 (strongly agree) | Responses | Average |
|--|-----------------------|-----------------|-----------------|-----------------|--------------------|-----------|---------------|
| 1. Corruption and/or fraud are NOT likely to impact the conduct of clinical trials in sub-Saharan Africa. | 15 (20%) | 32 (43%) | 24 (32%) | 3 (4%) | 1 (1%) | 75 | 2.24/5 |
| 2. Pharmaceutical companies are likely to exploit patients involved in clinical trials in sub-Saharan Africa. | 13 (17%) | 32 (43%) | 14 (19%) | 10 (13%) | 6 (8%) | 75 | 2.52/5 |
| 3. Investigators (clinicians) in sub-Saharan Africa are more likely than those in the West to exploit patients in clinical trials. | 8 (11%) | 21 (28%) | 26 (35%) | 17 (23%) | 2 (3%) | 74 | 2.78/5 |
| 4. Investigators in sub-Saharan Africa are more likely than those in the West to falsify data for financial gain. | 7 (10%) | 24 (33%) | 22 (30%) | 17 (23%) | 3 (4%) | 73 | 2.79/5 |
| 5. Pharmaceutical companies in the West do not always conform to GCP. | 7 (10%) | 24 (33%) | 17 (23%) | 22 (30%) | 3 (4%) | 73 | 2.86/5 |
| 6. Pharmaceutical companies do not want to engage in research in sub-Saharan Africa over fears of being considered exploitative. | 2 (3%) | 21 (28%) | 23 (31%) | 26 (35%) | 3 (4%) | 75 | 3.09/5 |
| | | | | | | | 2.71/5 |

Most common response is bolded.

Agree;

"I would like to disagree with this - but can't!" (PHARM(20))

3.2.2.3. *Investigators (clinicians) in sub-Saharan Africa are more likely than those in the West to exploit patients in clinical trials.* In response to the next statement suggesting that investigators treating clinical trial patients in developing countries were more likely than their counterparts in the West to exploit patients in clinical trials, 39% (n = 29) of respondents either strongly disagreed (11%, n = 8) or disagreed (28%, n = 21). 35% of respondents (n = 26) were neutral whilst 23% (n = 17) and 3% (n = 3) agreed and strongly agreed, respectively. The overall results suggested that HCPs mostly disagree with the statement. There were, however, some HCP respondents who strongly agreed (n = 1) and agreed (n = 3) with the statement.

Disagree;

"I think investigators will exploit patients (if given the opportunity) anywhere." (PHARM(32))

Neutral;

"I hope/ don't think there would be an intent to do this on a wide basis but societal norms are different and this would be likely to influence some investigators" (PHARM(44))

This is relevant because one could argue that there is an element or aspect of corruption which is subjective. This will be discussed in further detail later on in this article.

3.2.2.4. *Investigators in sub-Saharan Africa are more likely than those in the West to falsify data for financial gain.* Of the seventy-three respondents who responded to the question asking them to indicate their agreement with the following statement; Investigators in sub-Saharan Africa are more likely than those in the West to falsify data for financial gain, approximately 30% (n = 22) were neutral and a third (33%) disagreed with the statement. A further 23% (n = 17) and 4% (n = 3) agreed or strongly agreed, respectively, indicating that some felt investigators would potentially falsify data.

Neutral;

"I think there is more motivation in any developing country to falsify data than developed countries. I don't feel this is Africa specific" (PHARM(45))

3.2.2.5. *Pharmaceutical companies in the West do not always conform to GCP.* The next statements asked respondents to indicate whether or not they believed that pharmaceutical companies in the West do not always comply with GCP. Approximately a third (n = 24, 33%) of all seventy-three respondents disagreed with this statement. A further 10% (n = 7) strongly disagreed indicating that many believe that pharma is largely compliant with GCP. However, an observation worth noting (particularly considering the pharma bias sample population) is that over a fifth (23%, n = 17) agreed that pharma does not always comply with GCP in the West and a further 4% (n = 3), all of whom fell under the pharma stakeholder group, strongly agreed with the statement.

Disagree;

"On the whole they do!" (PHARM(14))

Neutral;

"true, any audit finding is a non-conformance to GCP. But if this question is seeking my thoughts on wilful non-conformance, then I'd be inclined to disagree, these days" (PHARM(12))

Strongly agree;

"Fact of life, sometimes intentionally, sometimes not" (PHARM(8))

3.2.2.6. *Pharmaceutical companies do not want to engage in research in sub-Saharan Africa over fears of being considered exploitative.* The final question around corruption and unethical behaviour asked respondents to indicate their agreement with the following statement; Pharmaceutical companies do not want to engage in research in sub-Saharan Africa over fears of being considered exploitative.

Of the seventy-five respondents, (35%, n = 26) agreed with the statement – three of these respondents fell under the HCP stakeholder group. This was followed by 31% (n = 23) who were neutral. One respondent who was in agreement went as far as to liken (in what may or may not be tongue in cheek) some of the people working in the region to the secret police of Nazi Germany commenting;

Agree;

"Agree. Many self-appointed "ethicists" in the region bear more resemblance to the Gestapo than to Gandhi." (PHARM(30))

Disagree;

"I do not think it is this fear that drives it, but the regulatory expectations, ethics, and reliability of data" (PHARM(11))

4. Discussion

The findings from both parts of the study will be treated together since there was no real disparity between them. The majority of the pharma industry respondents did not have experience of working in developing countries and the responses from this stakeholder group should be viewed with this in mind. Nevertheless, their views, irrespective of how they have been reached, are likely to be important within the industry especially given the seniority of pharma stakeholder groups involved in the interviews.

The responses from both the interviews and questionnaires highlight that there are still concerns from healthcare professionals in developing countries due to the conduct of some contentious trials in the past, more specifically the Pfizer Trovan trial in Nigeria [10]. This has led to questions around pharma's presence in the region because of the conduct of potentially unethical or corrupt studies. Healthcare professionals also highlight patient concerns around industry sponsored clinical trials with some believing that they're being used as guinea pigs by pharmaceutical companies. There appeared to be mutual suspicion between stakeholder groups with each concerned about the other's potential behaviour when conducting trials in sub-Saharan Africa.

On the part of pharma, there were several concerns around corruption and unethical behaviour, the first of these being around

perception. More specifically, concerns that even in instances where research is conducted ethically, there is a chance that it will still be perceived as exploitative simply because the trials are being carried out in this developing part of the world. The influence of media, whilst not explicitly mentioned, was evident throughout the interviews with pharma respondents as many had not worked in the region but had concerns based on things they had seen and heard in the media. The power of the media to influence perception is an important point to note on both sides the media could likewise influence healthcare professionals and the general public likewise by painting pharmaceutical companies engaging in research in this part of the world in a negative light.

Another concern on the part of pharma was around the misappropriation of resources (e.g. equipment, payments etc.) which may be given to hospital sites and investigators for the conduct of trials and where they would potentially be directed to. Although the majority of pharma representatives who were interviewed and who completed the questionnaire did not have experience working in the region, many were under the impression that there were higher levels of corruption in sub-Saharan Africa than in Western countries. This could lead to equipment and material not reaching its intended destination and being sold privately. It could also lead to experimental medicines being unlawfully sold on, which could have more serious consequences.

The research also showed that many feel as though pharmaceutical companies are largely compliant with ethical standards when conducting research in the West, however there were concerns even from pharma representatives themselves that companies may not be so compliant when conducting trials outside of the more closely regulated Western countries which are typically represented in industry-sponsored clinical trials. The research also highlighted the cynical views that members of the pharmaceutical group hold about current industry practices which are of concern and may indicate that current stringent regulations and self-policing of the industry are not producing the desired results.

4.1. Recommendations for moving forward

It is important that as discussions around sub-Saharan African countries participating in clinical trials begin to gain traction, issues such as the potential for corruption do not become the proverbial elephant in the room². The findings here suggest that there is some suspicion by all parties involved of the other groups, whether this be around corruption or exploitation. This might suggest that discussions need to be held openly with solutions around creating transparency and accountability mutually agreed by all parties. This mutual agreeability is an important component to making progress as it will demonstrate that pharma companies are avoiding the adopting of imperialistic strategies which fail to take into account the cultural and practical differences that exist between developing countries and the West.

It is important to note that many companies are beginning to take steps towards ensuring the conduct of ethical trials in developing countries and are benchmarked against one another. The Access to Medicines Index [17] assesses companies on their compliance to ICH-GCP standards and the Declaration of Helsinki [18,19], as well as companies' processes for monitoring compliance and taking disciplinary action when necessary, for both in-house and outsourced trials. Additionally, it examines companies' criteria for selecting Clinical Research Organisations (CROs) as well as compliance with WHO's 2005 Technical Consultation of Clinical

Trial Registration Standards [20] to ensure that trials are registered centrally and that results are published irrespective of outcomes. The selective registering of results of trials was a concern which was raised by a pharma respondent during the interviews and so compliance with these guidelines will help redress this concern. The Index's 2014 report showed that most pharmaceutical companies are generally setting high standards for trial conduct with a handful being exceptional in respect of high levels of transparency and clinical trial codes of conduct [17]. It is worth noting, however, that the Access to Medicines Index ratings are based on self-reporting, and not on actual inspections of the trials.

Taking into consideration the legacy of the historic examples of corrupt and unethical behaviour pharmaceutical companies ought to ensure they are conducting themselves with the same level (if not greater) of transparency and ethical integrity that they would when conducting trials in the West. This includes developing appropriate trial designs for this part of the world and ensuring that they do not compromise the health and wellbeing of patients due to corrupt business practices and ethically questionable research. This, along with education, two-way discussions and an appropriate code of conduct should help overcome the fear (and actuality) of being perceived as exploitative and/or corrupt simply by conducting research in developing countries. This will require further discussion on sensitive topics such as corruption – more specifically, conversation around whether or not the definition of 'corruption' is universally applicable or whether there are/should be allowances from Western interpretations of corruption in recognition of cultural or societal norms.

The countries which comprise sub-Saharan Africa are each unique in their landscape and in their cultural norms and this should be taken into account when engaging the relevant stakeholders in these various countries. The only way to effectively achieve this is to ensure those on the ground are engaged and consulted and that flexibility to allow for cultural nuances and norms is permitted, so long as they do not compromise the health and wellbeing of research participants nor the integrity of the data produced.

4.2. Limitations

4.2.1. Limitations of interviews

Numbers were not as high as originally planned for and only two of the stakeholder groups were well represented. A higher number of interviews with a more varied group of stakeholders based in the countries of interest might have been achieved either by travelling to the countries (which would have been prohibitively expensive) or recruiting a local interviewer. Whether the interviewer came from a drug company, was based in the West or was local there was the possibility they would always be seen as biased in some way by different groups.

Another limitation was the way in which interviewees, particularly those in the HCP group, were identified. These were mostly identified through academic journals and snowballing and as such, can be assumed to have at least some interest in clinical research. It would have been preferable to have had a mixed sample of HCPs from the region (i.e. those with and without research interests) however many of the HCPs contacted who were not identified through other methods such as internet searches did not respond to requests to participate in the interview. The findings may have been different if the HCPs did not have an interest or working knowledge of clinical research. Conversely, one could argue that HCPs with no research interest may not have been able to identify the relevant issues due to unfamiliarity with some of the relevant topics. This potential bias means it is difficult to ascertain whether or not the results of this study are representative of the general

² 'Elephant in the room' refers to an obvious problem or difficult situation that people do not want to talk about.

4.2.2. Limitations of questionnaire

The low overall response rate to the questionnaire was a limitation for this study. Furthermore, a similar and greater number of respondents across each stakeholder group would have allowed for a more balanced comparison. Within the pharma stakeholder group, it would have been preferable to have had greater cross functional representation. More specifically, the involvement of more respondents who work in, for example, commercial operations as opposed to the almost exclusively R&D based group of respondents who were contacted to complete the questionnaire.

Also, it is difficult to know whether the responses which indicated a neutral position were truly neutral or whether respondents did not know the answer and therefore chose a neutral response. In retrospect it may have been better to have added an option for respondents to indicate they did not know the answer to the question in order to gain a better understanding of how neutral responses should be interpreted. This was not raised in the piloting of the questionnaire.

5. Conclusions

Set against a context of under-representation in clinical trials and raising prevalence of chronic disease in sub-Saharan Africa this study looked at stakeholders' perceptions of corruption and unethical behaviour in such trials.

The main findings around corruption which came out of this research showed that there appears to be an element of mutual suspicion on the part of the two stakeholder groups best represented in both parts of this research. The perception of pharma respondents seemed to have been largely influenced by media, and important point to note, as many did not have any experience working in the region yet their responses indicated suspicion. Healthcare professionals in the region were suspicious of the pharmaceutical industry largely because of historical examples of corruption, most notably the Pfizer experiments.

There were concerns on both parts that patients may be exploited either by pharma companies conducting poorly designed or unethical studies or by healthcare professionals falsifying data or misappropriating resource intended for clinical trial use. Additionally, the fear of being perceived as corrupt plays a significant role in precluding the placement of trials in this part of the world as the risk of reputational damage may be greater than the reward.

Opening up the debate between pharmaceutical companies and local stakeholders would seem to be the first step to developing the clinical trial research capacity in the involved countries.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://>

References

- [1] G. Pappalwar, M. Mouny, G. Kadhe, A. Mane, Conducting clinical trials in emerging markets of sub-Saharan Africa: review of guidelines and resources for foreign sponsors, *Open Access J. Clin. Trials* 7 (2015) 23–24.
- [2] T. Lang, S. Siribaddana, Clinical trials have gone global: is this a good thing? *PLoS Med.* 9 (6) (2012).
- [3] C.S. Molyneux, et al., "Even if they ask you to stand by a tree all day, you will have to do it (laughter)...": community voices on the notion and practice of informed consent for biomedical research in developing countries, *Soc. Sci. Med.* 61 (2005) 443–454.
- [4] E.W. Emanuel, What makes clinical research in developing countries ethical? The benchmarks of ethical research, *J. Infect. Dis.* 189 (2004) 930–937.
- [5] A. Schulz-Baldes, E. Vayena, N. Biller-Andorno, Sharing benefits in international health research. Research-capacity building as an example of an indirect collective benefit, *Sci. Soc.* 8 (1) (2007) 8–13.
- [6] D. Limaye, J.M. Langer, T. Rühling, G. Fortwengel, A critical appraisal of clinical trials conducted and subsequent drug approvals in India and South Africa, *BMJ Open* 5 (8) (2015).
- [7] N. Homedes, A. Ugalde, Availability and affordability of new medicines in Latin American countries where pivotal clinical trials were conducted, *Bull. World Health Organ.* (2015) 674–683.
- [8] AfDB, Corruption and fragile institutions: mutual accountability between Africa and its partners as cited in Africa economic & financial brief, *Afr. Dev. Bank. Chief Econ. Complex* 4 (40) (2010), 2013.
- [9] Transparency International, Corruption Perceptions Index 2014: Results, 2014. Retrieved June 16, 2015, from Transparency International: <http://www.transparency.org/cpi2014/results>.
- [10] J. Wise, Pfizer accused of testing new drug without ethical approval, *BMJ* 327 (2001) 194.
- [11] Pfizer: Nigeria Drug Trial Victims Get Compensation. Retrieved from BBC News: <http://www.bbc.co.uk/news/world-africa-1449327>.
- [12] SOMO & Wemos, SOMO Briefing Paper on Ethics in Clinical Trials, 2008.
- [13] E. Brouwer, Clinical trials in developing countries: Unethical Practice or a Product of Necessity, *Global Medicine*. Available from: <http://globalmedicine.nl/issues/gm5/article2.pdf>.
- [14] V. Angwenyi, K.-P. Asante, A. Traoré, L.G. Febic, C. Tawiah, A. Kwarteng, et al., Health providers' perceptions of clinical trials: lessons from Ghana, Kenya and Burkina Faso, *PLoS ONE* 10 (5) (2015).
- [15] a M. Hay, D.W. Thomas, J.L. Craighead, C. Economides, J. Rosenthal, Clinical development success rate for investigational drugs, *Nat. Biotechnol.* 32 (2014) 40–51; b World Health Organisation, Preventing Chronic Disease: A Vital Investment, Geneva, 2005.
- [16] Trading Economics, Life Expectancy at Birth, Total (Years) in Sub-Saharan Africa, 2010. Retrieved March 16, 2013, from: <http://www.tradingeconomics.com/sub-saharan-africa/life-expectancy-at-birth-total-years-wb-data.htm>.
- [17] Access to Medicine Foundation, The Access to Medicine Index, 2014. Retrieved from http://www.access-to-medicine-index.org/sites/2015/atmiindex.org/files/2014_access-to-medicine-index_fullreport_clickable.pdf.
- [18] International Conference on Harmonisation, Guideline for Good Clinical Practice, 2014. Retrieved from Guidelines: <http://www.ich.org/products/guidelines.htm>.
- [19] World Medical Association, Ethical Principles for Medical Research Involving Human Subjects, 2013, October. Retrieved December 8, 2014, from WMA Declaration of Helsinki: <http://www.wma.net/en/30publications/10policies/b3/index.htm>.
- [20] World Health Organization, WHO Technical Consultation on Clinical Trial Registration Standards, April 25–27, 2005. Geneva, Switzerland. Available at: http://www.who.int/ictrp/news/ictrp_meeting_april2005_conclusions.pdf (accessed 09.03.16).

References

- Abegunde, D. M. (2007). The burden and costs of diseases in low and middle income countries. *The Lancet*, 370(9603), 1929-1938.
- Abu-Raddad, L. J. (2006). Dual infection with HIV and malaria fuels the spread of both diseases in sub-Saharan Africa. *Science*, 314(5805), 1603-1606.
- Adeloye, D., Basquill, C., Papana, A., Chan, K. Y., Rudan, I., & Campbell, H. (2014). An estimate of the prevalence of COPD in Africa: A systematic analysis. *Journal of Chronic Obstructive Pulmonary Disease*, 12(1), 71-81.
- Adjei, G., & Enuameh, Y. (2015). Community perceptions and beliefs of blood draws for clinical trials conducted in Africa and their management: A systematic review of qualitative evidence protocol. *JBIR Database of Systematic Reviews and Implementation Reports*, 13(6), 27-34.
- Africa Development Bank, C. E. (2011, October 13). The middle of the pyramid: Dynamics of the middle class in Africa. Retrieved 2011, from <http://www.afdb.org>
- African Library Project. (2013.). Africa literacy facts. Retrieved February 24, 2015, from African Library Project: <http://www.africanlibraryproject.org/our-african-libraries/africa-facts>
- Agyemang, C., Addo, J., Bhopal, R., De Graft Aikins, A., & Stronks, K. (2009). Cardiovascular disease, diabetes and established risk factors among populations of Sub-Saharan African descent in Europe: A literature review. *Globalization and Health*, 5(7), 1-17.
- Akazili, J., Chatio, S., Achana, F. S., Oduro, A., Kanmiki, E. W., & Baiden, F. (2016). Factors influencing willingness to participate in new drug trial studies: A study among parents whose children were recruited into these trials in northern Ghana. *BMC Research Notes*, 9(139), 1-10.
- Alden, C., & Davies, M. (2006). A profile of the operations of Chinese multinationals in Africa. *South African Journal of International Affairs*, 13(1), 83-96. doi:10.1080/10220460609556787
- Allen, E. N., Mushi, A. K., Massawe, I. S., Vesteergaard, L. S., Lemnge, M., Staedke, S. G., . . . Chandler, C. I. (2013). How experiences become data: The process of eliciting adverse event, medical history and concomitant medication reports in antimalarial and antiretroviral interaction trials. *BMC Medical Research Methodology*, 13(140), 1-13.

- Angwenyi, V., Asante, K., Traore, A., Febir, L. G., Tawiah, C., Kwarteng, A., . . . Jones, C. (2015). Health providers' perceptions of clinical trials: Lessons from Ghana, Kenya and Burkina Faso. *PLoS ONE*, 1-21.
- Anorlu, R. (2008). Cervical Cancer: The Sub-Saharan African perspective. *Reproductive Health Matters*, 16(32), 41-49.
- Appel, L. (2006). A primer on the design, conduct and interpretation of clinical trials. *Clinical Journal of the American Society of Nephrology*, 1(6), 1360-1367.
- Asuni, T. (1979). The dilemma of traditional healing with special reference to Nigeria. *Social Science & Medicine*, 13(1), 33-39.
- Attarwala, H. (2010). TGN1412: From discovery to disaster. *Journal of Young Pharmacists*, 2(3), 332-336.
- AVERT. (2011, October 21). Global HIV and aids statistics. Retrieved from HIV & AIDS Statistics from Around the World: <http://www.avert.org/aids-statistics.htm>
- Bach, J. F., Chalons, F., Forier, E., Elana, G., Jouanelle, J., Kayemba, J., . . . Berchel, C. (1996). 10-year educational programme aimed at rheumatic fever in two French Caribbean islands. *The Lancet*, 347(9002), 644-645.
- Bairu, M., & Chin, R. (2012a). *Building a healthy mechanism for good clinical practice-compliant global trials: African perspectives*. London, United Kingdom: Elsevier.
- Bairu, M., & Chin, R. (2012b). *Global clinical trials playbook: Capacity and capability building*. Waltham, MA: Academic Press.
- Ballard, B. E. (1974). Pharmacokinetics and temperature. *Journal of Pharmaceutical Sciences*, 92(1), 1345-1358.
- Barbour, R. (1999). The case for combining qualitative and quantitative approaches in health services research. *Journal of Health Services Research & Policy*, 4(1), 39-43.
- Barbour, R. S. (2001). Checklists for improving rigour in qualitative research. *British Medical Journal*, 322, 1115-1117.
- Barbour, R., & Kitzinger, J. (1999). *Developing Focus Group Research: Politics, theory and practice*. London: SAGE Publishing.
- Barry, C., Britten, N., Barber, N., Bradley, C., & Stevenson, F. (1999). Using reflexivity to optimize teamwork in qualitative research. *Qualitative Health Research*, 9, 26-44.

- Basit, T. (2003). Manual or electronic? The role of coding in qualitative data analysis. *Educational Research*, 45(2), 143-154.
- BBC. (2011, August 11). Pfizer: Nigeria drug trial victims get compensation. Retrieved from BBC News: <http://www.bbc.co.uk/news/world-africa-14493277>
- Belle, J., & Stewart, M. (2004). Evaluating qualitative research. In W. W. Rosser, D. C. Slawson, & A. F. Shaughnessy, *Family medicine* (p. 129132). London, United Kingdom: BC Decker.
- Bengtsson, M. (2016). How to plan and perform a qualitative study using content analysis. *NursingPlus Open*, 2, 8-14.
- Bennett, C. L., Stinson, T. J., Vogel, V., Robertson, L., Leedy, D., O'Brien, P., . . . Sutton, T. (2000). Evaluating the financial impact of clinical trials in oncology: Results from a pilot study from the Association of American Cancer Institutes/Northwestern University Clinical Trials Costs and Charges Project. *Journal of Clinical Oncology*, 18(5), 2805-2810.
- Beran, D., & Yudkin, J. (2006). Diabetes care in Sub-Saharan Africa. *The Lancet*, 368(9548), 1689-1695.
- Bertram, D. (2007). *Likert Scales...are the meaning of life*. Retrieved from The Faculty of Mathematics - University of Belgrade: <http://poincare.matf.bg.ac.rs/~kristina/topic-dane-likert.pdf>
- Bhatt, A. B., & Lind, J. (2010). Evolution of clinical research: A history before and beyond. *Perspectives in Clinical Research*, 1(1), 6-10.
- Bhowmik, D., Chandira, M., & Chiranjib, B. (2010). Emerging trends of scope and opportunities clinical trials India. *International Journal of Pharmacy and Pharmaceutical Sciences*, 2, 7-20.
- Black, N. (2001). Evidence based policy: Proceed with care. *British Medical Journal*, 323(7307), 275-278.
- Bloomfield, G. S., & Kimaiyo, S. (2011). Chronic non-communicable cardiovascular and culmonary disease in Sub-Saharan Africa: An academic model for countering the epidemic. *American Heart Journal*, 161(5), 842-847.

- Boahen, O., Owusu-Agyei, S., Febir, L. G., Tawiah, C., Tawiah, T., Afari, S., & Newton, S. (2013). Community perception and beliefs about blood draw for clinical research in Ghana. *Royal Society of Tropical Medicine and Hygiene*, 107, 261-265.
- Boers, M., Brooks, P., Fries, J. F., Simon, L. S., Strand, V., & Tugwell, P. (2010). A first step to assess harm and benefit in clinical trials in one scale. *Journal of Clinical Epidemiology*, 63(6), 627-632.
- Bonoma, T. (1985). Case research in marketing: Opportunities, problems and a process. *Journal of Marketing Research*, 2(2), 199-208.
- Bracken, S. (2010). Discussing the importance of ontology and epistemology awareness in practitioner research. *Worcester Journal of Learning and Teaching*, 4, 1-9.
- Braun, V., & Clarke, V. (2006). Using thematic analysis in psychology. *Qualitative Reserach in Psychology*, 3(2), 77-101.
- Braunholtz, D. A., Edwards, S. J., & Liliford, R. J. (2001). Are randomized clinical trials good for us (in the short term)? Evidence for a “trial effect”. *Journal of Clinical Epidemiology*, 54(3), 217-24.
- Braveman, P., & Tarimo, E. (2002). Social inequalities in health within countries: Not only an issue for affluent nations. *Social Science & Medicine*, 54(11), 1621-1635.
- Brewer, J., & Hunter, A. (1989). *Multimethod research: A synthesis of styles*. Thousand Oaks, CA: SAGE Publications.
- Bridger, A. J. (2014). The thorny issue of pluralism, 'paradigm wars' and politics in qualitative methods and mixed methods research. *QMIP Bulletin*, 18, 27-30.
- Brinks, A. J., & Aalbers, J. (2009). Strategies for heart disease in Sub-Saharan Africa. *Heart*, 95(19), 1559-1560.
- Bruner, J. (1986). *Actual minds, possible worlds*. Cambridge, MA: Harvard University Press.
- Bryman, A. (2016). *Social research methods*. Oxford, United Kingdom: University Press.
- Buist, A. S., McBurnie, M. A., Vollmer, W. M., Gillespie, S., Burney, P., Mannino, D. M., . . . Weiss, K. B. (2007). International variation in the prevalence of COPD (the BOLD Study): A population-based prevalence study. *The Lancet*, 370(9589), 741-750.
- Buregyeya, E., Kulane, A., Kiguli, J., Musoke, P., Mayanja, H., & Mitchell, E. M. (2015). Motivations and concerns about adolescent tuberculosis vaccine trial participation in rural Uganda: A qualitative study. *Pan African Medical Journal*, 22(76), 1-7.

- Burroughs, V. J., Maxey, R. W., & Levy, R. A. (2002). Response to medicines: Towards individualized pharmaceutical treatment. *Journal of the National Medical Association*, 94(10), 1-26.
- Cappuccio, F. P., & Miller, M. A. (2016). Cardiovascular disease and hypertension in Sub-Saharan Africa: Burden, risk and interventions. *Internal & Emergency Medicine*, 11, 299-305.
- Center for Disease Control and Prevention. (2011). Heart disease facts. Retrieved from <http://www.cdc.gov/heartdisease/facts.htm>
- Central Intelligence Agency. (2014). The World Factbook. Retrieved March 03, 2013, from https://www.cia.gov/library/publications/the-world-factbook/wfbExt/region_afr.htm
- Chantler, T., Otewa, F., Onyango, P., Okoth, B., Odhiambo, F., Parker, M., & Geissler, P. W. (2013). Ethical challenges that arise at the community interface of health research: Village reporters' experiences in western Kenya. *Developing World Bioethics*, 13(1), 30-37.
- Charatan, F. (2001). Surfactant trial in Latin American infants criticised. *British Medical Journal*, 322(7286), 575.
- Chatio, S., Baiden, F., Achana, F., Oduro, A., & Akazili, J. (2016). Knowledge and perceptions about clinical trials and the use of biomedical samples: Findings from a qualitative study in rural northern Ghana. *PLoS ONE*, 11(4), e0152854.
- Cho, J. Y., & Lee, E.-H. (2014). Reducing confusion about grounded theory and qualitative content analysis: Similarities and differences. *The Qualitative Report*, 19(64), 1-20.
- Chopra, S. A. (2003). Industry funding of clinical trials: Benefit or bias? *Journal of the American Medical Association*, 290(1), 113-114.
- Clarke, V., & Braun, V. (2013). Teaching thematic analysis: Overcoming challenges and developing strategies for effective learning. *The Psychologist*, 26(2), 120-123.
- Cohen, L., Manion, L., & Morrison, K. (2000). *Research methods in education* (5th ed.). London, United Kingdom: Routledge /Falmer.
- Collier, P. (2006). African Growth: Why a 'Big Push'? *Journal of African Economies*, 15(supplement 2), 188-211.

- Corneli, A. L., Piwoz, E., Bentley, E. M., Moses, A., Nkhoma, J. R., Tohill, B. C., . . . Van der Horstfor, C. (2007). Involving communities in the design of clinical trial protocols: The ban study in Lilongwe, Malawi. *Contemporary Clinical Trials*, 28(1), 59-67.
- Costello, A., & Zumla, A. (2000). Moving to research partnerships in developing countries. *British Medical Journal*, 321(7264), 827-829.
- Council for International Organizations of Medical Sciences. (2002). International ethical guidelines for biomedical research involving human subjects. *Bulletin of Medical Ethics*, 182, 17-23.
- Creswell, J. W. (2003). *Research design: qualitative, quantitative and mixed methods approaches*. Thousand Oaks, CA: SAGE Publications.
- Creswell, J. W., & Plano Clark, V. L. (2007). *Designing and conducting mixed methods research*. Thousand Oaks, CA: SAGE Publications.
- Curry, L. A., Nembhard, I. M., & Bradley, H. (2009). Qualitative and mixed methods provide unique contributions to outcomes research. *Journal of the American Heart Association*, 119(10), 1442-1452.
- Dalal, S., & Beunza, J. J. (2011). Non-communicable diseases in Sub-Saharan Africa: What we know now. *International Journal of Epidemiology*, 40(4), 885-901.
- Davis, K. (2013, April 26). Ventures Africa. Retrieved from African Healthcare Attracting Private Investors: <http://venturesafrica.com/african-healthcare-attracting-private-investors/>
- Dawson, L., & Kass, N. (2005). Views of US researchers about informed consent in international collaborative research. *Social Science & Medicine*, 61(6), 1211-1222.
- De Graft Aikins, A. (2010). Africa's neglected epidemic: Multidisciplinary research, intervention and policy for chronic disease. *Conference Report*. Ghana, Accra.
- De Graft Aikins, A., Unwin, N., Agyemang, C., Pascale, A., Campbell, C., & Arhinful, D. (2010). Tackling Africa's chronic disease burden: From the local to the global. *Global Health*, 6(5), 1-7.
- Dial, N. J., Ceesay, S. J., Gosling, R. D., D'Alessandro, U., & Baltzell, K. A. (2014). A qualitative study to assess community barriers to malaria mass drug administration trials in the Gambia. *Malaria Journal*, 13(47), 1-9.

- Downe-Wamboldt, B. (1992). Content analysis: method, applications and issues. *Health Care for Women International*, 13, 313-321.
- Drass, K. A. (1980). The Analysis of Qualitative Data. *Journal of Contemporary Ethnography*, 9(3), 332-353.
- Driscoll, D., Appiah-Yeboah, A., & Salib, P. (2007). Merging qualitative and quantitative data in mixed methods research: How to and why not. *Economical and Environmental Anthropology*, 3(1), 19-28.
- DuVal, G. (2005). The benefits and threats of research partnerships with industry. *Critical Care*, 9(4), 309-310.
- Earl-Slater, A. (2001). Advantages and disadvantages of evidence from clinical trials. *British Journal of Clinical Pharmacology*, 6(2), 136-139.
- Egharevba, T. (2008). The factors affecting the underrepresentation of ethnic minorities in clinical trials and redressing the imbalance. *MSc Thesis. Cardiff University, Cardiff Wales*.
- Egharevba, E., & Atkinson, J. (2016). The role of corruption and unethical behaviour in precluding the placement of industry sponsored clinical trials in Sub-Saharan Africa. *Contemporary Clinical Trials Communications*, 3, 102-110.
- Emanuel, E. J., Wendler, D., Killen, J., & Grady, C. (2004). What makes clinical research in developing countries ethical? The benchmarks of ethical research. *Journal of Infectious Diseases*, 189(5), 930-937.
- Erinosho, O. (2008). Developing ethical oversight of research in developing countries: Case study of Nigeria. *Proceedings of an International Workshop in collaboration with the Special Programme for Research and Training in Tropic Diseases of the World Health Organisation* (pp. 15-23). Abuja, Nigeria: Social Science Academy of Nigeria.
- Essack, Z., Koen, J., Barsdorf, N., Slack, C., Quayle, M., Milford, C., . . . Mukuka, R. (2009). Stakeholder perspectives on ethical challenges in HIV vaccine trials in South Africa. *Developing World Bioethics*, 10(1), 11-21.
- Europeans Medicines Agency. (2004). Clinical trials. Retrieved June 02, 2016, from Clinical trials in human medicines: http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000489.jsp&mid=WC0b01ac058060676f

- Export-Import Bank of the United States. (2011). Sub-Saharan Africa map. Retrieved May 29, 2013, from http://www.exim.gov/about/library/reports/annualreports/2011/map_subsaharan.html
- Fairhead, J., Leach, M., & Small, M. (2006). Public engagement with science? Local understandings of a vaccine trial in the Gambia. *Journal of Biosocial Science and Medicine*, 63(4), 1109-1120.
- Feilzer, M. Y. (2010). Doing mixed methods research pragmatically: Implications for the rediscovery of pragmatism as a research paradigm. *Journal of Mixed Methods*, 4(1), 6-16.
- Fekadu, A., Teferra, S., Hailu, A., Gebre-Mariam, T., Addissie, A., Deressa, W., . . . Reja, A. (2014). International clinical trial day and clinical trials in Ethiopia and Africa. *Trials*, 15(493), 1-6.
- Fenton, L., Rigney, M., & Herbst, R. S. (2009). Clinical trial awareness, attitudes, and participation among patients with cancer and oncologists. *Community Oncology*, 6(5), 207-213.
- Fisher, M. J., & Marshall, A. P. (2009). Understanding descriptive statistics. *Australian Critical Care*, 22, 93-97.
- Fitchett, J. R. (2009). Ethical considerations of clinical trials in the developing world. *Royal Society of Tropical Medicine and Hygiene*, 103(8), 756-760.
- Floredi, L. (2003). *Blackwell guide to the philosophy of computing and information*. Oxford, United Kingdom: Blackwell.
- Flory, J. F., & Emmanuel, E. (2004). Interventions to improve research participants' understanding in informed consent for research. *The Journal of the American Medical Association*, 292(13), 1593-1601.
- Ford, J. G., Howerton, M., Lai, G. Y., Gary, T. L., Bolen, S., Gibbons, M. C., . . . Tanpitukpongse, T. P. (2008). Barriers to recruiting underrepresented populations to cancer clinical trials: A systematic review. *Cancer*, 112(2), 228-242.
- Fram, S. M. (2013). The constant comparative analysis method outside of grounded theory. *The Qualitative Report*, 18(1), 1-25.
- Fuchs, F. D., Klag, M. J., & Whelton, P. K. (2000). The classics: A tribute to the fiftieth anniversary of the randomized clinical trial. *Journal of Clinical Epidemiology*, 335-42.

- Gantley, M. (1999). *An Introduction to Qualitative Methods for Health Professionals*. London: Royal College of General Practitioners.
- Garfield, F. (1999). Post marketing studies: Benefits & risks. *Value in Health*, 2(4), 295-307.
- Gehanno, J.-F., Rollin, L., & Darmoni, S. (2013). Is the coverage of Google Scholar enough to be used alone for systematic reviews. *BMC Medical Informatics and Decision Making*, 13(7), 1-5.
- Ghana Food & Drugs Authority. (2013, March 01). *Guidelines for authorization of clinical trials of medicines, Ghana*. Retrieved May 13, 2016, from Ghana Food & Drugs Authority: <http://www.fdaghana.gov.gh/images/stories/pdfs/downloads/drugs%20guidelines/Clinical%20Trials/GUIDELINES%20FOR%20AUTHORIZATION%20OF%20CLINICAL%20TRIALS%20OF%20MEDICINES,%20GHANA.pdf>
- Ghana Health Services. (2015.). *Requirements for submission of new protocols for review*. Retrieved May 23, 2016, from Ghana Health Services: [http://www.ghanahealthservice.org/downloads/Requirement%20for%20Submission%20of%20New%20to%20the%20ERC%20-%20Revised%20\(Feb.%202014\).pdf](http://www.ghanahealthservice.org/downloads/Requirement%20for%20Submission%20of%20New%20to%20the%20ERC%20-%20Revised%20(Feb.%202014).pdf)
- Gikonyo, C., Bejon, P., Marsh, V., & Molyneux, S. (2008). Taking social relationships seriously: Lessons learned from the informed consent practices of a vaccine trial on the Kenyan coast. *Social Science & Medicine*, 67, 708-720.
- Gilland, T. (2012). Developing countries & clinical trials: Clinical trials in developing countries are exploitative. Retrieved October 27, 2012, from Debating Matters: http://www.debatingmatters.com/topicguides/topicguide/Developing_Countries_and_clinical_trials/
- Giovanna, I., & Hayes, G. (2001). *Principals of clinical research*. Petersfield, United Kingdom: Wrightson Biomedical Publishing.
- Grady, C. (2005). Payment of clinical research subjects. *Journal of Clinical Investigation*, 115(7), 1681-1687.
- Grover, R., & Vriens, M. (2006). *The handbook of marketing research: Uses, misuses, and future advances*. Thousand Oaks, CA: SAGE Publications.
- Gubrium, J. F., & Holstein, J. A. (1997). *The New Language of Qualitative Method*. New York: Oxford University Press.

- Gul, R. B., & Ali, P. A. (2010). Clinical trials: The challenge of recruitment and retention of participants. *Journal of Clinical Nursing*, 19(1-2), 227-233.
- Gupta, A. (2013). Fraud and misconduct in clinical research: A concern. *Perspectives in Clinical Research*, 4(2), 144-147.
- Hanson, S. (2009, August 06). *Corruption in sub-Saharan Africa*. Retrieved December 08, 2014, from Council on Foreign Relations: <http://www.cfr.org/africa-sub-saharan/corruption-sub-saharan-africa/p19984>
- Harvard Magazine. (2009, March-April). Global health view. Retrieved from Harvard Magazine: <http://harvardmagazine.com/2009/03/global-health-view>
- Hawkins, J., & Emanuel, E. (2008). *Exploitation and developing countries: The ethics of clinical research*. Princeton, NJ: University Press.
- Heiat, A., Gross, C., & Kruholz, H. (2002). Representation of the elderly, women, and minorities in heart failure clinical trials. *Journal of the American Medical Association*, 162(15).
- Heyns, C. F., & Borman, M. S. (2008). Men's Health in Africa Part 2: Non-communicable diseases, malignancies and socio-economic determinants of health. *Journal of Men's Health*, 5(2), 127-132.
- Hill, Z., Tawiah-Agyemang, C., Odei-Danso, S., & Kirkwood, B. (2006). Informed consent in Ghana: What do participants really understand? *Journal of Medical Ethics*, 34, 48-53.
- Hofer, B. K. (2001). Personal epistemology research: Implications for learning and teaching. *Journal of Educational Psychology Review*, 13(4), 353-383.
- Holliday, A. (2007). *Doing and Writing Qualitative Research*. London: SAGE Publishing.
- Hotez, P. J., & Kamath, A. (2009). Neglected tropical diseases in sub-Saharan Africa: Review of their prevalence, distribution, and disease burden. *PLoS Neglected Tropical Disease*, 3(8), e412.
- Hsieh, H.-F., & Shannon, S. E. (2005). Three Approaches to Qualitative Content Analysis. *Qualitative Health Research*, 15(9), 2005.
- Hunig, T. (2012). The storm has cleared: Lessons from the CD28 superagonist TGN1412 trial. *Nature Reviews Immunology*, 12(5), 317-318.
- Hussain-Gambles, M., Atkin, K., & Leese, B. (2004). Why ethnic minority groups are under-represented in clinical trials: A review of the literature. *Health & Social Care in the Community*, 12(5), 382-388.

- International Conference on Harmonisation. (2014). Guideline for good clinical practice. Retrieved from Guidelines: <http://www.ich.org/products/guidelines.html>
- International Diabetes Foundation. (2003). *Diabetes Atlas*. Brussels, Belgium: International Diabetes Foundation.
- International Monetary Fund. (2014, October). World Economic Outlook Database. Retrieved March 23, 2015, from International Monetary Fund: Data & Statistics: <http://www.imf.org/external/pubs/ft/weo/2014/02/weodata/weorept.aspx?sy=2013&ey=2013&ssd=1&sort=country&ds=.&br=1&pr1.x=16&pr1.y=7&c=512%2C668%2C914%2C672%2C612%2C946%2C614%2C137%2C311%2C962%2C213%2C674%2C911%2C676%2C193%2C548%2C122%2C556%2C912%2C678%2C31>
- Isenberg, D., Appel, G. B., Contreras, G., Dooley, M. A., Ginzler, E. M., Jayne, D., . . . Solomons, N. (2009). Influence of race/ethnicity on response to lupus nephritis treatment: The ALMS study. *Rheumatology*, 49(1), 128-140.
- Jansen, L. A. (2009). The ethics of altruism in clinical research. *Hastings Center Report*, 39(4), 26-36.
- Jegede, A. S. (2007). What led to the Nigerian boycott of the polio vaccination campaign? *PloS Medicine*, 4(3), e73.
- Joanna Briggs Institute. (2003). *QARI user manual*. Retrieved from <https://joannabriggs.org/assets/docs/sumari/SUMARI-V5-User-guide.pdf>.
- Johnson, R. B., & Onwuegbuzie, A. J. (2004). Mixed methods research: A research paradigm whose time has come. *Educational Researcher*, 33(7), 14-26.
- Johnson, R. B., Onwuegbuzie, A. J., & Turner, L. A. (2007). Toward a definition of mixed methods research. *Journal of Mixed Methods Research*, 1(2), 112-133.
- Jones, R. (2002). Declining altruism in medicine. *British Medical Journal*, 324(7338), 624-625.
- Joshi, A., Kale, S., Chandel, S., & Pal, D. K. (2015). Likert Scale: Explored and explained. *British Journal of Applied Science & Technology*, 7(4), 396-403.
- Kamuya, D. M., Marsh, V., Kombe, F. K., & Geissler, W. P. (2013). Engaging communities to strengthen research ethics in low-income settings: Selection and preceptions of members of a network of representatives in coastal Kenya. *Developing World Bioethics*, 13(1), 10-20.

- Kassianos, A. P. (2014). The use of telephone interviews in qualitative psychology research: A reflective methodological exercise. *QMiP Bulletin*, 18, 23-25.
- Kenge, A., Choukem, S. P., Dehayem, Y. M., Simo, N. L., & Mbanya, J. C. (2007). Hypertension in people with diabetes in Sub-Saharan Africa. *Diabetes Research and Clinical Practice*, 77(2), 293-299.
- Kim, S. Y., Schrock, L., Wilsom, R. M., Frank, S. A., Holloway, R. G., Kiebertz, K., & De Vries, R. G. (2009). An approach to evaluating the therapeutic misconception. *Ethics & Human Research*, 31(5), 7-14.
- Kingori, P., Muchimba, M., Sikateyo, B., Amadi, B., & Kelly, P. (2010). 'Rumours' and clinical trials: A retrospective examination of a paediatric malnutrition study in Zambia, southern Africa. *BMC Public Health*, 10(556), 1-8.
- Koc, E., & Boz, H. (2014). Triangulation in tourism research: A bibliometric study of top three tourism journals. *Tourism Management Perspectives*, 12, 9-14.
- Koen, J., Essack, Z., Slack, C., Lindegger, G., & Newman, P. (2013). 'It looks like you just want them when things get rough': Civil society perspectives on negative trial results and stakeholder engagement in HIV prevention trials. *Developing World Bioethics*, 13(3), 138-148.
- Kola, I., & Landis, J. (2004). Can the pharmaceutical industry reduce attrition rates? *Nature Reviews*, 3, 711-715.
- Krippendorff, K. (2004). *Content Analysis: an introduction to its methodology*. Thousand Oaks, California: SAGE Publications.
- Krogstad, D. J., Diop, S., Diallo, A., Mzayek, F., Keating, J., Koita, O. A., & Toure, Y. T. (2010). Informed consent in international research: The rationale for different approaches. *American Journal of Tropical Medicine and Hygiene*, 83(4), 743-747.
- Krzyzanowska, M. K., Kaplan, R., & Sullivan, R. (2011). How may clinical research improve healthcare outcomes? *Annals of Oncology*, 22(7), 10-15.
- Kupfer, I., & Burri, C. (2009). Reflections on clinical research in sub-Saharan Africa. *International Journal for Parasitology*, 39(9), 947-954.
- Kvale, S. (1983). The qualitative research interview. *Journal of Phenomenological Psychology*, 14(1), 171-196.

- Lairumbi, G. M., Parker, M., Fitzpatrick, R., & English, M. C. (2012). Forms of benefit sharing in global health research undertaken in resource poor settings: A qualitative study of stakeholders' views in Kenya. *Philosophy, Ethics, and Humanities in Medicine*, 7(7), 1-8.
- Lang, T. A., & Kokwaro, G. D. (2008). Malaria drug and vaccine in Africa: Obstacles and opportunities. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 102(1), 7-10.
- Lapadat, J., & Lindsay, A. C. (1999). Transcription in research and practice: From standardization of technique to interpretive positionings. *Qualitative Inquiry*, 5(1), 64-86.
- Lawrence, J., & Tar, U. (2013). The use of grounded theory technique as a practical tool for qualitative data collection and analysis. *The Electronic Journal of Business Research Methods*, 11(1), 29-40.
- Leach, A., Hilton, S., Greenwood, B. M., Manneh, E., Dibba, B., Wilkins, A., & Mulholland, E. K. (1999). An evaluation of the informed consent procedure used during a trial of Haemophilus influenzae type B conjugate vaccine undertaken in The Gambia, West Africa. *Social Science & Medicine*, 48, 139-148.
- Levitt, N. (2008). Diabetes in Africa: Epidemiology, management and healthcare challenges. *Heart*, 94(11), 1376-1382.
- Li, Q. (2013). A novel Likert scale based on fuzzy sets theory. *Expert Systems with Applications*, 40(5), 1609-1618.
- Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., & Gotzsche, P. C. (2009). The PRISMA statement for Reporting Systematic Reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. *PLoS Medicine*, 6(7), e1000100
- Lidz, C. W., Appelbaum, P. S., Grisso, T., & Renaud, M. (2004). Therapeutic misconception and the appreciation of risks in clinical trials. *Social Science & Medicine*, 58(9), 1689-1697.
- Liheluka, E. A., Lusingu, J. P., & Manongi, R. N. (2013). Community perceptions on the secondary health benefits established by malaria vaccine trials (RTS, S phase 2 and phase 3) at the Korogwe site in North Eastern Tanzania. *Malaria Journal*, 12(157), 1-9.
- Lincoln, Y. S., & Guba, E. G. (1985). *Naturalistic Inquiry*. Newbury Park, CA: SAGE Publications.

- Lip, G. H., Barnett, A. H., Bradbury, A., Cappuccio, F. P., Gill, P. S., Hughes, E., . . . Patel, K. (2007). Ethnicity and cardiovascular disease prevention in the United Kingdom: A practical approach to management. *Journal of Human Hypertension*, 21, 183-211.
- Lo, C. (2014, February 06). The numbers game: Boosting clinical trial enrolment. Retrieved from Pharmaceutical-Technology.com: <http://www.pharmaceutical-technology.com/features/featurethe-numbers-game-boosting-clinical-trial-enrolment-4171654/>
- Lynch, G. F., Gorelick, P. B., Raman, R., & Leurgans, S. (2001). A pilot survey of African-American physician perceptions about clinical trials. *Journal of the National Medical Association*, 93(12), 8S-13S.
- Lynch, T., & Price, A. (2007). The effect of cytochrome P450 metabolism on drug response, interactions, and adverse effects. *American Family Physician*, 76(3), 391-396.
- Macklin, R. (2004). *Double standards in medical research in developing countries*. Cambridge, United Kingdom: Cambridge University Press.
- Macmillan Cancer Support. (2016, March 01). Capecitabine (Xeloda). Retrieved June 07, 2016, from Cancer treatment: <http://www.macmillan.org.uk/cancerinformation/cancertreatment/treatmenttypes/chemotherapy/individualdrugs/capecitabine.aspx>
- Magazi, B., Stadler, J., Delany-Moretlwe, S., Montgomery, E., Mathebula, F., Hartmann, M., & Van der Straten, A. (2014). Influences on visit retention in clinical trials: Insights from qualitative research during the VOICE trial in Johannesburg, South Africa. *BMC Women's Health*, 14(88), 1-8.
- Makita-Ikouaya, E., Mombo, J. B., Rudant, J. P., & Milleliri, J. M. (2010). Availability and access to the public healthcare facilities in Sub-Saharan Africa: Situation in Libreville, Gabon. *Medecine Tropicale (Marseilles)*, 70(2), 123-129.
- Malan, T., & Moodley, K. (2016). Phase 3 oncology clinical trials in South Africa: Experimentation or therapeutic misconception. *Journal of Empirical Research on Human Research Ethics*, 11(1), 47-56.
- Marmot, M., Friel, S., Houwelling, T. A., & Taylor, S. (2008). Closing the gap in a generation: Health equity through action on the social determinants of health. *The Lancet*, 372(9650), 1661-1669.
- Marroni, A. S., Metzger, I. F., Souza-Costa, D. C., Nagassaki, S., Sandrim, V. C., Correa, R. X., . . . Tanus-Santos, J. E. (2005). Consistent interethnic differences in the distribution of

- clinically relevant endothelial nitric oxide synthase genetic polymorphisms. *Nitric Oxide*, 12(3),177-182.
- Mason, J. (2002). *Qualitative Researching*. London: SAGE Publishing.
- Masiye, F., Kass, N., Hyder, A. , Ndbele, P., & Mfutso-Bengo, J. (2008). Why mothers choose to enrol their children in malaria clinical studies and the involvement of relatives in decision making: evidence from Malawi. *Malawi Medical Journal*, 20(2), 50-56.
- Mathers, N., Fox, N., & Hunn, A. (2007). Suveys and Questionnaires. *The NIHR RDS for the East Midlands / Yorkshire & the Humber*.
- Mattson, M. E., Curb, J. D., & McArdle, R. (1985). Participation in a clinical trial: The patients' point of view. *Controlled Clinical Trials*, 6(2), 156-167.
- Maxwell, J. (1997). Designing a Qualitative Study. In L. Bickman, & D. J. Rog, *Handbook of applied social research methods* (pp. 69-100). Thousand Oaks, CA: SAGE Publications.
- May, N., & Pope, C. (1995). Rigour and qualitative research. *British Medical Journal*, 311(6997), 109-112.
- Maykut, P., & Morehouse, R. (1994). *Beginning Qualiative Research: A philosophic and practical guide*. Basingstoke: Burgess Science Press.
- Mays, N., & Pope, C. (2000). Assessing quality in qualitative research. *British Medical Journal*,
- Mbarika, W. W., & Mbarika, I. (2006). Africa calling [African wireless connection]. *Spectrum*, 43(5), 56-60.
- McAlearney, A. S., Song, P. H., & Reiter, K. L. (2012). Why providers participate in clinical trials: Considering the national cancer institute's community clinical oncology program. *Contemporary Clinical Trials*, 33(6), 1143-1149.
- McGraw, J., & Waller, D. (2012). Cytochrome P450 variations in different ethnic populations. *Informa Healthcare*, 8(3), 371-382.
- Medicine and Healthcare Products Regulatory Agency. (2014, December 18). *Guidance for the notification of serious breaches of GCP or the trial protocol*. Retrieved February 28, 2015, from gov.uk: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/404588/GCP_serious_breaches_guide.pdf
- Meetoo, D., & Temple, B. (2003). Issues in multi-method research: Constructing self-care. *International Journal of Qualitative Methods*, 2(3), 1-12.

- Menezes, A. M., Perez-Padilla, R., Jardim, J. R., Muno, A., Lopez, M. V., Valdivia, G., . . . Hallal, P. C. (2005). Chronic obstructive pulmonary disease in five Latin American cities (the PLATINO study): A prevalence study. *The Lancet*, 366(9500), 1875-1881.
- Mensah, G. A. (2006). Ischaemic Heart Disease in Africa. *Heart*, 94(7), 836-843.
- Meyers, L., Frawley, T., Goss, S., & Kang, C. (2014). Ebola virus outbreak 2014: Clinical review for emergency physicians. *Annals of Emergency Medicine*, 65(1), 1-8.
- Mfutso-Bengo, J., Ndebele, P., Jumbe, V., Mkunthi, M., Masiye, F., Molyneux, S., & Molyneux, M. (2008). Why do individuals agree to enrol in clinical trials? A qualitative study of health research participation in Blantyre, Malawi. *Malawi Medical Journal*, 20(2), 37-41.
- Miles, M. B., & Huberman, M. A. (1994). *Qualitative data analysis: An expanded sourcebook*. Thousand Oaks, CA: SAGE Publications.
- Miller, F. G., & Rosenstein, D. L. (2003). The therapeutic orientation to clinical trials. *New England Journal of Medicine*, 348(14), 1383-1386.
- Minozzi, S., Pistotti, V., & Forni, M. (2000). Searching for rehabilitation articles on MEDLINE and EMBASE. An example with cross-over design. *Archives of Physical Medicine & Rehabilitation*, 81(6), 720-722.
- Mintz, J. A. (2004). Some thoughts on the merits of pragmatism as a guide to environmental protection. *Boston College Environmental Affairs Law Review*, 31(1), 1-26.
- Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 6(7).
- Molyneux, C. S., Peshu, N., & Marsh, K. (2005). Trust and informed consent: Insights from community members on the Kenyan coast. *Social Science & Medicine*, 61, 1463-1473.
- Molyneux, C. S., Wassenaar, D. R., Peshu, N., & Marsh, K. (2005). Even if they ask you to stand by a tree all day, you will have to do it (laughter)...!: Community voices on the notion and practice of informed consent for biomedical research in developing countries. *Social Science & Medicine*, 61, 443-454.
- Molyneux, S., Njue, M., Boga, M., Akello, L., Olupot-Olupot, P., Engoru, C., . . . Maitland, K. (2013). 'The words will pass with the blowing wind:' Staff and parent views of the deferred consent process, with prior assent, used in an emergency fluids trial in two African Hospitals. *PLoS ONE*, 8(2), e54894.

- Moodley, K. Staunton, C. de Roubaix, M., & Cotton, M. (2015). HIV cure research in South Africa: A preliminary exploration of stakeholder perspectives. *AIDS Care*, 28(4), 524-527.
- Moretti, F., van Vliet, L., Bensing, J., Deledda, G., Mazzi, M., Rimondini, M., . . . Zimmerman, C. (2011). A standardized approach to qualitative content analysis of focus group discussions from different countries. *Patient Education and Counseling*, 82(3), 420-8.
- Morgan, D. L. (1998). Practical Strategies for Combining Qualitative and Quantitative Methods: Applications to Health Research. *Qualitative Health Research*, 8, 362-376.
- Morse, J. M. (1991). Approaches to qualitative-quantitative methodological triangulation. *Nursing Research*, 40(2), 120-123.
- Morse, J. M. (2003). *Principles of mixed method and multimethod research design*. Thousand Oaks, CA: SAGE Publications.
- Munya, M., & Lestedi, G. (1998). Interrogating our past: Colonialism and corruption in sub-Saharan Africa. *African Journal of Political Science*, 3(2), 15-28.
- Nalubega, S., & Evans, C. (2015). Participant views and experiences of participating in HIV research in Sub-Saharan Africa: A qualitative systematic review. *JBIR Database of Systematic Reviews and Implementation Reports*, 13(5), 330-420.
- Napier, A. D., Ancarno, C., Butler, B., Calabrese, J., Chater, A., Chatterjee, H., & Guesnet, F. (2014, October 28). Culture and health. *The Lancet*, 384(9954), 1607-1639.
- National Heart, Lung & Blood Institute. (2014). Why are clinical trials important? Retrieved February 01, 2015, from National Institute for Health: <http://www.nhlbi.nih.gov/studies>
- National Institute for Health. (2017, January 27). Map of all studies on clinical trials. Retrieved from <https://clinicaltrials.gov/ct2/search/map/click?map.x=419&map.y=237>
- Ndubele, P., Wassenaar, D., Masiye, F., & Munalula-Nkandu, E. (2014). Trial participants' understanding of randomization, double-blinding, and placebo use in low literacy populations: Findings from a study conducted within a microbicide trial in Malawi. *Journal of Empirical Research*, 9(3), 2-10.
- New, W. (2014, April 14). Clinical trial transparency, medicines access on agendas today. Retrieved from IP Watch: <http://www.ip-watch.org/2015/04/14/clinical-trial-transparency-medicines-access-on-agendas-today/>

- Nigeria National Health Research Ethics Committee. (2016, June 02). Nigeria clinical trials registry. Retrieved from Learn about Clinical Trials:
http://nhrec.net/nctr/Clinical_Trials.php
- Njue, M., Kombe, F., Mwalukore, S., Molyneux, S., & Marsh, V. (2014). What are fair study benefits in international health research? Consulting community members in Kenya. *PLoS ONE*, 9(12), e113112.
- Novick, G. (2008). Is there a bias against telephone interviews in qualitative research? *Research in Nursing & Health*, 31(4), 391-398.
- Ntusi, N., & Mayosi, M. (2009). Epidemiology of heart failure in Sub-Saharan Africa. *Cardiovascular Drugs & Therapy*, 7(2), 169-180.
- Nugent, R. (2008). Chronic diseases in developing countries: Health and economic burdens. *Annals of the New York Academy of Sciences*, 1136, 70-79.
- Nyblade, L., Singh, S., Ashburn, K., Brady, L., & Olenja, J. (2011). "Once I begin to participate, people will run away from me": Understanding stigma as a barrier to HIV vaccine research participation in Kenya. *Vaccine*, 29, 8924-8928.
- Nyika, A., Kilama, W., Chilengi, R., Tangwa, G., Tindana, P., Ndebele, P., & Ikingura, J. (2009). Composition, training needs and independence of ethics review committees across Africa: Are the gate-keepers rising to the emerging challenges? *Journal of Medical Ethics*, 35(3), 189-193.
- Oates, J. (2015). Use of Skype interviews: the impact of the medium in a study of mental health nurses. *Nurse Researcher*, 22(4), 13-17.
- O'Gorman, K., & MacIntosh, R. (2015). *Research methods for business and management*. Oxford, United Kingdom: Goodfellow Publishers.
- Okonta, P. (2014). Ethics of clinical trials in Nigeria. *Nigerian Medical Journal*, 55(3), 188-194.
- Oldroyd, J., Bannerjee, M., Heald, A., & Cruickshank, K. (2005). Diabetes and ethnic minorities. *Postgraduate Medical Journal*, 81(958), 486-490.
- Olson, J. D., McAllister, C., Grinnell, L. D., Walters, K. G., & Appun, F. D. (2016). Applying constant comparative method with multiple investigators and inter-coder reliability. *The Qualitative Report*, 21(1), 26-42.
- Onen, C. L. (2013). Epidemiology of ischaemic heart disease in Sub-Saharan Africa. (2013). *Cardiovascular Journal of Africa*, 24(2), 34-42.

- Opdenakker, R. (2006). Advantages and disadvantages of four interview techniques in qualitative research. *Qualitative Social Research*, 7(4), 1-13.
- Ormston, R., Barnard, M., & Snape, D. (2014). The foundations of qualitative research. In J. Ritchie, J. Lewis, C. Nicholls, & R. Ormston, *Qualitative Research Practice: A Guide for Social Science Students and Researchers* (pp. 1-25). Los Angeles. CA: SAGE Publications.
- Osamor, P. E., & Kass, N. (2012). Decision-making and motivation to participate in biomedical research in Southwest Nigeria. *Developing World Bioethics*, 12, 87-95.
- Osei, K., & Schuster, D. P. (2003). Diabetes in Africa. Pathogenesis of type 1 and type 2 diabetes mellitus in Sub-Saharan Africa: Implications for transitional populations. *Journal of Cardiovascular Risk*, 10(2), 85-96.
- Participants. (2002). Ethics: Fair benefits for research in developing countries. *Science*, 298(5601), 2133-2134.
- Peer, N., Kengne, A.-P., Motala, A., & Mbanya, J. C. (2014). Diabetes in the Africa region: An update. *Diabetes Research and Clinical Practice*, 103(2), 197-205.
- Pereira, M., Lunet, N., Azevedo, A., & Barros, H. (2009). Differences in prevalence, awareness, treatment and control of hypertension between developing and developed countries. *Journal of Hypertension*, 27(5), 963-975.
- Platanov, P. (2003). Clinical trials in Russia and Eastern Europe: Recruitment and quality. *International Journal of Clinical Pharmacology and Therapeutics*, 41(7), 277-280.
- Powell, T. C. (2001). Competitive advantage: Logical and philosophical considerations. *Strategic Management Journal*, 22, 875-888.
- Puppallwar, G., Mourya, M., Kadhe, G., & Mane, A. (2015). Conducting clinical trials in emerging markets of Sub-Saharan Africa: Review of guidelines and resources for foreign sponsors. *Open Access Journal of Clinical Trials*, 7, 23-34.
- Raftery, J. (2001). NICE: Faster access to modern treatments? Analysis of guidance on health technologies. *British Medical Journal*, 323(7324), 1300-1303.
- Ramsay, M., De Vries, J., Soodyall, H., Norris, S. A., & Sankoh, O. (2014). Ethical issues in genomic research on the African continent: Experiences and challenges to ethics review committees. *Human Genomics*, 8(15), 1-6.

- Resnik, D. B. (2008). Social benefits of human subjects research. *Journal of Clinical Research Best Practice*, 4(11), 1-7.
- Richards, L. (1999). *Using NVIVO in Qualitative Research*. London: SAGE Publishing.
- Richardson, L. (1991). Postmodern social theory: Representational practices. *Social Theory*, 9, 173-179.
- Robertson, N., Polonsky, M., & McQuilken, L. (2014). Are my symptoms serious Dr Google? A resource-based typology of value co-destruction in online self-diagnosis. *Australasian Marketing Journal*, 22(3), 246-256.
- Robinson, O.C. (2014). Sampling in interview-based qualitative research: a theoretical and practical guide. *Qualitative Research in Psychology*, 11(1), 25-41.
- Rorty, R. (1999). *Philosophy and social hope*. New York, NY: Penguin.
- Rosenbaum, J. R., Wells, C. K., Viscoli, C. M., Brass, L. M., Kernan, W. M., & Horwitz, R. M. (2005). Altruism as a reason for participation in clinical trials was independently associated with adherence. *Journal of Clinical Epidemiology*, 58(11), 1109-1114.
- Schneider, F. (2014, February 18). Politics East Asia. Retrieved February 03, 2017, from What's in a methodology?: [http:// www.politicseastasia.com/studying/whats-methodology/](http://www.politicseastasia.com/studying/whats-methodology/)
- Schreier, M. (2012). *Qualitative content analysis in practice*. Thousand Oaks, CA: SAGE Publications.
- Schueler, P., & Buckely, B. (2014). *Re-engineering clinical trials: Best practices for streamlining the development process*. Cambridge, MA: Academic Press.
- Schulz-Baldes, A., Vayena, E., & Biller-Andorno, N. (2007). Sharing benefits in international health research. Research-capacity building as an example of an indirect collective benefit. *Science and Society*, 8(1), 8-13.
- Scott, D. (2007). Resolving the quantitative–qualitative dilemma: A critical realist approach. *International Journal of Research and Method in Education*, 30(1), 3-17.
- Seale, C. (1999). *The Quality of Qualitative Research*. London: SAGE Publishing.
- Sertkaya, A., Wong, H. H., Jessup, A., & Beleche, T. (2016). Key cost drivers of pharmaceutical clinical trials in the United States. *Clinical Trials*, 13(2), 117-26.
- Shacklock, G., & Smyth, J. (1998). *Being Reflexive in Critical and Social Educational Research*. London: Falmer Press.

- Shaffer, D. N., Yebei, V. N., Ballidawa, J. B., Sidle, J. E., Greene, J. Y., Meslin, E. M., . . . Tierney, W. M. (2006). Equitable treatment for HIV/AIDS clinical trial participants: A focus group study of patients, clinician researchers, and administrators in western Kenya. *Journal of Medical Ethics*, 32, 55-60.
- Shenton, A. K. (2004). Strategies for ensuring trustworthiness in qualitative research projects. *Education for Information*, 22(2), 63-75.
- Siegfried, N., Volmink, J., & Dhansay, A. (2010). Does South Africa need a national clinical trials support unit? *South African Medical Journal*, 100(8), 521-524.
- Simon, A. E., Wu, A. W., Lavori, P. W., & Sugarman, J. (2007). Preventive misconception: Its nature, presence, and ethical implications for research. *American Journal of Preventive Medicine*, 32(5), 370-374.
- Simon, C., Eder, M., & Kodish, E. (2006). Altruistic discourse in the informed consent process for childhood cancer clinical trials. *American Journal of Bioethics*, 6(5), 40-47.
- Snilstveit, B., Oliver, S., & Vojtkova, M. (2012). Narrative approaches to systematic review and synthesis of evidence for international development policy and practice. *Journal of Development Effectiveness*, 4(3), 409-429.
- SOMO & Wemos. (2008). *Somo briefing paper on ethics in clinical trials*. Retrieved from <https://www.somo.nl/wp-content/uploads/2008/02/Examples-of-unethical-trials.pdf>
- Stadler, J. J., Delany, S., & Mntambo, M. (2008). Women's perceptions and experiences of HIV prevention trials in Soweto, South Africa. *Social Science & Medicine*, 66, 189-200.
- Stadler, J., & Saethre, E. (2010). Rumours about blood and reimbursements in a microbicide gel trial. *African Journal of AIDS Research*, 9(4), 345-353.
- Stange, K. C., Crabtree, B. F., & Miller, W. L. (2006). Publishing multimethod research. *Annals of Family Medicine*, 4(4), 292-294.
- Steele, B. (2013, January 18). Clinical trials worldwide struggle to find participants. Retrieved from Eye for Pharma: <http://social.eyeforpharma.com/market-access/clinical-trials-worldwide-struggle-find-participants>
- Strauss, A., & Corbin, J. (1990). *Basics of qualitative research: Grounded theory procedures and techniques*. Newbury Park, CA: SAGE Publications.
- Streefland, P. (2005). Public health care under pressure in Sub-Saharan Africa. *Health Policy*, 71(3), 375-382.

- Su, Z. (2012, July 12). Challenges and opportunities in global clinical trials. Retrieved February 01, 2015, from PharmaPhorum: <http://www.pharmaphorum.com/articles/challenges-and-opportunities-in-global-clinical-trials>
- Sullivan, J. R. (2012). Skype: An appropriate method of data collection for qualitative interviews? *The Hilltop Review*, 6(1), 54-60.
- Tangrea, J. A., Adrianza, M. E., & Helsel, W. E. (1992). Patients' perceptions on participation in a cancer chemoprevention trial. *Cancer Epidemiology, Biomarkers & Prevention*, 1(4), 325-330.
- Tarimo, E. A., Thorson, A., Kohl, T. W., Bakari, M., Sandstrom, E., Mhalu, F., & Kulane, A. (2011). A qualitative evaluation of volunteers' experiences in a phase I/II HIV vaccine trial in Tanzania. *BMC Infectious Diseases*, 11(283), 1-13.
- Tarimo, E. A., Thorson, A., Kohl, T. W., Bakari, M., Mhlalu, F., & Kulane, A. (2011). Reasons for declining to enroll in a phase I and II HIV vaccine trial after randomisation among eligible volunteers in Da es Salaam, Tanzania. *PLoS ONE*, 6(2), e14619.
- Tashakkori, A., & Teddlie, C. (1998). *Mixed methodology: Combining qualitative and quantitative approaches*. Thousand Oaks, CA: SAGE Publications.
- Tashakori, A., & Teddlie, C. (2002). *Handbook of mixed methods in social & behavioral research*. Thousand Oaks, CA: SAGE Publications.
- Taylor, S. J., & Bogdan, R. (1984). *Introduction to qualitative research methods: The search for meanings*. New York, NY: Wiley.
- Teddlie, C., & Yu, F. (2007). Mixed methods sampling: A typology with examples. *Journal of Mixed Methods Research*, 1(1), 77-100.
- The Center for Managing Chronic Disease. (2011). What is chronic disease? Retrieved from The Center for Managing Chronic Disease: <http://www.centerformanagingchronicdisease.org/what-is-chronic-disease.html>
- The World Bank. (2015). Life expectancy at birth, total (years). Retrieved May 21, 2015, from Indicators: <http://data.worldbank.org/indicator/SP.DYN.LE00.IN/countries?display=map>
- Thiers, F. A., Sinskey, A. J., & Bendt, E. R. (2008). Trends in the globalization of clinical trials. *Nature Reviews Drug Discovery*, 7, 13-14.
- Thomas, D. R. (2006). A general inductive approach for analyzing qualitative evaluation data. *American Journal of Evaluation*, 27(2), 237-246.

- Thomas, J., Harden, A., & Newman, M. (2012). Synthesis: Combining results systematically and appropriately. In D. Gough, S. Oliver, & J. Thomas, *An introduction to systematic reviews* (pp. 179-226). Thousand Oaks, CA: SAGE Publications .
- Thomson Reuters. (2014). *Overcoming clinical challenges in BRIC markets* [White Paper]. Retrieved from <https://www.thomsonreuters.com/content/dam/openweb/documents/pdf/pharma-life-sciences/white-paper/overcoming-clinical-challenges-in-bric-markets.pdf>
- Timmermans, S., & McKay, T. (2009). Clinical trials as a treatment option: Bioethics and healthcare disparities in substance dependency. *Social Science & Medicine*, 69(12), 1784-1790.
- Toe, L. P., Ravinetto, R. M., Dierickx, S., Gryseels, C., Tinto, H., Rouamba, N., . . . Grietens, K. P. (2013). Could the decision of trial participation precede the informed consent process? Evidence from Burkina Faso. *PLoS ONE*, 8(11), e80800.
- Trading Economics. (2010). Life expectancy at birth; Total (years) in sub-Saharan Africa. Retrieved March 16, 2013, from <http://www.tradingeconomics.com/sub-saharan-africa/life-expectancy-at-birth-total-years-wb-data.html>
- Transparency International. (2014). Corruption perceptions index 2014: Results. Retrieved June 16, 2015, from Transparency International: <http://www.transparency.org/cpi2014/results>
- Truong, T. H., Weeks, J. C., Cook, E. F., & Joffe, S. (2000). Altruism among participants in cancer clinical trials. *Clinical Trials*, 8(5), 616-623.
- Tuei, V. C., Maiyoh, G. K., & Chung-Eun, H. (2010). Type 2 Diabetes Mellitus and Obesity in Sub-Saharan Africa. *Diabetes/Metabolism Research and Reviews*, 26(2), 433-445.
- Unwin, N., Setel, P., Rashid, S., Mugusi, F., Mbanya, J.-C., Kitange, H., . . . Alberti, K. G. (2001). Noncommunicable diseases in Sub-Saharan Africa: Where do they feature in the health research agenda? *Bulletin of the World Health Organization*, 79(10), 947-953.
- US Department of Health and Human Services. (n.d.). Agency for healthcare research and quality. Retrieved December 09, 2014, from Glossary of Terms: <http://effectivehealthcare.ahrq.gov/index.cfm/glossary-of-terms/?pageaction=showterm&termid=49>

- US National Library of Medicine. (2002, June 07). PubMed®: MEDLINE® Retrieval on the World Wide Web. Retrieved from US National Library of Medicine: <https://www.nlm.nih.gov/pubs/factsheets/pubmed.html>
- Van der Sande, M. (2003). Cardiovascular disease in Sub-Saharan Africa: A disaster waiting to happen. *Netherlands Journal of Medicine*, 61(2), 32-36.
- Van Loon, K., & Lindegger, G. (2009). Informed consent in clinical trials: Perceptions and experiences of a sample of South African researchers. *Health SA Gesondheid*, 14(1), 81-88.
- Venables, E., & Stadler, J. (2012). 'The study has taught me to be supportive of her': Empowering women and involving men in microbicide research. *Culture, Health & Sexuality*, 14(2), 181-194.
- Vischer, N., Pfeiffer, C., Joller, A., Klingmann, I., Ka, A., Kpormegbe, S. K., & Burri, C. (2016). The good clinical practice guideline and its interpretation - perceptions of clinical trial teams in Sub-Saharan Africa. *Tropical Medicine and International Health*, 21(8), 1040-1048.
- Visser, S., Stappers, P. J., Van der Lugt, R., & Sanders, E. B. (2005). Contextmapping: Experiences from practice. *International Journal of CoCreation in Design and the Arts*, 1(2), 119-149.
- Wadman, R., & Hutt, R. (2004). The need for a new go-to-market strategy in Europe: How to survive and thrive in the new more complex healthcare marketplace. *International Journal of Medical Marketing*, 4(2), 154-162.
- Wang, D. W., & Ferraz, O. L. (2012). Pharmaceutical companies vs. the State: Who is responsible for post-trial provision of drugs in Brazil? *Journal of Law, Medicine & Ethics*, 40(2), 188-196.
- Wang, S. Y., Windsor, C., & Yates, P. (2012). Introduction to grounded theory. *Hu Li Za Zhi*, 59(1), 91-95.
- Weigmann, K. (2015). The ethics of global clinical trials. *EMBO Reports*, 16(5), 565-570.
- Wellcome Trust. (n.d.). Research involving people living in low and middle income countries: Position statement and guidance notes for applicants. Retrieved December 16, 2011, from <http://www.wellcome.ac.uk/About-us/Policy/Policy-and-position-statements/WTD015295.htm>

- Wemos Foundation. (2013). *The clinical trials industry in South Africa: Ethics, rules and realities*. Retrieved from https://www.wemos.nl/wp-content/uploads/2016/06/Clinical_Trials_Industry_South_Africa_2013.pdf
- Wilcox, M., & Schroer, S. (1994). The perspective of patients with vascular disease on participation in clinical trials. *Journal of Vascular Nursing*, 12(4), 112-116.
- Wolinski, H. (2006). The Battle of Helsinki: Two troublesome paragraphs in the Declaration of Helsinki are causing a furore over medical research ethics. *Science and Society*, 7(7), 670-672.
- Woodson, C., Alleman, P., Musara, P., Chandipwisa, A., Chirenje, M., Martinson, F., & Irving, I. (2012). Preventative misconception as a motivation for participation and adherence in microbicide trials: Evidence from female participants and male partners in Malawi and Zimbabwe. *Aids Behaviour*, 16(3), 785-790.
- World Bank. (2011). *Statistics in Africa*. Retrieved March 03, 2013, from <http://go.worldbank.org/3HA04HGU20>
- World Bank. (2017). *DataBank*. Retrieved March 02, 2017, from World Development Indicators: <http://databank.worldbank.org/data/reports.aspx?source=2&country=SSF>
- World Health Organisation, Regional Office for Africa. (2006). *The work of the WHO in the African Region; 2004-2005. Biennial report of the Regional Director*. Retrieved from http://afro.who.int/sites/default/files/pdf/report%20pdf/afr_rc56_2_rd-biennial-report-comb_final.pdf.
- World Health Organisation. (2005). *Preventing chronic disease. A vital investment*. Geneva.
- World Health Organization, Department of Measurement and Health Information. (2006). *Projections of mortality and burden of disease by region, 2006*. Retrieved December 21, 2012, from http://www.who.int/healthinfo/statistics/bod_deathbyregion.xls
- World Medical Association. (2013, October). Ethical principles for medical research involving human subjects. Retrieved December 08, 2014, from WMA Declaration of Helsinki: <http://www.wma.net/en/30publications/10policies/b3/index.html>
- Wright, K. B. (2005). Researching internet-based populations: Advantages and disadvantages of online survey research, online questionnaire authoring software packages, and web survey services. *Journal of Computer-Mediated Communication*, 10(3), 00

- Wynder, E. L. (1989). An American health foundation monograph. Coronary artery disease prevention: Cholesterol, a pediatric perspective. *Preventative Medicine*, 18(3), 323-409.
- Yasuda, S. U., Zhang, L., & Huang, S. M. (2008). The role of ethnicity in variability in response to drugs: Focus on clinical pharmacology studies. *Clinical Pharmacology & Therapeutics*, 84(3), 417-23.
- Young, F., Critchley, J. A., & Johnstone, L. K. (2006). A review of co-morbidity between infectious and chronic disease in sub-Saharan Africa: TB and Diabetes Mellitus, HIV and Metabolic Syndrome, and the impact of globalization. *Globalization and Health*, 5(9), 5-9.
- Zühlke, L. J., & Engel, M. E. (2013). The importance of awareness and education in prevention and control of RHD. *Global Heart*, 8(3), 235-239.
- Zumla, A., Petersen, E., Nyirenda, T., & Chakaya, J. (2015). Tackling the tuberculosis epidemic in Sub-Saharan Africa – Unique opportunities arising from the second European Developing Countries Clinical Trials Partnership (EDCTP) Programme 2015-2024. *International Journal of Infectious Diseases*, 32, 46-49.
- Zvonareva, O., & Akrong, L. (2015). Developing clinical research relationship: Views from within. *Developing World Bioethics*, 15(3), 257-266.
- Zvonareva, O., Engel, N., Ross, E., Berghmans, R., Dhai, A., & Krumeich, A. (2015). Engaging diverse social and cultural worlds: Perspectives on benefits in international clinical research from South African communities. *Developing World Bioethics*, 15(1), 8-17.