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**IS THE LEGAL PROTECTION FOR THE FOETUS ADEQUATE IN
CLINICAL TRIALS?**

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B.Sc., M.M.L., PH.D.

**SUBMITTED IN FULFILMENT OF THE REQUIREMENTS FOR
THE DEGREE OF DOCTOR OF PHILOSOPHY**

SCHOOL OF LAW

COLLEGE OF SOCIAL SCIENCE

UNIVERSITY OF GLASGOW

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Is the Legal Protection for the Foetus Adequate in Clinical Trials?

Abstract

In 2009 and 2010, the major drug regulatory bodies, the European Medicines Agency and the Food and Drug Administration in the USA, issued requests for the generation of information relating to the absorption, distribution, metabolism, excretion, efficacy and safety of investigational drugs in pregnant women prior to approval. In the wake of thalidomide, research involving pregnant women other than for obstetric or gynaecologic purposes became rare, and studies of investigational drugs practically unknown. Consequently, none of the legislation applicable in the UK and few of the guidelines introduced in the last 40 years properly addresses the conduct of clinical trials of investigational drugs in this population. This thesis questions whether the legal protection for the foetus is adequate in clinical trials. The answer appears to be a qualified “no”.

Arguments persist regarding the moral standing of the foetus, particularly regarding abortion. That will not be the intent of such trials, and a moral case is made for the conduct of clinical trials in this population by analogy with the neonate, and the pregnant woman’s autonomy. Legally, we already recognise the foetus has ‘interests’ which crystallise upon live birth, and that compensation is recoverable for harm inflicted *in utero* manifesting as congenital injury. The essence of research is quite different from medical practice, and the extent to which this is understood by trial participants is unclear. The approvals processes contain a number of inadequacies which have the potential to expose the foetus to harm and affect the consent of the pregnant woman. The recovery of compensation in the event of children born injured following clinical trials during pregnancy in many ways may be more complex than other personal injury cases..

The conclusions of this thesis are that the existence of a foetus does merit recognition by the law in this setting and that morally such studies are justifiable. However, the present legislation and approval processes potentially expose the foetus to avoidable risk and may not be appropriate to enable the recovery of compensation, thereby creating potential to deter future trial participants. A proposal is made regarding an approach to simplify the process for recovery of compensation, and thereby strengthen the approval and consent processes.

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Authors Declaration

" I declare that, except where explicit reference is made to the contribution of others, that this dissertation is the result of my own work and has not been submitted for any other degree at the University of Glasgow or any other institution.

Signature _____

Printed name _____ "

Chapter 1 Introduction

1.1 Introduction

In the weeks following the “9/11” terrorist attacks on the World Trade Centre and the Pentagon in 2001, envelopes containing anthrax spores were mailed to news media companies and government officials, leading to the first bioterrorism-related cases of anthrax in the United States of America.¹ The following year, the American College of Obstetricians and Gynaecologists (ACOG) issued recommendations regarding anthrax post-exposure prophylaxis in asymptomatic pregnant and lactating women,² which were similar to those contained within the consensus statement from the Working Group on Civilian Biodefense.³ Both organisations advocated the use of the antibiotic amoxicillin. Five years later, in 2007, a study was published which demonstrated that serum levels of amoxicillin adequate to prevent anthrax were unattainable during pregnancy. Due to altered renal function in pregnancy, amoxicillin was cleared from the body by excretion in urine so rapidly that it did not accumulate in the bloodstream sufficiently to attain the concentration necessary to combat anthrax.⁴ The treatment recommendations intended to prevent the development of anthrax were therefore both inaccurate and inadequate; the treatment could not work, and time to institute alternative treatment lost while waiting for the recommended approach to be effective.

The inaccurate advice from these groups was hardly surprising. At the time it was issued, an evaluation of the pharmacokinetics, i.e., the patterns of absorption, distribution, metabolism and excretion (normally abbreviated to ADME) of amoxicillin during pregnancy had not been conducted. Indeed, the same statement was and remains applicable to the vast majority of medicines in clinical use.⁵ However, the lack of characterisation of medicines in pregnant women is not restricted to pharmacokinetics: it applies equally to the assessment of efficacy and safety; for example, at the time of the

¹ Daniel B.; Jernigan, D.B. and the National Anthrax Epidemiologic Investigation Team. (2002). Investigation of Bioterrorism-Related Anthrax, United States, 2001: Epidemiol.Findings Emerg. Infect.Dis., **8**, 1019–1028.

² American College of Obstetricians and Gynecologists. Committee opinion 268, February 2002. Management of asymptomatic pregnant or lactating women exposed to anthrax. Obstet.Gynecol., **99**, 366–368.

³ Inglesby, T.V., *et al* and for the Working Group on Civilian Biodefense. (2002). Anthrax as a biological weapon, updated recommendations for management. J.Am.Med.Ass. **287**, 2236–2252.

⁴ Andrew MA, Easterling TR, Carr DB, *et al.* (2007). Amoxicillin pharmacokinetics in pregnant women: modeling and simulations of dosage strategies. Clin.Pharmacol.Ther., **81**, 547-56.

⁵ Anger, G.J., Piquette-Miller, M. (2008). Pharmacokinetic studies in pregnant women. Clin.Pharmacol. Ther., **83**,184–87.

2009 H1N1 pandemic, no vaccine had undergone sufficient testing to support approval for use in pregnancy.⁶

With the exception of a few medicines intended to treat specific complications in pregnancy, almost no medicines are licenced for *antenatal* prescription.⁷ To put this into context, from 1980 to 2007, 660 drugs were under development for cardiovascular disease (a high-prevalence indication), 34 for amyotrophic lateral sclerosis, an orphan indication, and only 17 drugs were under development for obstetric indications.⁸

Pregnancy is not a prophylaxis against illness; recent research shows that poor asthma control during pregnancy increases the risk of preeclampsia, low birth-weight and prematurity;⁹ women with pre-pregnancy diabetes are at significantly increased risk of adverse maternal and foetal outcomes, both of which are improved in diabetic women who achieve good glycaemic control throughout pregnancy.¹⁰ Pregnancy itself is associated with a range of conditions ranging from the difficult (extreme nausea and vomiting) to disabling (sciatic nerve compression) to life-threatening for the woman or her foetus (preeclampsia) resulting in a significant additional burden of potentially-avoidable conditions. As a result, most women take a medicine at some point during pregnancy. A recent Scottish study showed that for more than 80% of pregnant women this included at least one prescribed medication.¹¹ The Scottish figure is consistent with data from other OECD countries, including France (93%), Germany (85%)¹² and the USA (64%).¹³

⁶ See www.ClinicalTrials.gov. Maternal vaccine studies.

<http://www.clinicaltrials.gov/ct2/results?term=maternal+vaccine>, accessed 9th September, 2015; Saito, S., Minakami, H., Nakai, A. *et al.* (2013). Outcomes of infants exposed to oseltamivir or zanamivir in utero during pandemic (H1N1) 2009. *Am.J.Obstet.Gyn.*, 209, Article No: 130.e1; Lacroix, I. Beau, A. B. Hurault-Delarue, C. *et al.* (2013). Safety of neuraminidase inhibitors, oseltamivir and zanamivir, during pregnancy: a comparative study in the EFEMERIS database. *Fund.Clin.Pharmacol.*, 27, Suppl.1, 106

⁷ Buhimschi, C.S., Weiner, C.P. (2009). Medications in Pregnancy and Lactation; Part 1: Teratology. *Obs.Gyn.*, **113**, 166-188.

⁸ Zajicek, A.; Barrett, J.S. (2013). The grand challenges in obstetric and pediatric pharmacology. *Front. Pharmacol.*, **4**, 170. doi: 10.3389/fphar.2013.00170.

⁹ Murphy, V.E., Namazy, J.A., Powell, H., Schatz, M., Chambers, C., Attia, J. and Gibson, P.G. (2011). A meta-analysis of adverse perinatal outcomes in women with asthma. *Br.J.Obstet.Gyn.*, **118**, 1314–23.

¹⁰ Steel, J.M., Johnstone, F.D., Hepburn, D.A., Smith, A.F. (1990). Can pre-pregnancy care of diabetic women reduce the risk of abnormal babies? *Br.Med.J.*, **301**, 1070–1074.; Kinsley, B. (2007). Achieving better outcomes in pregnancies complicated by type 1 and type 2 diabetes mellitus. *Clin.Ther.*, **29** (Suppl.D), S153–60.

¹¹ Irvine, L., Flynn, R.W., Libby, G., Crombie, I.K. and Evans, J.M. (2010). Drugs dispensed in primary care during pregnancy: a record-linkage analysis in Tayside, Scotland. *Drug Safety*, **33**, 593–604.

¹² Daw, J.R., Hanley, G.E.R., Greyson, D.L., Morgan, S.G. (2011). Prescription drug use during pregnancy in developed countries: a systematic review. *Pharmacoepidemiology Drug Safety*, **20**, 895–902.

¹³ Andrade, S.E., Gurwitz, J.H., Davis, R.L., Chan, K.A. *et al.* (2004). Prescription drug use in pregnancy. *Am.J.Obstet.Gynecol.*, **191**, 398–407.

The Global Burden of Disease Study estimated that maternal disorders accounted for 1.7% and perinatal disorders for 5.9% of Disability Adjusted Life Years.¹⁴ In the USA alone, this results in a substantial economic cost, estimated at over US\$15bn annually,¹⁵ as a result of extended in-patient stays for both mother and child, often prior to and post-delivery, as well as increased medical management costs. Similar economic data for other countries does not appear to have been published, but there seems no *a priori* reason to suspect the USA is unique regarding the need for additional medical care associated with the management of illness during pregnancy. Compelling medical and financial reasons therefore exist to use a range of medications in women whilst they are pregnant, yet the vast majority of drugs available have not been evaluated in pregnant women, and as the amoxicillin example illustrates, physiological changes during pregnancy can significantly alter drug disposition. Recognising this, both the Food and Drugs Agency (FDA) in the USA and the European Medicines Agency¹⁶ (EMA) have requested that data relating to the pharmacokinetics of investigational drugs are provided prior to their registration as new medicines.¹⁷

Thus, from a position of ‘protecting’ the foetus from possible harm by excluding pregnant women from clinical trials, we have moved to a situation in which pregnant women have become a specifically-targeted population. As will be discussed later in this chapter, a variety of approaches have been employed to evaluate the effects of drugs in this population in the wake of thalidomide, but in a pre-approval setting, the normal way in which to generate data, and particularly pharmacokinetic data, systematically, is in a clinical trial setting, which leads to the central questions of this thesis: what particular issues are raised by clinical trials involving pregnant women, how is the presence of the foetus addressed and is the legal protection for the foetus appropriate and adequate?

¹⁴ Lopez, A.D., Mathers, C.D., Ezzati, M., *et al.* (2006). Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet*, **367**, 1747–1757.

¹⁵ Gill, K., Pande, R., Malhotra, A. (2007). Women deliver for development. *Lancet*, **370**, 1347–1357.

¹⁶ The European Medicines Agency is a decentralised agency of the European Union, responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the European Union; see http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000235.jsp, accessed 18th September, 2015.

¹⁷ FDA, Health Organizations to Study Safety of Medications Taken During Pregnancy, FDA News Release 10 Journal of Biomedicine and Biotechnology 2009, <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2009/ucm195934.htm> See also <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093310.htm> both accessed 9th September, 2015; http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/03/WC500076321.pdf accessed 9th September, 2015.

1.2 Historical Perspective

Almost certainly, no drug has done more than thalidomide to stimulate the strengthening of drug regulation, and to raise awareness of the risks to the foetus resulting from women taking medicines during pregnancy. Over 12,000 children – the exact number is unknown - were born with various deformities attributable to their mothers having taken the drug during pregnancy.¹⁸ These deformities were usually in the skeletal system, of which phocomelia - in which the long bones of the limb (humerus or femur, radius or tibia, ulna or fibula) are absent or markedly hypoplastic, with normal or nearly normal hand or foot - was the most common. With the exception of thalidomide-related phocomelia, this congenital abnormality is extremely rare. The largest epidemiological survey yet undertaken reported an incidence of 0.62 per 100,000 births.¹⁹ The incidence of abnormalities (including phocomelia as well as a range of other defects) with thalidomide was between 20% and 30%,²⁰ approximating to a 40,000-fold increase above the spontaneous rate, and the abnormalities were distinctive, normally involving multiple limbs.²¹ In contrast, approximately 50% of spontaneous cases show an isolated defect.²² As a result, the link between thalidomide and phocomelia was recognised relatively quickly.

Thalidomide had been synthesised by the German pharmaceutical company Grunenthal in 1953, possibly as an antidote to nerve gas poisoning.²³ Initially, in many countries, the drug was made available without prescription because of its apparent wide margin of safety.²⁴ The first clinical report describing the now-familiar teratologic signature

¹⁸ Thalidomide was not approved for use in North America because of the courageous stand by Frances Kelsey from the United States Food and Drug Administration (FDA); she gives her perspective in Kelsey, F.O. (1967). Events after thalidomide. *J.Dent.Res.*, **46**, 1199-2006. For a broader review, see Koren, G., Pastuszak, A., Ito, S. *Drugs in pregnancy*. (1998). *N.Engl.J.Med.*, **338**, 1128-37.

¹⁹ Bermejo-Sanchez, E., Cuevas, L., Amar, E., Bianca, S. *et al.* (2011). Phocomelia: a worldwide descriptive epidemiologic study in a large series of cases from the international clearinghouse for birth defects surveillance and research, and overview of the literature. *Am.J.Med.Gen.*, **157C**, 305-320.

²⁰ Mitchell, A.A. (2003). Systematic identification of drugs that can cause birth defects—a new opportunity. *N.Engl.J.Med.*, **349**, 2556–2559; Etwel, F., Hutson, J.R., Madadi, P., *et al.* (2014). Fetal and perinatal exposure to drugs and chemicals: novel biomarkers of risk. *Ann.Rev.Pharm.Tox.*, **54**, 295-315.

²¹ Lenz W. (1980). Genetics and limb deficiencies. *Clin.Orthop.* **148**, 9–17.

²² Bermejo-Sanchez, E., Cuevas, L., Amar, E., Bianca, S. *et al.* (2011). Phocomelia: a worldwide descriptive epidemiologic study in a large series of cases from the international clearinghouse for birth defects surveillance and research, and overview of the literature. *Am.J.Med.Gen.*, **157C**, 305-320.

²³ Lachmann, P.J. (2012). The penumbra of thalidomide, the litigation culture and the licensing of pharmaceuticals. *Q.J.Med.*, **105**, 1179–1189.; Foggo, D. (2009). "Thalidomide 'was created by the Nazis'". www.thesundaytimes.co.uk/sto/style/living/Health/article148972.ece accessed 9th September, 2015.

²⁴ See, for example, De Souza, L.P. (1959). Thalidomide. *Br.Med.J.*, **2**, 635, describing the lack of consequence of a 10-fold overdose.

appeared in 1961,²⁵ and in 1962 the drug was withdrawn in certain countries, although not without some protests from the medical community.²⁶ It was finally withdrawn in 1969, eight years after the initial reports of serious developmental abnormalities. In each country in which the drug had been marketed and which had a reliable reporting system for such abnormalities, the number of reported cases of these characteristic limb defects declined rapidly following the withdrawal of thalidomide.²⁷

Until maternal rubella infection during pregnancy had been identified as a cause of birth defects and developmental disabilities in 1941,²⁸ congenital malformations had generally been believed to be inherited.²⁹ The uterus and placenta were thought to serve as a barrier, protecting the foetus from the effects of external factors.³⁰ The recognition of maternal rubella syndrome only slightly modified this view: the development of the embryo or foetus could be influenced by both genetic factors and maternal infection, both of which were essentially intrinsic in nature. Thalidomide provided the first example of a truly extrinsic factor which could have such an effect.

The number of properly-controlled clinical trials of potential new medicines conducted around the time of the thalidomide tragedy was small, and the representation of women, particularly those of child-bearing potential, in these trials was practically non-existent³¹. From the investigators' and sponsors' perspectives, this was due to a combination of the challenges of assessing drug effect against the changes associated with the menstrual cycle³², the unknown impact of chemical contraception which was starting to come into

²⁵ McBride W. (1961). Thalidomide and congenital abnormalities. *Lancet*, **2**, 1358; Lenz W. (1962). Thalidomide and congenital abnormalities. *Lancet*, **279**, 303–305 (This letter to the *Lancet* was a sequel to a 1961 conference presentation describing abnormalities in 52 infants born to mothers taking thalidomide during pregnancy following which the author received 115 additional reports of similarly affected infants from physicians in Germany, Belgium, Sweden, and England).

²⁶ Gosling, P.H. (1961). Withdrawal of Thalidomide ("Distaval"). *Br.Med.J.* **2**, 1644; Warkany, J. (1988). Why I doubted that thalidomide was the cause of the epidemic of limb defects of 1959 to 1961. *Teratology*, **38**, 217-219.

²⁷ Običan, S., Scialli, A.R. (2012). Teratogenic exposures. *Am.J.Med.Genet.C; Semin.Med.Genet.*, **157**, 150–169.

²⁸ Gregg, N.M. (1941). Congenital cataract following German measles in the mother. *Trans.Ophthalmol. Soc.Aust.*, **3**, 35–45.

²⁹ Webster, W.S. (1998). Teratogen update: Congenital rubella. *Teratology*, **58**,13–23.

³⁰ Fraser, F.C. (2010). Foreword: What is teratology? In: Hales, B., Scialli, A., Tassinari, M.S., eds. *Teratology primer: Teratology society*. http://teratology.org/pubs/ts_primer/TeratologyIntroweb10_11.pdf . pp viii–ix, accessed 10th September, 2015.

³¹ Kinney, E. L., Trautmann, J., Gold, J.A., *et al.* (1981). Underrepresentation of women in new drug trials: ramifications and remedies. *Ann.Intern.Med.*, **95**, 495–499.

³² Chester Berlin. *The Use of Drugs During Pregnancy and Lactation*. *Pub.Health Rep.*, **102**(Supp.), 53-54 (1987). For a contrary view, see Cotton, P. (1990). Is there still too much extrapolation from data on middle-aged white men? *J.Am.Med.Ass.*, **263**, 1049-1050.

widespread use, and probably also because of an instinctive concern around the possibility that a woman of child bearing potential (WoCBP) may be, unknown to herself, in the early stages of pregnancy.³³ From the patients' perspective, there was a reluctance to participate in an activity now seen as burdensome, time-consuming, potentially dangerous, and of little value to participants.³⁴

1.3 The Formal Exclusion of Women from Clinical Trials

In the wake of thalidomide, patients and physicians naturally adopted a conservative approach to the inclusion of women, and particularly those of child-bearing potential, in clinical research. In the USA, three events occurred in the early 1970's which eventually triggered the legislative change that effectively prohibited the participation of women of child-bearing potential (WoCBP) from clinical trials.³⁵ The first was the national "war on cancer" announced by President Nixon,³⁶ which created the impression that cures would soon be found and that the need for participation in clinical trials was likely to decline. Secondly, the Tuskegee syphilis experiment became known; this drew attention to the lack of safeguards for trial participants in the USA, which further deterred individuals from volunteering to participate and to decline when invited to do so by investigating physicians. The third event was the passionate and often heated debate following the *Roe v Wade*³⁷ decision which had a chilling effect on all research involving WoCBP and fetuses. As a consequence of these three events, clinical trials in women known to be pregnant were simply not instituted in the USA: investigators were reluctant to accept the risk to their reputations of participating in a trial of a drug which may prove to be teratogenic, and sponsors were deterred by the potential for adverse publicity and costs which would arise in such circumstances. Although these three events arose in the USA, elsewhere in the world the same issues of reluctance by sponsors to instigate, by investigators to undertake and by WoCBP to participate in such trials resulted in the absence of controlled clinical trials of new investigational drugs in this patient population.

In 1977, the FDA mandated the exclusion of women of WoCBP from early-phase clinical trials, i.e., Phases I and II, on the grounds that such trials held no prospect of benefit for the

³³ Schiebinger, L. (2003). Women's health and clinical trials. *J.Clin.Invest.*, **112**, 973–977.

³⁴ Young, C., Dombrowski, M. (1989). Psychosocial influences on research subject recruitment, enrollment and retention. *Social Work in Health Care*, **14**, 43-57.

³⁵ McCarthy, C.R. (1994). Historical background of clinical trials involving women and minorities. *Acad.Med.*, **69**, 695-698.

³⁶ Embodied in the National Cancer Act 1971.

³⁷ *Roe v Wade* [1973] 410 U.S. 113, 165.

participants, and that, at such an early stage in the development of a new drug, the required preclinical teratology studies would be unlikely to be complete;³⁸ a specific exemption was made for women with life-threatening conditions.

Clinical trials are research studies which explore whether a medical strategy, treatment, or device is safe and effective for humans. Pharmaceutical clinical trials are designed to answer the same questions of safety and efficacy in respect of new drugs, new formulations of existing drugs, additional indications for existing drugs, or their effects in patient populations not previously studied, such as pregnant women. The purpose of clinical trials is to generate generalisable information in a sample of patients representative in various ways of the population which would use the drug were it to be approved, and trials follow strict scientific standards to ensure the data generated are fit for this purpose. Pharmaceutical clinical trials constitute one of the final stages of the drug development process, which normally starts in a laboratory, moves on to involve animal testing, then into human volunteers (Phase I studies) and followed by trials in patients with the condition the drug is intended to treat. For safety purposes, clinical trials in patients begin with small groups of subjects with the target condition (Phase II studies) to assess the safety and tolerability of the drug and to establish the relevant dose-range for efficacy. In later Phase III studies, substantially more subjects with the target condition will be studied.³⁹

The national regulatory agencies within Europe did not follow the FDA's approach of introducing a ban, but that made little difference. The FDA's position was binding within the USA; most pharmaceutical companies were USA-headquartered organisations and considered that the FDA position bound them globally. With the exception of drugs developed specifically for conditions unique to pregnancy, there was no requirement in any country to conduct trials of investigational drugs in WoCBP, far less pregnant women, in order for the drug to be approved for use, and so there was no incentive for pharmaceutical companies to incur the perceived risks of such trials. Thus, many drugs became available for use by women, including pregnant women, despite having been studied exclusively in males, i.e., no distinction was made between the sexes for licensing purposes.

³⁸ Department of Health and Human Services, US Food and Drug Administration (1977). *General Considerations for the Evaluation of Drugs*. Publication No. HEW (FDA). 88-3040 Washington D.C. Government Printing Office, 1977.

³⁹ See <http://www.nhlbi.nih.gov/studies/clinicaltrials>, accessed 9th September, 2015; also Bhatt, A. (2010). Evolution of clinical research: a history before and beyond James Lind. *Perspect. Clin. Res.*, **1**, 6-10.

During this period, in the UK the issues relating to foetal research generally had been considered in 1972 (the Peel Report⁴⁰) and again in 1989 (the Polkinghorne Report⁴¹). The Peel Report was the output of an Advisory Group on the Use of F(o)etuses and F(o)etal Material for Research created after parliamentary reports of the commercial sale of human foetuses for research purposes. The main conclusions of the Peel Committee were that foetal experiments were permissible up to 20 weeks' gestation, i.e., while the foetus was 'pre-viable', and 300g bodyweight, provided the information could not be obtained in any other way, and the intent of the research was not one of ascertaining whether the intervention caused foetal harm. The Polkinghorne Committee, formed in the wake of the first operations to transplant foetal tissue into the brains of sufferers from Parkinson's Disease, was tasked to examine the UK Code of Practice for foetal research which had developed following the Peel Report. The Polkinghorne Report removed the distinction based upon viability and recommended that research on the foetus should be governed by principles 'broadly similar' to those applicable to research on children and adults, including the conditions that research should entail a minimal risk of harm unless the intervention was for the benefit of the foetus, and that trial procedures involving greater than minimal risk be considered in a manner 'broadly similar' to that in which they are considered for children and adults, i.e., on a group benefit basis. Thus, the conduct of clinical trials in pregnant women would have been acceptable in the UK, but the absence of a commercial incentive to do so for potential new medicines remained.

The exclusion of WoCBP from early-phase clinical trials effectively resulted in the exclusion of women from most trials. At that time, few if any approved drugs had different dosing recommendations for men and women, and the assumption seemed to carry that there was no advantage of incurring the perceived risks of including WoCBP in later-phase trials. The extent of this exclusion is clear from review of a number of substantial clinical trials in which no women were enrolled:

- the Physicians' Health Study of the effects of aspirin on cardiovascular disease (22,071 men);⁴²

⁴⁰ Peel, Sir J. Report of the Advisory Group on the Use of Fetuses and Fetal Material for Research. London: HMSO, 1972.

⁴¹ Polkinghorne, J. for Her Majesty's Government. Review of the Guidance of the Research Use of Fetuses and Fetal Material (The Polkinghorne Report). London: HMSO, 1989.

⁴² Committee of the Physicians' Health Study Research Group. (1989). Final report on the aspirin component of the ongoing Physicians' Health Study. *N.Engl.J.Med.*, **321**, 129–135.

- the Multiple Risk Factor Intervention Trial (MRFIT), a randomised trial conducted from 1973 to 1982 to evaluate correlations among blood pressure, smoking, cholesterol, and coronary heart disease (12,866 men);⁴³
- the Baltimore Longitudinal Study of Aging, extending from 1958 to 1975, which initially excluded females despite the fact that women constitute the majority of the population over age 65,⁴⁴ although women were latterly included.

Perhaps the most surprising illustration comes from the first study of the potential role of oestrogen in the prevention of heart disease, which also was conducted solely in men.⁴⁵

1.4 The Impacts of the Exclusion

By the late 1970s clinical evidence was emerging of sex-related differences in the responses to various drugs, which were not amenable to simple pharmacokinetic explanation, i.e., greater weights and different body composition in males,⁴⁶ and in only some cases had a hormonal basis,⁴⁷ although pre-clinical reports of sex-related differences had first emerged in 1932.⁴⁸ The exclusion of women from clinical trials meant that many medicines became available for prescription to women without knowledge of any differences regarding pharmacokinetics, efficacy or safety compared to data generated in males. Of course, safety data would be generated in time through normal safety reporting systems relating to approved drugs, and during the 1990s, of the ten approved drugs completely withdrawn from use, one factor in eight of these cases was that adverse event reports indicated they posed significantly higher safety risks for women than for men.⁴⁹ However, no similar process exists to gather the information necessary to answer the questions regarding pharmacokinetics and efficacy to guide dosing regimens in women; this information would need to come from other sources.

⁴³ Multiple Risk Factor Intervention Trial Research Group. (1982). Multiple risk factor intervention trial. Risk factor changes and mortality results. *J. Am. Med. Ass.*, **248**, 1465–1477.

⁴⁴ Shock, N.W., *et al.* (1984). Normal human aging: the Baltimore Longitudinal Study of Aging. NIH Publication No. 84-2450. Washington, DC, USA.

⁴⁵ Rosser, S. *Women's health: missing from U.S. medicine.* Bloomington, Indiana: Indiana University Press, 1994.

⁴⁶ For early reviews, see Proksch, R.A., Lamy, P.P. (1977). Sex variation and drug-therapy. *Drug Intell. Clin. Pharm.*, **11**, 398-406; Hamilton, J., Parry, B. (1983). Sex-related differences in clinical drug response: implications for women's health. *J. Am. Med. Women's Ass.*, **38**, 126-32.

⁴⁷ Hreiche, R.; Morissette, P.; Turgeon, J. (2008). Drug-induced long QT syndrome in women: Review of current evidence and remaining gaps. *Gender Med.*, **5**, 124-135.

⁴⁸ Cited in Czerniak, C. (2001). Gender-based differences in pharmacokinetics in laboratory animal models. *Int. J. Tox.*, **20**, 161-163.

⁴⁹ Simon, V. (2005). Wanted: Women in clinical trials. *Science*, **308**.5728., 1517.

The male-female comparison described above makes (at least) one crucial oversimplification, which is that all women are sufficiently similar to form a homogeneous group - yet few non-pathological conditions produce the extent of physiological, endocrine and biochemical changes which occur during pregnancy. As pregnancy progresses, gastric emptying is slowed, potentially delaying maximal drug concentrations after ingestion, and gastric acidity is reduced, which affects the absorption of certain drugs, with some showing increases and others reductions. Nausea and vomiting, common in early pregnancy, will also affect – generally reducing - absorption of ingested medicines. The increases in total body water and fat stores during pregnancy increase the volume of distribution within the body of many drugs, thereby lowering the plasma and target organ concentrations. The increased cardiac output associated with pregnancy increases the speed at which drugs are distributed throughout the body. Pregnancy has variable effects on hepatic metabolism, with some metabolic pathways induced and others inhibited, again resulting in differences of circulating and target organ concentrations of both parent drugs and metabolites. In the kidney, filtration rate and renal secretion increase during pregnancy, thereby enhancing clearance from the body of renally excreted drugs (such as amoxicillin) and their metabolites.⁵⁰ Thus, many changes occur during pregnancy which are likely to affect the absorption, distribution, metabolism and excretion of drugs, with consequent impacts upon their efficacy and safety. The majority of the few studies which have been published confirm not only significant differences between pregnant and non-pregnant women in the pharmacokinetic characteristics for drugs, but also that such differences are not consistent throughout pregnancy.⁵¹

Convincing medical reasons exist to administer a range of medications to women whilst they are pregnant, and due to the physiological changes described above, pregnant women may require different dosing regimens to both men and non-pregnant women.⁵² The exclusion of WoCBP from clinical trials meant that, for almost all new drugs introduced, guidance regarding dose regimens applicable to women and, particularly, pregnant women,

⁵⁰ Simon H.L., Thomas, S.H.L., Yates, L.M. (2012). Prescribing without evidence – pregnancy. *Br.J.Clin. Pharmacol.*, **74**, 691–697.

⁵¹ Feghali, M.N., Mattison, D.R. (2011). Clinical Therapeutics in Pregnancy. *J.Biomed.Biotech.* Article ID 783528; Frederikson, M.C. (2001). Physiologic changes in pregnancy and their effect on drug disposition. *Sem.Perinat.*, **25**, 120-123; Ke, A.B, Rostami-Hodjegan, A., Zhao,P., Unadkat, J.D. (2014). Pharmacometrics in pregnancy: an unmet need. *Ann.Rev.Pharm.Tox.*, **54**, 53-69.

⁵² Chambers, C., D., Polifka, J., E., Friedman, J.M. (2008). Drug safety in pregnant women and their babies: ignorance not bliss. *Clin.Pharmacol.Ther.*, **83**, 181–183; Little, B.B. (1999). Pharmacokinetics during pregnancy: Evidence-based maternal dose formulation. *Obs.Gyn.*, **93**, 858–868.

was not available. As a consequence, patients in these groups may be treated sub-effectively or exposed to excessive doses. If an approved drug was not studied in pregnant subjects, then its use in that population is considered as off-label usage, which engages a range of medical and legal issues.⁵³ If a licenced drug harms a patient, under the Consumer Protection Act 1987, the responsibility lies with the manufacturer. However, should an off-licence drug cause harm, the liability, potentially, lies with the prescriber. In theory, a prescriber could face a negligence claim solely for using an off-licence drug if harm was caused and if a licenced alternative was available, although a failure to provide adequate information upon which a patient could base consent is perhaps a more likely cause for litigation. The situation was clearly unsatisfactory from many perspectives.

1.5 The Change of Perspective - Towards the Inclusion of Women

Since the 1980's, opinion had been growing that the exclusion of women from clinical trials was discriminatory, disadvantaging not only the present generation but also subsequent ones.⁵⁴ The ethical perspective was changing from the earlier, paternalistic, focus on protecting a population perceived as vulnerable to one which increasingly recognised the concept of autonomy for would-be participants.⁵⁵ In the USA, in their Belmont Report, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research had defined beneficence, justice, and respect for persons as the ethical principles that should govern research, and took the view that beneficence had both micro- and macro-ethics dimensions, in that while individual subjects should be protected against risk of harm, that had to be balanced against the potential loss of substantial benefits to society that might accrue from research.⁵⁶

In 1991, in *United Automobile Workers v Johnson Controls*,⁵⁷ the Supreme Court of the USA ruled that, under the terms of the Pregnancy Discrimination Act (1978),⁵⁸ pregnant

⁵³ Shah, S., van Geijn, H. (2007). Managing the risks of off-licence prescribing in pregnancy; Expert Opinion—Legal Questions. *Eur.J.Obs.Gyn.Rep.Biol.*, **130**, 156–159; Webb, R.T., Howard, L., Abel, K.M. (2004). Antipsychotic drugs for non-affective psychosis during pregnancy and postpartum. *Cochrane Database of Systematic Reviews*, no.2, Article ID CD004411, 2004.

⁵⁴ For a broad review, see Schiebinger, L. (2003). Women's health and clinical trials. *J.Clin.Invest.*, **112**, 973–977.

⁵⁵ Merkatz, R.B. (1997). Inclusion of women in clinical trials: a historical overview of scientific, ethical, and legal issues. *JOGNN*, **27**, 78-84.

⁵⁶ National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. (1979). Belmont report: Ethical principles and guidelines for the protection of human subjects of research. Washington, DC: Government Printing Office.

⁵⁷ International Union, United Automobile, Aerospace and Agricultural Implement Workers of America, UAW, *et al v Johnson Controls Inc.*, 111 SCT 1196, 1991.

women could not be excluded from employment solely on the premise that their working conditions posed a potential foetal risk. Although significant differences exist between employment rights and participation in clinical trials, the court's decision added fuel to the growing debate around the importance of autonomy and consent, and in particular the practice of exclusion by gender.⁵⁹ The decision indirectly raised the question of the constitutionality of excluding women from government-funded or government-funded research. In 1993, the FDA issued a new Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs, which called for a “reasonable” number of women to be included in new clinical trials.⁶⁰ The Guideline also interpreted that the principle of justice enunciated in the Belmont Report was best served when research benefited men and women equally. The following year, the Institute of Medicine (IoM) argued that the continued practice of excluding women from clinical trials diminished their autonomy, and that justice required all therapeutic interventions (not just new medicines) should be adequately tested in the population(s) in which they were intended to be used.⁶¹ The same year, a new National Institutes of Health (NIH) Guideline was jointly issued by the Office of Research on Women’s Health and the Office of Research on Minority Health, stipulating that women and members of minority groups and their subpopulations (*sic*) were to be included in all human subject research.⁶²

Of course, the same principles which drove the FDA to rescind its 1977 exclusion of WoCBP from early-phase clinical trials also apply to pregnant women. Pregnant women constitute a definable population to whom medicines are likely to be administered, and so, following the IoM’s argument above, justice also requires that investigational drugs should

⁵⁸ Pregnancy Discrimination Act. (1978). 92 Stat.2076, 42 USC 200c (k).

⁵⁹ See, for example, Grossman, J.L. (1994). Womens jury service - right of citizenship or privilege of difference. *Stanford Law Rev.*, **46**, 1115-1160; Hasday, J.E. (2013). Women's exclusion from the constitutional canon. *Univ.Illinois Law Rev.*, **5**, 1715-1732; Feenan, D. (2008). Women judges: gendering judging, justifying diversity. *J.Law Soc.*, **35**, 490-519.

⁶⁰ U.S. Department of Health and Human Services, Food and Drug Administration. (1993). Guideline for the study and evaluation of gender differences in the clinical evaluation of drugs: Notice. *Fed.Reg.*, **58**, 39406-39416.

⁶¹ Mastroianni, A.C., Faden, R., Federman, D (Eds). *Institute of Medicine: Committee on the Ethical and Legal Issues Relating to the Inclusion of Women in Clinical Studies. Women and health research: Ethical and legal issues of including women in clinical studies.* Washington DC: National Academy Press, 1994.

⁶² U.S. Department of Health and Human Services, National Institutes of Health. (1994). NIH guidelines on the inclusion of women and minorities as subjects in clinical research. *Fed.Reg.*, **59**, 14508-14513.

be adequately tested in this population too. Similarly, the principle of respect for persons requires that pregnant women be accorded the same respect as non-pregnant women.⁶³

After the FDA rescinded its ruling precluding the recruitment of WoCBP into early-phase clinical trials, the number of trials including women increased rapidly. A systematic review of the inclusion of women in clinical trials for investigational drugs approved by the FDA between 2000 and 2002 showed that 47% of participants were male, and 49% were female (the gender of 4% of subjects was not specified). However, a significant under-representation of women in early phase trials remained.⁶⁴ An analysis of marketing authorisation applications in Europe submitted between 2000 and 2003 also concluded there was no evidence of gender bias.⁶⁵

Thus, in both Europe and the USA, the practice of excluding women, a large proportion of whom would be of child-bearing potential, from clinical trials changed rapidly following the reversal of the FDA's 1977 decision. However, the conduct of trials involving pregnant women was another matter. The most recent review of clinical trials in pregnant women concluded their exclusion from industry-sponsored clinical trials continues to be common practice; in a 4-month snapshot, only 1% of industry-sponsored studies were designed specifically for pregnant women and 95% of studies of conditions that can affect pregnant women excluded pregnant women from participation.⁶⁶ The reasons the authors advance are not surprising: the paternalistic attitude regarding a 'vulnerable' population is probably still more embedded regarding the foetus,⁶⁷ as is the desire to 'do no harm', yet clinical care during pregnancy often requires the use of medications untested in pregnancy. In addition, the FDA classifies pregnant women as a vulnerable population, which deters researchers from including pregnant subjects in clinical trials.

⁶³ See *Women and Health Research; Ethical and Legal Issues of Including Women in Clinical Studies*. Vol.2. National Academy Press, 1994.

⁶⁴ Yang, Y.S., Carlin, A.S., Faustino, P.J., Motta, M.I.P., *et al.* (2009). Participation of women in clinical trials for new drugs approved by the Food and Drug Administration in 2000-2002. *J.Womens Health*, **18**, 303-310.

⁶⁵ Mullner, M., Vamvakas, S., Rietschel, M., van Zwieten-Boot, B.J. (2007). Are women appropriately represented and assessed in clinical trials submitted for marketing authorization? A review of the database of the European medicines agency. *Int.J.Clin.Pharm.Ther.*, **45**, 477-484.

⁶⁶ Shields, K.E.; Lyerly, A.D. (2013). Exclusion of pregnant women from industry-sponsored clinical trials. *Obs.Gyn.*, **122**, 1077-1081.

⁶⁷ See Wild, V. (2012). How are pregnant women vulnerable research participants? *Int.J.Fem.App. Bioethics*, **5**, 82-104.

1.6 The Requests from the Regulatory Agencies for better data

The lack of information available to guide drug use in pregnant women, together with the changing perspective on the inclusion of pregnant women in clinical trials, led the FDA in 2009 to release its Pregnancy and Lactation Rule,⁶⁸ intended to promote more systematic collection of information relating to drug efficacy and pharmacokinetics during pregnancy, to achieve a balance between possible harms and benefits to both the mother and foetus. The following year, the EMA, of which the UK regulatory authority, the Medicines and Healthcare Regulatory Agency (MHRA) is a part, announced “Medicine Use in Pregnancy” as one of its priorities for drug safety research, with comparative safety (presumably for both pregnant women and foetuses, although this is not explicitly stated) of different therapeutic options in pregnancy as one of the key objectives.⁶⁹

Neither announcement makes reference to trials of medicines intended to benefit the foetus; they do not seem to be intended to provide a framework for or promote trials in which the foetus is the potential beneficiary. Rather, they seem to be part of the Agencies’ desire to stimulate properly conducted clinical trials of investigational drugs in the pregnant population, with the objective of encouraging the collection of data which will provide a dosing regimen and guide the use of the drug, once approved, should it be prescribed to a patient known to be pregnant.

The ethical arguments in support of conducting controlled clinical trials in this population seem to be well-founded from utilitarian, deontological, and consequentialist perspectives. Pregnant women do and will continue to suffer from a range of conditions amenable to medical management with drugs when they occur in males and non-pregnant females, and the reality is that drugs will be prescribed to pregnant women, either innocently (neither the prescriber nor the woman is aware of the pregnancy) or off-label. From the individual pregnant woman’s viewpoint, the fact that a drug which she is prescribed has been assessed in other pregnant women, and so the efficacy, safety and dose regimen have all been established, may alleviate some concerns, although one might imagine those concerns would be more likely focussed on the impact on the foetus than the condition for which the

⁶⁸ FDA, Health Organizations to Study Safety of Medications Taken During Pregnancy, FDA News Release 10 Journal of Biomedicine and Biotechnology 2009, <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2009/ucm195934.htm> See also <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093310.htm> both accessed 9th September, 2015.

⁶⁹ http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/03/WC500076321.pdf accessed 9th September, 2015.

drug is being given. For pregnant women as a group, assurance that many - ideally, all, but that seems unlikely - of the medicines they might be administered have been assessed in pregnant women should do much to reduce worries regarding the use of medically-prescribed drugs during pregnancy.

The deliberate, systematic conduct of trials of investigational drugs in pregnant women will inevitably raise concerns regarding ‘another thalidomide’, but the Agencies’ requests specifically do not make reference to the detection of possible teratogenesis. This is hardly surprising, for three reasons. The first of these is a matter of statistics: assuming a baseline malformation rate of 3%, detecting a twofold increased risk for malformations would require a study involving 800 exposed subjects and 800 unexposed controls,⁷⁰ far beyond the size (and cost) of study necessary to provide pharmacokinetic information. As an illustration, a recent study demonstrating that antidepressant use (so, all antidepressant agents, rather than a single drug) during pregnancy was associated with the development of autism in the exposed children included 4,429 cases of autism spectrum disorder and compared them to 43,277 matched controls, concluding that antidepressant use was associated with more than a 3-fold increased risk of autism in the children.⁷¹ Trials of such size and cost are neither practicable nor financially viable in this population prior to drug approval. The second reason is a matter of ethics: an objective of conducting trials specifically to detect a potential teratogenic effect would probably be held to be unethical. Finally, the time course for the emergence of such injury is too variable to be detected in this way. Injury may be immediately obvious, as was the case with thalidomide, it may be latent, as reported for the antidepressants,⁷² or it may be intergenerational, with diethylstilboestrol (DES)⁷³ as the leading illustration. Evidence is now emerging that abnormalities may also occur in the grandchildren of women who took DES in pregnancy.⁷⁴

⁷⁰ Etwel, F., Hutson, J.R., Madadi, P., *et al.* (2014). Fetal and perinatal exposure to drugs and chemicals: novel biomarkers of risk. *Ann.Rev.Pharm.Tox.*, **54**, 295-315.

⁷¹ Rai, D., Lee, B.K., Dalman, C., Golding, J, *et al* (2013). Parental depression, maternal antidepressant use during pregnancy, and risk of autism spectrum disorders: population based case-control study. *Br.Med.J.*, **346**, 2059-2073.

⁷² Croen, L.A., Grether, J.K., Yoshida, C.K., Odouli, R., Hendrick, V. (2011). Antidepressant use during pregnancy and childhood autism spectrum disorders. *Arch.Gen.Psych.*, **68**, 1104-1112.

⁷³ Milhan, D. (1992). DES exposure: implications for childbearing. *Int.J.Childbirth*, **7**, 21-28; Harris, R.M., Waring, R.H. (2012). Diethylstilboestrol—A long-term legacy. *Maturitas* **72**, 108– 112.

⁷⁴ See, for example, Blatt, J., Le L.V., Weiner, T., Sailer, S. (2003). Ovarian carcinoma in an adolescent with trans generational exposure to diethylstilbestrol. *J.Ped.Hem.Onc.*, **25**, 635-636; Kalfa, N., Paris, F., Soyer-Gobillard, M.O., Daures, J.P., Sultan, C. (2011). Prevalence of hypospadias in grandsons of women exposed

In the wake of thalidomide, a range of approaches was developed to try to enable early detection of possible teratogenesis. Opportunistic case reports of children born with a birth defect are collated; case series, comparing the outcome of pregnancies in one group to that in another, matched, group, has detected foetal alcohol syndrome⁷⁵ and the embryopathies associated with the rubella virus,⁷⁶ thalidomide⁷⁷ and isotretinoin;⁷⁸ the small numbers of female participants who do become pregnant during clinical trials are (usually) excluded from further participation then rigorously followed up. Pregnancy registries, involving women who have become pregnant while taking an approved medicine, are retrospectively opportunistic, rather than prospective and planned, and in the absence of an appropriate control group, comparisons are often made to ‘expected’ rates of congenital anomalies obtained from dedicated birth defects registries to assess whether the medicine expresses teratogenic effect.⁷⁹ However, none of these approaches can, or is intended to, capture systematically information relating to drug efficacy and pharmacokinetics during pregnancy. The Agencies’ requests for such information prior to the approval of new drugs are therefore best satisfied by the conduct of formal controlled trials.⁸⁰

Thus, the intent behind the Agencies’ requests seems not to be that of “avoiding another thalidomide”, as such studies simply cannot detect such effects. The reference by the EMA to “comparative safety of different therapeutic options in pregnancy” seems to denote a desire for a holistic evaluation of safety for both pregnant women and foetuses. The requests from the Authorities for data prior to receiving applications to consider drugs for approval are likely to result in an increased volume of clinical research in the pregnant population. Given the 2-3% underlying incidence of spontaneous congenital abnormalities (1 in 45 live births in England and Wales⁸¹; the figure for Scotland is comparable,⁸² and the

to diethylstilbestrol during pregnancy: a multigenerational national cohort study. *Fertil.Steril.*, **95**, 2574–2577.

⁷⁵ Jones, K.L., Smith, D.W. (1973). Recognition of the foetal alcohol syndrome in early infancy. *Lancet* **2**, 999–1001.

⁷⁶ Gregg, N.M. (1991). Congenital cataract following German measles in the mother. 1941. *Aust.NZ J. Ophthalmol.*, **19**, 267–276.

⁷⁷ Lenz, W., Knapp, K. (1962). Thalidomide embryopathy. *Arch.Environ.Health.* **5**, 100–105.

⁷⁸ Lammer, E.J., Chen, D.T., Hoar, R.M., Agnish, N.D., *et al*(1985). Retinoic acid embryopathy. *N.Engl.J. Med.*, **313**, 837–841.

⁷⁹ Correa, A., Cragan, J.D., Kucik, J.E., Alverson, C.J., *et al*(2007). MACDP 40th anniversary edition surveillance report: Reporting birth defects surveillance data 1968–2003. *Birth Defects Res. A Clin.Mol. Teratol.*, **79**,65–93.

⁸⁰ Hannan, E.L. (2008). Randomized clinical trials and observational studies: Guidelines for assessing respective strengths and limitations. *JACC Cardiovasc.Interv.* **1**,211–217; Parfrey, P., Ravani, P. (2009). On framing the research question and choosing the appropriate research design. *Methods Mol.Biol.*, **473**, 1–17.

⁸¹ Correa, A., Cragan, J.D., Kucik, J.E., *et al*. (2007). MACDP 40th anniversary edition surveillance report: Reporting birth defects surveillance data 1968–2003. *Birth Defects. Res. A Clin.Mol.Teratol.*, **79**, 65–93.

UK is in line with figure for Europe⁸³), inevitably, as the number of trials in this population increases, a foetus with a congenital anomaly will be born to a woman who participated in a clinical trial, and in an unknowable proportion of cases, the anomaly will have been caused by the investigational product.

1.7 The Legal and Ethical Issues of Clinical Trials in Pregnant Women

The requirements regarding the proper conduct of clinical trials of investigational medicinal products (IMP) in the UK are specified in the EU Clinical Trials Directive (CTD) and codified in the Medicines for Human Use (Clinical Trials) Regulations 2004.⁸⁴ Under the regulations, ‘conducting a clinical trial’ comprises, *inter alia*, carrying out any test or analysis with the intent:

- (i) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of the investigational medicinal products administered in the course of the trial,
- (ii) to identify any adverse reactions to those products, or
- (iii) to study absorption, distribution, metabolism and excretion of those products.

These intentions seem to accord well with the requests from the Agencies regarding the generation of information relating to drug disposition, efficacy and safety in the pregnant population. Clinical trials in pregnant women generally will entail administering the investigational drug (or placebo or comparator agent) to each subject, and knowing that the foetus may also be exposed to the drug, or to the consequences of its actions in pregnant women, the *sequelae* will be monitored in both the pregnant woman and the foetus. The embargo on clinical trials in this population for so many years means that we lack a body of relevant experience upon which to rely regarding the acceptability of such trials. As a consequence of the embargo, the pathways to recovery of compensation in the event of injury are less well-trodden than for trials in other populations, and given the stage of development at which the foetus may be exposed to an investigational drug, any harm may not become apparent for a considerable period. The ramifications of clinical trials in

⁸² British Isles Network of Congenital Anomaly Registers. Congenital Anomaly Statistics 2010 (England & Wales). http://www.binocar.org/content/Annual%20report%202010%20FINAL%2031_07_12%20v2.pdf, accessed 9th September, 2015; Scottish Perinatal and Infant Mortality and Morbidity Report, 2011. Healthcare Improvement Scotland, 2013.

⁸³ Dolk, H., Loane, M., Garne, E. (2010). The prevalence of congenital anomalies in Europe. *Adv.Exp.Med. Biol.*, **686**, 349–364.

⁸⁴ SI 2004/1031 as amended.

pregnancy are both so insidious and extensive that from both deontological and consequentialist perspectives, trials involving the foetus require special consideration. The requests from the EMA and FDA will require a range of legal and ethical matters to be addressed which, until now, have been avoidable by the practices of not conducting clinical trials of investigational drugs in pregnant women, and withdrawing from trials female participants who become pregnant during the course of the trial.

A key aspect is the extent to which the law already recognises and protects the foetus, and its future ‘interests’, in particular its interest in being born uninjured. As will be discussed in the next chapter, the foetus lacks legal personality, but a range of societal constraints have been generated which provide increasing protection to the foetus as the pregnancy proceeds. How applicable are these mechanisms to the clinical trial setting? Chapter 3 will address these questions, and conclude that there is little relevant precedent from which to draw conclusions.

Another fundamental question is whether, ethically, the foetus ‘deserves’ protection, and, if it does, by what right do we ‘experiment’ on an entity which lacks legal personality? Vivisection is subject to more extensive legislation than clinical trials in pregnant women, whilst others who cannot consent, minors and the *incapax*, enjoy all of the protections arising from the possession of legal personality. Does - should - the decision to participate rest with the pregnant woman alone, and if so, is that authority unfettered? Chapter 4 will explore the moral standing of the foetus, and the main models which have been used to describe its status, concluding that one particular model probably represents the best balance between the future interests of the foetus as perhaps most commentators see them and the pregnant woman’s autonomy.

Our clinical trial approval processes were not developed with trials involving pregnant women in mind and so the adequacy of the existing processes may be open to question. The current and future processes for approval of clinical trials in pregnant women will be reviewed in Chapter 6, examining in particular the extent to which foetal risk is already controlled and reduced, and might be further decreased. Consent, the bedrock upon which clinical trials are founded, both legally and ethically, will be explored to assess whether pregnant women - or foetuses - constitute a ‘vulnerable population’, the extent to which the consent and trial approval processes take account of that, and whether the foetus should be considered as an ‘indirect’ trial subject. The understanding trial subjects have of the legal

relationship they have with investigators, and the consequence that has in the event of injury, will be assessed, leading to the conclusion that this is a topic which is poorly understood by most participants. Lastly, the future regulations for the conduct of clinical trials which suggest a different maternal-foetal balance and impart a greater moral standing to the foetus than the conclusions in Chapter 4 suggested was best, will be considered.

Clinical research is inherently uncertain; if we knew how the body would respond to investigational drugs, trials would be unnecessary, but we do not. Inevitably, that means trial subjects are exposed to risk and, despite the proper execution of the approval processes, those risks will, on occasion, be realised. Trial participants are all volunteers, and many engage these risks, at least in part, altruistically - but in the event of injury, are our compensatory mechanisms adequate? The review in Chapter 7 of the processes and instruments available will find that their adequacy is at best questionable, and that trial participants are unlikely to be aware of such deficiencies until the need arises to seek compensation on behalf of a child born injured.

The argument for the conduct of clinical trials in pregnant women is compelling, to ensure that conditions which may be harmful to the woman's health and that of the foetus she is carrying, are optimally-managed, and that new medicines can be deployed safely and effectively. However, the existing processes intended to protect the foetus and compensate children born injured as a result of their mothers' participation in clinical trials are unclear, and arguably do not reflect the moral debt which we as a society owe to those who 'go first' for the benefit of others. Many commentators have advocated the introduction of various 'no fault' mechanisms to compensate those injured in clinical practice and clinical research. A more radical approach which will create an enduring obligation that will in turn raise wider questions regarding the reasons special provision is required for this population of 'indirect' trial subjects is described in Chapter 8.

1.8 Conclusions

Over 50 years have passed between thalidomide and the regulators' reactions to it which conspired to exclude women of child-bearing potential from clinical trials with investigational drugs, and the *volte-face* which has led to the request to study investigational drugs in women who are pregnant. During that time, those who developed new regulations and legislation to control the conduct of clinical trials, understandably, did not have this population in their contemplation as evidenced *inter alia* by the absence of

the word “pregnant” from these regulations, although a future regulation (Regulation 536, discussed in Chapter 6) explicitly addresses this population. As a result, we lack a legal framework within which to conduct such studies: one which takes account of the particular issues which arise regarding the involvement of the foetus. This thesis seeks to address these challenges and to begin to develop such a framework.

Chapter 2 Protection of the Foetus from Destruction

2.1 Introduction

In considering whether the current clinical trial processes afford adequate legal recognition of the foetus, one must first consider the legal recognition already given to the foetus, whether that recognition is qualified in any way, and what the consequences of existing recognition and any qualifications may be in a clinical trial setting. Legal recognition might be considered from two perspectives: in relation to the foetus *in utero per se*, and in relation to the child subsequently born, i.e., events that affected the foetus before birth, the consequences of which manifest *postnatally*. As will be discussed later in this chapter,⁸⁵ the foetus lacks legal capacity, and so issues relating to its protection and compensation in the event of injury sustained *in utero* become actionable only upon live birth. However, provision for protection and compensation involve consideration of the existence and future interests of the foetus. This chapter will briefly explore the development of approaches within Canon and criminal law to recognise and protect the foetus, both of which were largely concerned with preventing intentional abortion and the killing of newborn children, and will illustrate that the legal protection for the foetus in that regard has become less extensive over the last 50 years. However, as described in Chapter 1, given that the intent of conducting clinical trials in pregnant women would not be that of procuring abortion, the relevance of this to the topic at hand is that of establishing the legal status of the foetus.

Chapter 3 will trace the application of Criminal and Common law in England and Wales to the child born injured as a consequence of harm inflicted *in utero*, illustrating how the legal approaches in this regard have changed, and the notion of ‘trans-natal’ action has developed;⁸⁶ where relevant, comparisons will be made to Scotland, Ireland, the USA and the European Community. Clearly, this is a quite unintended potential consequence of the conduct of clinical trials in pregnant women, and the points addressed in this chapter will put context around such injuries when sustained in a non-trial setting. This will be relevant to the question of whether the protection for the foetus in clinical trials is adequate.

⁸⁵ See Chapter 2.6.

⁸⁶ The term is intended to convey the relating of ante-natal events or actions to post-natal outcomes. Although this is now common practice in criminal and common law, the term does not appear to have been employed in a legal setting, but has been used in psychology, perinatology and obstetrics for over 20 years.

Foetal ‘rights’, interests and protection are amongst the more contentious topics in medical law. In the last 50 years alone, the 1967 Abortion Act in the UK, the 1973 judgment in *Roe v Wade* in the USA,⁸⁷ the birth in 1978 of Louise Brown, the world’s first ‘test-tube’ baby,⁸⁸ and the 1984 Warnock report⁸⁹ on *in vitro* fertilisation, amongst other events, all provoked intense, heated and emotional debate.⁹⁰ One of the golden threads which ran through these debates was that of ‘protecting’ the foetus from intentional or careless destruction; the foetus might not be considered as a ‘person’, but nevertheless deserved protection by the law, precisely the same consideration which applies in the clinical trial setting. The issue is not a new one, of course - it has been with us almost since the beginnings of civilisation.

2.2 The Early Legal and Religious Views of Foetal Status

The Babylonian Code of Hammurabi and ancient Hebrew, Assyrian and Hittite laws all contained evidence of two concepts which persist in much present-day jurisprudence: that the preservation of pregnant woman’s life took precedence over that of the foetus and that the foetus became more worthy of recognition and protection as it developed.⁹¹ Early Christian writings also adopted the latter concept, endowing the foetus with the description of ‘human’, mostly based on physical appearance.⁹² In the late 16th Century, the Roman Catholic Church declared the foetus worthy of the full protection of the church (and hence

⁸⁷ *Roe v Wade* [1973] 410 U.S. 113, 165. See commentary by Warren, M.A. (1973). Moral and legal status of abortion. *Monist*, 57, 43-61.

⁸⁸ Steptoe, P.C., Edwards, R.G. (1978). Birth after reimplantation of a human embryo. *Lancet*, 2, 366. See USA commentary <http://www.pbs.org/wgbh/americanexperience/features/interview/ethical-questions/> accessed 5th September, 2015. Also *Prospettive nel Mondo*, 1 August 1978; Luciani, *Opera Omnia*, vol. 8, pp. 571-572 for comment from The Vatican.

⁸⁹ Human Embryology and Fertilisation Authority; The Warnock Report, 11th April 2009, available at <http://www.hfea.gov.uk/2068.html>, accessed 5th September, 2015. For commentary, see Cannel, F. (1990), Concepts of parenthood: the Warnock Report, the Gillick debate, and modern myths. *Am. Ethnologist*, 17, 667-686; Gillon, R. (1987). In Britain, the debate after the Warnock Report. *Hast.Cent.Rep.*, 17, S16-18.

⁹⁰ See, for example, Cameron, N.M. de S. *Embryos and Ethics: Warnock Report in Debate*. Rutherford House, 1987; Walters, W.A.W., Singer, S. *Test-tube Babies: A Guide to Moral Questions, Present Techniques and Future Possibilities*. Oxford: OUP, 1982; Mahowald, M.B. (1989). Is there life after *Roe v Wade*? *Hast.Cent.Rep.*, 19, 22-29.

⁹¹ Driver, G.R., Miles, J.C. *The Babylonian Laws*. Oxford: Clarendon Press, 1953: II: 209-214; Paul, S.M. *The Book of the Covenant*. 1965 quoted by Hyatt, J.R. in *Commentary on Exodus*. London: Oliphants, 1971: p233; Driver, G.R., Miles, J.C. *Middle Assyrian Law Code, Tablet A*, paragraph A21, available at <http://jewishchristianlit.com/Texts/ANELaws/midAssyrLaws.html>, accessed 5th September, 2015; Sigerist, H.E. *A History of Medicine*. New York and Oxford: OUP 1951: 1: 430.

⁹² For a review of the historical approaches, see Casey, G. *Born Alive: The Legal Status of the Unborn Child*. Chichester: Barry Rose Law Publishers, 2005. Available at http://www.academia.edu/191110/Born_Alive_The_Legal_Status_of_the_Unborn_Child. The 20th Century version of this - ‘personhood’ - will be discussed in Chapter 4.5.

the law, in many countries) from the point at which its existence was known,⁹³ the intention of this declaration being to deter or prevent deliberate abortion. The Catholic Church's declaration also recognised the concept now termed 'double effect',⁹⁴ permitting the use of medication or other intervention to save the pregnant woman's life but which, as an unintended consequence, resulted in miscarriage.

This probably marks a turning point in thinking between injury to the foetus arising as a consequence of an accident or malicious intent towards the pregnant woman alone, and action deliberately taken in the knowledge, and possibly with the intent, that it could harm the foetus. Conceptually, this is similar to the situations which obtain in both medical practice and medical research involving pregnant women: drugs are administered in the knowledge, although not with the intent, that despite best efforts being made, harm to the foetus may occur.

By this time advances in medicine and surgery were making targeted abortion both more possible and safer, and the incidence of abortion rose.⁹⁵ This led to a Papal Bull in 1869 declaring that all those, including pregnant women, who procured abortion would henceforth be excommunicate,⁹⁶ although the Bull preserved the 'double effect' exception. This remains the position of the Roman Catholic Church.⁹⁷

2.3 Early English Legal Approaches to the Protection of the Foetus

The common law, broadly, reflected Canon law and focussed on the matter of foetal destruction. One of the earliest legal opinions on this comes from De Bracton, in his

⁹³ Pope Sixtus v *Effraenatum*. October 29th, 1588.

⁹⁴ John de Lugo, S.J. *Responsa Moralia*. 1651.

⁹⁵ See, for example, McLaren, A. (1978). Abortion in France: women and the regulation of family size 1800–1914. *French Historical Studies*, **10**, 461–484; Brodie, J.F. *Contraception and Abortion in Nineteenth-Century America*. Ithaca, New York: Cornell University Press, 1997.; Beahen, W. (1986). Abortion and infanticide in Western Canada 1874 to 1916: a criminal case study. *Historical Studies (The Canadian Catholic Historical Association)* **53**, 53–70.; Rentoul RR: *The Causes and Treatment of Abortion*. London, Pentland, 1889, cited in Potts, M., Campbell, M. (2002) *History of Contraception*, available at <http://web.archive.org/web/20030701162741/http://big.berkeley.edu/ifplp.history.pdf> accessed 5th September, 2015.

⁹⁶ Pope Pius IX. *Apostolicae sedis*. October 12th 1869.

⁹⁷ Catholic News Agency: The Catholic Church and Abortion, available at <http://www.catholicnewsagency.com/resources/abortion/catholic-teaching/the-catholic-church-and-abortion/>, accessed 5th September, 2015.

treatise *On the Laws and Customs of England*, in which he declared that an action which led to the miscarriage of an “animated” foetus constituted homicide.⁹⁸

Later commentators, including Staunforde, Lambarde, Horne, Coke, Hale, and Blackstone (initially), all held some variety of the doctrine that while causing the death of a child *in utero* might support a criminal charge, it would not be one of homicide.⁹⁹ These opinions make an interesting comparison with *R v Tait*¹⁰⁰ and the *Attorney-General's Reference (No. 3 of 1994)*, a century later,¹⁰¹ in which the House of Lords concluded that *postnatal* death resulting from injury inflicted *in utero* constituted manslaughter, but not murder.¹⁰²

At the same time, the beginnings of the uncertainties and contradictions which pervade the debates around foetal status to this day were becoming apparent. In *Wallis v Hodson*, in 1740, the child *en ventre sa mere* at the time of her benefactor's death was held by the Lord Chancellor to be *in rerum natura*, only four years after Coke's insistence to the contrary¹⁰³ - an early example of ‘*trans-natal*’ legal thinking. Perhaps in part attempting to fill the vacuum resulting from the reduced standing of the Ecclesiastical Courts following the Reformation, the law had taken the step of attempting to deter the immediate killing of newborn children in the form of the Act to Prevent the Destroying and Murthing of Bastard Children 1624.¹⁰⁴ Infanticide had been considered by some to be a practical resolution to the problem of an unwanted child where abortion had either not been attempted or had failed. The lack of clarity regarding the distinction between abortion and

⁹⁸ Bracton, H. *De legibus et consuetudinibus Anglie*. (On the Laws and Customs of England), F 120, 437. Woodbine, G.E., ed., translated, with revisions and notes, by Samuel E. Thorne, (Cambridge, Massachusetts, 1968). Published in association with the Selden Society.

⁹⁹ Guillaume Staunford, *Les Plees Del Corone, dividees in plusor titles & Common Lieux*, Cap. 13. William Lambarde, *Eirenarcha or The Office of Justices of Peace*. A. Horne, *The Mirror of Justices*. For Coke, see 3 Co Inst (1648) 50. Sir Matthew Hale, *Historia Placitorum Coronae* (The History of the Pleas of the Crown). William Hawkins, *A Treatise of the Pleas of the Crown*. Sir William Blackstone, *Commentaries on the Laws of England* (1765), cited in Casey, G. (2002). Pregnant woman and unborn child: legal adversaries? *M.L.J.I.*, **8**, 75-81; see also http://books.google.co.uk/books?id=Ik0AAAIAAJ&printsec=frontcover&source=gbs_ge_summary_r&cad=0#v=onepage&q&f=false, Chapter 7, Section 51, accessed 5th September 2015; Hale, M. *A History of the Pleas of the Crown*, 1:433; Blackstone's *Commentaries on the Laws of England*, Book the Fourth - Chapter the Ninth : Of Mispriisions and Contempts, Affecting the King and Government, at p119, available at http://avalon.law.yale.edu/18th_Century/blackstone_bk4ch14.asp, accessed 5th September, 2015; Blackstone's *Commentaries on the Laws of England*, Book the Fourth - Chapter the Fourteenth : Of Homicide, at p.198, available at http://avalon.law.yale.edu/18th_Century/blackstone_bk4ch14.asp, accessed 5th September, 2015

¹⁰⁰ *R v Tait* [1990] 1 Q.B. 290.

¹⁰¹ See discussion in Chapter 3.3

¹⁰² *Attorney-General's Reference (No. 3 of 1994)* [1998] AC 245.

¹⁰³ Foetal recognition for the purposes of succession will be discussed further in Chapter 3.2.

¹⁰⁴ 21 James I, cap. 27.

infanticide was to arise again some 300 years later,¹⁰⁵ when it led to the passing of the Infant Life (Preservation) Act 1929.¹⁰⁶

The law recognised the existence of the foetus, and sought to protect it, in other contexts. For example, in 1387, the Winchester Assize condemned a gentlewoman to death for aiding in the murder of her husband, but her execution was postponed because of her pregnancy, her foetus being held to have been animated.¹⁰⁷ Even in the 18th Century, the notion of quickening (detectable foetal movement) as a determining point for some purposes remained in the common law. In his *Commentaries*, Blackstone wrote that “life begins in contemplation of law as soon as an infant is able to stir in the mother's womb”. He also agreed with Coke, who, nearly a Century earlier, had stated his view that “to be saved from the gallows a woman must be quick with child - for barely with child, unless he be alive in the womb, is not sufficient.”¹⁰⁸ Thus, the state took the view that whilst a pregnant woman should be punished according to the standards of the time, the foetus she carried was an innocent party and, having shown some evidence of ‘life’, should be given the opportunity to be born. The law was, in effect, protecting the foetus from the destruction which would inevitably follow the pregnant woman’s execution.

2.4 19th Century Legislation affecting the Foetus

Before the 19th Century, the Common law position on penalties for harming a child in utero or causing it to miscarry were unclear, and references to prosecutions for procuring abortions were rare,¹⁰⁹ yet deliberate attempts to procure miscarriage obviously occurred, otherwise no stimulus would have existed to introduce the legislation intended to bring an end to the practice. Sections 1 and 2 of Lord Ellenborough’s Act of 1803 constituted the first attempt to put the offence of abortion on a statutory basis in England and Wales,¹¹⁰ The offences created by the 1803 Act were replaced by section 13 of Lord Lansdowne’s Offences Against the Person Act of 1828,¹¹¹ which, like its predecessor, did not extend to Scotland or Ireland. Under section 1 of the 1803 Act and the first offence created by section 13 of the 1828 Act, abortion post-quickening was punishable by the death penalty

¹⁰⁵ See UK Parliamentary Debates, House of Lords, 6 December 1928, 74, 430 (Lord Merrivale) and 444 (Earl Russell).

¹⁰⁶ See discussion in Chapter 2.5.

¹⁰⁷ Harvey B.F. (Ed) *The Westminster Chronicle 1381-1394*. Oxford: The Clarendon Press, 1982, pp.322ff.

¹⁰⁸ Blackstone, W. *Commentaries*. 4th edition, 1770. i: 129; iv: 388.

¹⁰⁹ Dickens, B. *Abortion and the Law*. Bristol: Macgibbon and Kee, 1966, at p.23.

¹¹⁰ 43 Geo. 3, C. 58; S.2.

¹¹¹ 9 Geo. IV. Chapter 31.

or transportation for life. Under section 2 of the 1803 Act and the second offence created by section 13 of the 1828 Act (attempting to procure miscarriage before quickening) the penalty was transportation for 14 years. Thus, the law sought to prevent intentional abortion by creating harsh penalties for those convicted, and also attached relevance to the stage of foetal development. The criminalisation of intentional abortion was continued by section 6 of the Offences Against the Person Act 1837,¹¹² which replaced section 13 of the 1828 Act and removed the death penalty as a possible punishment. The 1837 Act made no distinction based on quickening, thereby effectively outlawing all abortion, although it did recognise the ‘double effect’ provision. Thus, these three items of legislation signalled that the law recognised the foetus and was set upon deterring its deliberate termination.

The possibility that violence resulting in *postnatal* harm following live birth could give rise to criminal liability was addressed by the Fourth Report of the Commissioners on Criminal Law (1839),¹¹³ and the Second Report of the Commissioners for Revising and Consolidating Criminal Law (1846).¹¹⁴ The notion was rapidly extended to the situation in which the assault caused the death of the child after live birth, not as a result of direct injury, but arising as a consequence of the injury causing the child to be born prematurely (*R v West*¹¹⁵ 1848).

The 1837 Act was replaced by the Offences Against the Person Act 1861,¹¹⁶ applicable in England and Wales, and to varying extents Ireland (now Northern Ireland), but not to Scotland. Like the 1837 Act, it did not discriminate between stages of foetal development. The offence of procuring abortion is addressed in sections 58-59 and “may be committed at any time before the natural birth of the child, whether it is in the embryonic or foetal stage of development”;¹¹⁷ the penalties originally included life imprisonment, so the harsh regime of the earlier legislation was continued. The 1861 Act does not contain a ‘double effect’ provision. Section 58 specifically addresses the issue of a pregnant woman seeking to procure her own abortion.¹¹⁸ It has been suggested that the rationale behind sections 58-

¹¹² 1 Vict. Cap. 85, S.VI.

¹¹³ British Parliamentary Papers (1839) vol. 19, pp. 235, 266.

¹¹⁴ British Parliamentary Papers (1846) vol. 24, pp. 107, 127.

¹¹⁵ *R v West* [1848] 2 Car. & K. 784

¹¹⁶ 24 & 25 Vict. C.100.

¹¹⁷ Casey, G. *Born Alive: The Legal Status of the Unborn Child*. Chichester: Barry Rose Law Publishers, 2005. Available at http://www.academia.edu/191110/Born_Alive_The_Legal_Status_of_the_Unborn_Child. accessed 5th September, 2015.

¹¹⁸ This will become relevant when the maternal exemption regarding foetal harm is discussed later in Chapter 3.5.

59 of the 1861 Act was a combination of a Victorian puritanical response to an increase in the incidence of abortion and infanticide as a means of controlling family size¹¹⁹ and a desire of the medical profession to eliminate the threat to their power from midwives.¹²⁰ These statutory provisions remain the basis for the criminal offence of abortion in England and Wales, and contravention is likely to result in imprisonment.¹²¹

Thus, within the relatively short period of 60 years, Parliament had created four statutes imposing a variety of penalties relating to abortion, two Commissioners Reports recognising *postnatal* injury resulting from injury sustained *in utero* as creating criminal liability, and the criminal courts had extended these constructions to death resulting from injury-related premature birth. Parliament seemed intent on preventing foetal destruction.

That said, the lawful conduct of abortion by appropriately qualified medical practitioners for the purpose of saving the pregnant woman's life was accepted by the courts following both the 1837 Act (see *R v Wilhelm*¹²²) and the 1861 Act (see *R v Collins*¹²³). Both cases concerned acute interventions intended to avert immediate maternal life-threatening situations, and in both cases the courts held that the appropriate intervention by a physician necessary to save the life of a pregnant woman, but which resulted in the loss of the foetus, was not illegal, a position consistent with the 'double effect' doctrine of the Roman Catholic Church.

2.5 20th Century British Legislation and Reduced Protection for the Foetus

The Infant Life (Preservation) Act 1929, applicable in England, Wales, and Northern Ireland, but not in Scotland, introduced the new crime of child destruction, closing a *lacuna* which had existed since the repeal of the 1624 Act, and allowed infants to be killed during the birth process. This was not an offence under section 58 of the 1861 Act because it could not be said to be procuring a miscarriage, nor did it constitute homicide since the child would not yet have an existence independent of its mother, a prerequisite for a homicide charge.¹²⁴ Presciently, a specific point in gestational development became

¹¹⁹ For a review, see Robinson, W.C. (2002). Population policy in early Victorian England. *Eur.J.Population* **18**, 153–173

¹²⁰ Feminist.com. A history of Abortion, available at <http://www.feminist.com/resources/ourbodies/abortion.html>, accessed 8th September, 2015

¹²¹ See, for example, *R. v Catt (Sarah Louise)* [2013] EWCA Crim 1187 [2014] Cr App R (S) 35.

¹²² *R v Wilhelm* [1858] *Medical Times Gazette* 658.

¹²³ *R v Collins* [1898] 2 *Br.Med.J.*, 122-130.

¹²⁴ Hansard. Child Destruction Bill, House of Lords, 12th July, 1928, available at <http://hansard.millbanksystems.com/lords/1928/jul/12/child-destruction-bill-hl> accessed 10th September,

central to the new crime: the foetus had to have reached a stage of development sufficient to be capable of being born alive,¹²⁵ with the threshold for presumption of such capacity being set at 28 weeks gestation. This distinction is now termed viability, and is influenced by multiple factors, of which gestational age is but one.¹²⁶ Although the basis of the distinction varied from earlier approaches, the law was again creating a deterrent to the destruction of more developed foetuses. The pregnant woman herself was not exempted from liability under this Act. The second paragraph of section 1(1) of the 1929 Act introduced a defence of acting in good faith to save the life of the woman¹²⁷ - the equivalent to the 'double effect' exception in the Papal Bull of 1869. Thus, the law once again recognised the primacy of the pregnant woman over the foetus, should such a decision need to be made.

The meaning of the phrase 'capable of being born alive' has been the subject of much debate, mostly around the potential distinction between 'life', however evanescent, and viability.¹²⁸ In law, 'born' is defined as expulsion of the whole body,¹²⁹ but 'alive' is more contentious. The interpretation was finally settled nearly 60 years later, in *C v S (Foetus: Unmarried Father)*;¹³⁰ the scope of the Act is restricted to the protection of a foetus which has the capacity to survive, whether naturally or by reasonable artificial means, the Court holding that a foetus of between 18 and 21 weeks' gestation was not "a child capable of being born alive" as it could not breathe naturally or with the aid of a ventilator and that termination of a pregnancy of that length was not an offence under section 1 of the Infant Life (Preservation) Act 1929.¹³¹

2015. This was not the first time the *lacuna* had been identified; see Keown, I.J. (1988), The scope of the offence of child destruction. L.Q.R. **104**, 120-142.

¹²⁵ In 1987, the Court of Appeal ruled that a foetus between 18 and 21 weeks was not capable of being born alive; *C v S (Foetus: Unmarried Father)* [1988] Q.B. 135. The first successful prosecution under the 1929 Act occurred nearly 80 years later: Britten, N. Jury convicts mother who destroyed foetus, 26th May, 2007, available at <http://www.telegraph.co.uk/news/uknews/1552651/Jury-convicts-mother-who-destroyed-foetus.html> accessed 5th September, 2015.

¹²⁶ Select Committee on Science and Technology. Upper gestational limit. 6th November, 2007, available at <http://www.publications.parliament.uk/pa/cm200607/cmselect/cmsctech/1045/104505.htm> accessed 3rd September, 2015; Morse, S.B., Wu, S.S., Ma, C. *et al*(2006). Racial and gender differences in the viability of extremely low birth weight infants: a population-based study. *Pediatrics*, **117**, e106 -e112.

¹²⁷ British Parliamentary Papers (1846) vol. 24, pp. 107, 127.

¹²⁸ For a review of the origin of the Act and the various definitions proposed, see Keown, I.J., (1988). The scope of the offence of child destruction. L.Q.R., **104**, 120-14; Wright, G. (1981). Capable of being born alive. *New L.J.*, **131**, 188-192; Wright, G. (1984). The legality of abortion by prostaglandin. *Crim.L.R.* **347**, 348-349.

¹²⁹ *R v Poulton* [1832] 5 C & P 329, 330.

¹³⁰ *C v S (Foetus: Unmarried Father)* [1988] 1 QB 135.

¹³¹ The concept of viability also arises in discussions regarding the moral status of the foetus, and will be considered in that context in Chapter 4.

In 1938, the landmark case of *R v Bourne*,¹³² in which a surgeon performed an abortion on a 14 year old girl pregnant as the result of rape, extended this exception for the preservation of maternal life to the preservation of the future mental health of a pregnant woman, in effect, introducing the concept of therapeutic abortion. In his charge to the jury, Macnaghten J said (at 693-694):

“the law does not require the doctor to wait until the unfortunate woman is in peril of immediate death.... If the doctor is of the opinion that the probable consequence of the continuance of the pregnancy will be to make the woman a physical or mental wreck the doctor is operating for the purpose of preserving the life of the mother.”

In effect, Macnaghten J was highlighting to the jury that the use of the term ‘unlawful’ in section 58 of the 1861 Act implied that lawful reasons might also exist for the procurement of a miscarriage. The jury acquitted Bourne. In two later cases brought under the 1861 Act, the courts further clarified the scope for therapeutic abortion. In *R v Bergmann and Ferguson*¹³³ in 1948, Morris J rejected Macnaghten J’s view in *Bourne* that the physician’s belief regarding the impact of continued pregnancy should be ‘reasonable’ and, instead, directed the jury to focus on the “honesty” of the physician’s belief, pointing out that the jury was not concerned with whether the doctor had made a mistake. In *R v Newton and Stungo*¹³⁴ in 1958, Ashworth J stated that abortions could be lawfully performed “... in good faith for the purpose of preserving the life or health of the woman when I say health I mean not only her physical health, but her mental health.”

Thus, the courts were perpetuating the doctrine of the primacy of the pregnant woman’s life over that of her foetus, and were now extending that consideration beyond the acute preservation of the life *per se*, and sanctioning therapeutic abortion to protect the quality of that life.

The law regarding abortion throughout the UK was transformed by the Abortion Act 1967,¹³⁵ applicable to England, Wales and Scotland. This Act was intended *inter alia* to

¹³² *R v Bourne* [1938] 3 All ER 615.

¹³³ Anonymous(1948) Alleged conspiracy to procure miscarriages 1 Br.Med.J.1(4559), 1008-1009.

¹³⁴ *R v Newton, R v Stungo* [1958] Crim.L.Rev. 469.

¹³⁵ 15 & 16 Eliz. 2, c. 87. S.5(1) of the Abortion Act 1967 reads : “Nothing in this Act shall affect the provisions of the Infant Life (Preservation) Act 1929” (protecting the life of the viable foetus). The Human Fertilisation and Embryology Act 1990, s.37(4) and reads: “No offence under the Infant Life (Preservation) Act shall be committed by a registered medical practitioner who terminates a pregnancy in accordance with

bring to an end the practice of “back street abortion” and to provide a specific defence against the “missing exception” of the 1861 Act, that of performing an abortion to protect the pregnant woman’s life or health. As originally passed, the 1967 Act did not limit the duration of pregnancy up to which an abortion could lawfully be performed, but did stipulate in section 5(1) that nothing in the 1967 Act would affect the provisions of the 1929 Act. Thus, in England and Wales the upper time limit for a termination was effectively set at 28 weeks. The Act therefore maintained a greater degree of protection for the more developed foetus. Consistent with the 1929 Act, this presumption relieved the prosecution of the burden of proving viability at 28 weeks, but did not prevent proof that a particular foetus was viable at an earlier stage of its development, in which case termination would have been unlawful.

The criteria to be satisfied to allow an abortion were perpetuated in section 37 of the Human Fertilisation and Embryology Act 1990 (HFEA 1990), applicable in Scotland, England and Wales. The structure of the defences was revised to separate some of the accepted reasons, giving four grounds under section 1 rather than the two grounds in the original Act. It also made a number of other revisions, including the time limit, section 37(1)(a) stipulating an upper limit of 24 weeks for termination of a pregnancy under the new section 1(1)(a) of the Abortion Act 1967, perhaps reflecting the impact of advances in medical sciences upon the viability threshold defined some 60 years earlier. The amendments made by the 1990 Act overrule the foetal viability clause in the 1929 Act and permit abortion for foetal handicap up until birth. Accordingly, the 1929 Act has lost significance regarding abortion in English law. There are no time limits for the other two grounds under section 1 (necessary to prevent grave permanent injury to the pregnant woman’s physical or mental health (S.1(b)); that the continuance of the pregnancy would involve a risk to the pregnant woman’s life greater than if the pregnancy were terminated (S.1(c)).

Section 1(1)(a) of the 1967 Act permitted the termination of a pregnancy on the grounds that its continuance would involve a greater risk to life or of injury to the pregnant woman’s physical or mental health than if the pregnancy were terminated. However, present-day medical techniques may make abortion performed in early pregnancy safer

the provisions of this Act.” From this, it seems that S.1(1) of the Infant Life (Preservation) Act is not preserved in s. 5(1) of the Abortion Act 1967.

than giving birth,¹³⁶ a situation not foreseen when the 1967 Act was passed, and so, statistically, abortion can always be justified. That said, the 1967 Act requires the physician to make an individualised decision so a particular woman's medical condition may mean that the risk of termination in a specific case is greater than the statistical risk of morbidity during pregnancy, when the data are adjusted for relevant risk factors.

The 1967 Act also extended the grounds for a lawful termination of pregnancy to consideration of the physical or mental health of any existing children within the family, presumably contemplating circumstances in which the pregnant woman's future health and/or that of the child she would produce could be compromised, either by the introduction of "another mouth to feed" in an already large family, or a housing standard which was already inadequate. In essence, statutory law was now codifying and extending the therapeutic abortion construction developed in common law, allowing consideration of other factors to mitigate against prevention of acts harmful to the foetus.

The 'foetal abnormality' ground in section 1(1)(d) was the first explicit recognition that an abortion could be justified on such a premise, and was made possible largely through the development of better foetal visualisation and biochemical testing technologies than had been available previously.¹³⁷

At least three senior judges have commented that the 1967 Act liberalised abortion in England and Wales significantly. In 1978, Sir Roger Ormrod, then a judge of the Court of Appeal and a qualified physician himself, wrote "Abortion has become generally available, if not yet quite on demand, but subject only to the attitude of the surgeon concerned or of the clinic to which the woman is referred".¹³⁸ Similarly, Lord Denning MR observed in a 1981 case that the 1967 Act "... has been interpreted by some medical practitioners so loosely that abortion has become obtainable virtually on demand. Whenever a woman has an unwanted pregnancy, there are doctors who will say it involves a risk to her mental health".¹³⁹ In *Paton v British Pregnancy Advisory Service Trustees*, Sir Stephen Brown P commented "...it would be quite impossible for the courts....to supervise the operation of

¹³⁶ Raymond, E.G., Grimes, D.A. (2012). The comparative safety of legal induced abortion and childbirth in the United States. *Obs.Gyn.*, **119**, 215–219.

¹³⁷ The consequences of improved visualisation on the maternal-foetal relationship will be discussed in Chapter 4

¹³⁸ Ormrod, R. (1978). A lawyer's look at medical ethics. *Med-Leg.J.*, **46**, 18-22.

¹³⁹ *Royal College of Nursing of the UK v DHSS* [1981] AC 800.

the Abortion Act 1967. The great social responsibility is firmly placed upon the shoulders of the medical profession...”.¹⁴⁰

Thus, the 1967 Act, in addition to removing the near-absolute protection for the foetus from termination, had also succeeded in transferring the responsibility for ‘policing’ the law to the medical profession.

2.6 The Foetus (and Embryo) Lacks Legal Personality

The legalisation of abortion, albeit with certain restrictions, brought a number of cases before the courts which would not have arisen prior to the 1967 Act. Many of these concerned the potential applicability of European Convention for the Protection of Human Rights and Fundamental Freedoms (hereafter referred to as the Convention), which the UK had ratified in 1951, to the foetus. Most cases have been brought under Articles 2 (right to life) or 3 (prohibition of inhumane or degrading treatment) and the majority under Article 8 (right to respect for family life).

One of the central issues to emerge in this area is that the law in England, Wales and Scotland does not accord legal personality to the foetus until it is born alive,¹⁴¹ whereupon the newborn child immediately acquires full legal personality. The delivery of the foetal body together with the existence of circulation or the taking of breath *post-partum* are sufficient for a finding that the foetus was born alive, however evanescent that life may be, thereby maintaining the distinction between ‘life’ and ‘viability’.¹⁴²

The attractions of the position taken by the courts in the UK regarding the point at which legal capacity and thus rights come into being - live birth - are those of consistency and certainty: the blastocyst / embryo / foetus has no legal standing (consistency) until born alive (certainty), notwithstanding the debates around that phrase mentioned earlier, whereupon it enjoys full legal standing. These attractions are rarely present in the arguments advanced to establish legal rights for the same organisms prior to birth. An exception to this generality is the position held by the Roman Catholic Church, which accords the same moral status to the blastocyst / embryo / foetus, thereby being

¹⁴⁰ *Paton v British Pregnancy Advisory Service Trustees* [1979] 1 Q.B. 276 at 281.

¹⁴¹ *Paton v British Pregnancy Advisory Service Trustees* [1979] Q.B. 276; *In F (In Utero), Re* [1988] Fam. 122; *Hamilton v Fife Health Board* [1993] S.C. 369; *MB (Caesarean Section), Re* [1997] 2 F.L.R. 426; *St George's Healthcare NHS Trust v S* [1998] 3 W.L.R. 936.

¹⁴² *Rance v Mid-Downs HA* [1991] 1 Q.B. 587; *A (Children) (Conjoined Twins: Medical Treatment) (No.1), Re* [2001] Fam. 147.

consistent.¹⁴³ Of course, women will rarely know they are pregnant immediately upon conception, and so the point at which a moral obligation is recognised, as opposed to exists, is more variable and so less certain than the point at which legal status is recognised.

Although live birth had been recognised as the requirement for legal personality for many centuries, as discussed earlier in this chapter, the modern landmark case in the UK is *Paton*,¹⁴⁴ in which the claimant sought to prevent his wife undergoing an abortion. Having failed to establish his case in the UK, he appealed to the European Commission, basing his argument on Articles 2 and 8. The Commission did not explicitly decide whether the term ‘everyone’ in Article 2 embraced the unborn child, but adduced that since the four situations in which Article 2 rights could be taken away (judicial execution, self-defence, effecting a lawful arrest or detention, suppression of riot or insurrection) were applicable only to those who had been born, they could not be applied to an unborn child, and so the foetus did not come within the purview of Article 2. His claim under Article 8 was also dismissed, the Commission holding that Paton’s rights were limited by his wife’s rights as a pregnant woman carrying the foetus; interference with his convention rights was justified “as being necessary for the protection of the rights of another person”, i.e., the pregnant woman. The Commission emphasised that their judgment was limited to the circumstances of the case: the ‘right to life’ of a non-viable foetus. The Commission also made clear that it was not concerned with balancing the rights of a mature foetus with those of the mother, so the application of Article 2 to a potentially viable foetus remained unanswered. Thus, the autonomous right of pregnant women to seek a termination of pregnancy where this was permitted by a member state was confirmed in European law in the context on a pre-viable foetus only.

The European Court of Human Rights came to the same conclusion in the tragic case of *Vo v France*¹⁴⁵ in 2004, in which a gynaecologist’s errors resulted in an unwanted therapeutic abortion. Having exhausted the national procedures, Mrs. Vo appealed to the European

¹⁴³ See, for example, Hug K. (2006). Therapeutic perspectives of human embryonic stem cell research versus the moral status of a human embryo – does one have to be compromised for the other? *Medicina*, **42**, 107-14; House of Lords Stem Cell Research Report, 2002, Chapter 4.18; see also Irving, D.N., Catholic Culture. Human Embryology and Church Teachings, 15th September, 2008, available at <https://www.catholicculture.org/culture/library/view.cfm?recnum=8541#C2> accessed 5th September, 2015.

¹⁴⁴ *Paton v UK* [1980] 3 EHRR 408, p413, s.8.

¹⁴⁵ *Vo v France* [2004] 2 F.C.R. 577; (2005) 40 E.H.R.R. 12.

Court of Human Rights. The Grand Chamber¹⁴⁶ held there had been no violation of Article 2 because the foetus could not be considered as a 'person' directly protected by Article 2. However, if the foetus did have a 'right' to 'life', it was limited by the mother's rights and interests, as defined in Article 8. Therefore, it was not necessary to answer the question of whether the unborn child was a 'person' for the purposes of Article 2; the relevant question was whether the legal protection afforded to the applicant by the French government regarding the loss of the foetus satisfied the procedural requirements inherent in Article 2, and the Grand Chamber considered that it did. *Vo* has been widely considered a lost opportunity for the European Court of Human Rights to clarify the law in this regard, by leaving open the question of whether the more-developed foetus falls within the scope of Article 2.¹⁴⁷

Despite having found it unnecessary to decide whether the foetus was protected by Article 2, the majority of the Chamber then opined that the term 'everyone' in several Articles of the convention could not ordinarily apply *antenatally*, but in rare (unspecified) cases the applicability of Article 2,¹⁴⁸ could not be excluded.¹⁴⁹ This raised the issue that abortion is not one of the specified exceptions to Article 2, and would therefore be unlawful if Article 2 applied to the foetus. The Commission's response was that abortion is compatible with Article 2 in the interests of protecting the mother's life and health because this provision – assuming the applicability of Article 2 at the initial stage of the pregnancy - contains an implied limitation on the foetus's right to life, to protect the life and health of the woman at that stage.¹⁵⁰ The Commission excluded an absolute right to life for the foetus on the premise that to do so would mean the life of the foetus was regarded as being of a higher value than the life of the pregnant woman.¹⁵¹

The European Court has been careful to avoid taking a clear stance on the balance between foetal interests and women's rights or to dictate national policy in this culturally-sensitive area. Women have no right of access to an abortion under the Convention, nor has the

¹⁴⁶Under Article 43 of the Convention a case shall be referred to the Grand Chamber if it "raises a serious question affecting the interpretation or application of the Convention or the protocols thereto, or a serious issue of general importance."

¹⁴⁷ See, for example, Te Braake, T.A.M. (2004). Does a foetus have a right to life? The Case of *Vo v France*. *Eur.J.Health Law* **11**, 381-389; Pichon, J. (2006). Does the unborn child have a right to life? The insufficient answer of the European Court of Human Rights in the Judgment *Vo v France*. *German Law J.*, **7**, 433-444.

¹⁴⁸ *Eur. Comm. H.R., H. v Norway*, Decision of 19 May 1992, Decision and Reports vol. 73, 155, 167, para.1.

¹⁴⁹ *Eur. Comm. H.R., X. v the UK*, Decision of 5 November 1981, Decision and Reports vol. 19, 244, 249, para. 7.

¹⁵⁰ *Eur. Comm. H.R., X. v the UK*, (note 12), 252-53, para. 22.

¹⁵¹ *Eur. Comm. H.R., X. v the UK*, (note 12), 252-53, para. 19.

Court recognised the foetus as capable of possessing Convention rights,¹⁵² although it has accepted those which may be accorded in national legislation. Termination of a pregnancy engages the sphere of the private life of the mother as well as the father of the foetus under Article 8, but the ECHR has ruled that the pregnant woman's interests must prevail;¹⁵³ termination of the pregnancy may justify an interference of rights under Article 8 if it is to protect the life of another. Article 8 has also been invoked when national law has failed to provide an effective mechanism to determine whether the conditions for a lawful abortion had been met,¹⁵⁴ to clearly outline how that right can be accessed,¹⁵⁵ and to enable compliance with national legislation.¹⁵⁶

Given the stated position regarding the foetus, the matter of the legal status of the embryo could perhaps be inferred. The Warnock Committee Report, published in 1984, confirmed that the "human embryo (defined as the developing pregnancy from the time of fertilization until the end of the eighth week of gestation) *per se* has no legal status. It is not, under law in the UK, accorded the same status as a child or an adult, and the law does not treat the human embryo as having a right to life".¹⁵⁷ Nearly 20 years later, in *Evans v Amicus Healthcare Ltd*,¹⁵⁸ the applicability of Article 2 of the Human Rights Act 1998 to frozen embryos was explored. Grubb, a decade earlier, had suggested that as frozen embryos could not be classified as persons, then the only option was to consider them as chattels, and therefore subject to property law.¹⁵⁹ *Evans* raised a number of profound issues, and was, as Baroness Warnock commented in a brief note, "... the sort of case where the lines between law and morality become blurred."¹⁶⁰ In his judgment, Lord Donaldson stated "no convention jurisprudence extends the right (to life under Article 2) to an embryo, much less to one which at the material point of time is non-viable",¹⁶¹ in a

¹⁵² *Open Door and Dublin Well Woman v Ireland* [1992], (App. No.14234/88), at 61.

¹⁵³ See *Paton v UK* Application No 8416/87 [1987]; *Boso v Italy* Application No 50490/99 [1999].

¹⁵⁴ *Tysic v Poland*, App 5410/03 [2007].

¹⁵⁵ *A, B and C v Ireland*. [2011] 53 E.H.R.R. 13.

¹⁵⁶ *RR v Poland (27617/04) [2011]*, 53 E.H.R.R. 31.

¹⁵⁷ Warnock, M. *A Question of Life: The Warnock Report on Human Fertilisation and Embryology* para 11:16 1985. Oxford: Basil Blackwell.

¹⁵⁸ *Evans v Amicus Healthcare Ltd* [2003] EWHC 2161 (Fam).

¹⁵⁹ Grubb, A. *The Legal Status of the Frozen Human Embryo* in A. Grubb (Ed.). *Challenges in Medical Care*. Chichester: John Wiley, 1991.

¹⁶⁰ Warnock, M. "Court followed the law, but is the law out of date?" *The Times*, 2 Oct 2003.

¹⁶¹ *Evans v Amicus Healthcare Ltd* [2003] EWHC 2161 (Fam) at s.19.

sense reflecting the possible qualification he had expressed in *in re T* a decade earlier.¹⁶² Arden LJ raised a similar point regarding viability:

“...neither convention jurisprudence nor English law provides a clear cut answer to the question: at what point does human life attain the right to protection by law? For many purposes, the viability of a foetus is taken as the benchmark for determining the legal status of a child.”¹⁶³

The latter sentence in Arden LJ’s point is somewhat perplexing; a foetus lacks legal status until it is born, whereupon it becomes a child endowed with legal personhood. Viability is a question of fact and medical judgement,¹⁶⁴ and is a highly variable condition. The information which led to the reduction of the abortion limit under the HFEA 1990 indicated that, even at 24 weeks’ gestation, survival varied from 13% to 33%,¹⁶⁵ due to the combination of intrinsic and extrinsic factors as they existed for that foetus at that time. Medical advances have made the viability of a foetus a shifting standard¹⁶⁶ which seems an unsatisfactory basis upon which to accord legal status. The matter of foetal viability has been considered in a number of cases,¹⁶⁷ and the gist of these deliberations seems to be that whilst the law will not intervene to protect a non-viable entity, there may be (undefined) circumstances in which intervention to protect a potentially-viable foetus might be justified, a notion consistent with the greater recognition of the more developed foetus which has long been a feature of the law.

Nevertheless, the position within the UK is consistent: neither the foetus nor the embryo has legal personality. The foetus’ lack of legal personality provides the basis upon which termination of a pregnancy does not constitute murder. That said, the offences defined in the 1861 Act acknowledge that, although not a person, the foetus is an entity of value. This appreciation of the foetus is continued in the 1967 and 1990 Acts. So, whilst not enjoying legal personality, the foetus is clearly not considered worthless.

¹⁶² *In Re T (Adult: Refusal of Treatment)* [1993]. Fam. 95 at 102.

¹⁶³ *Evans v Amicus Healthcare Ltd* [2003] EWHC 2161 (Fam) at 106.

¹⁶⁴ See discussion in Chapter 4.5.

¹⁶⁵ Scientific Developments Relating to the Abortion Act 1967. House of Commons Science and Technology Committee. Twelfth Report of Session 2006–07, Volume I. Published by TSO on 6 November 2007 as HC 1045-I.

¹⁶⁶ In the USA, Court decisions after *Roe v Wade*, such as *Webster v Reproductive Health Services* (492 U.S. 490, 1989) have recognised the prospect that developing technology may move the age of viability to an earlier gestational age.

¹⁶⁷ *In Re T. (Adult: Refusal of Treatment)* [1993]. Fam. 95 at 102; *St George’s Healthcare N.H.S. Trust v S.* [1998]; *R. v Collins and Others., ex p S* [1999] Fam 26, at s.45; *Paton v British Pregnancy Advisory Service Trustees* [1979] Q.B. 276;

2.7 Conclusions

Over nearly 6,000 years, numerous civilisations have introduced a range of provisions with the common aims of preventing the destruction of the foetus and punishing those whose acts resulted in foetal ‘death’, although the driving philosophy behind these provisions has generally not been one of foetal benefit. Arguably, the 1929 Act is the only one which has its origins in a desire to protect the foetus *per se*.

The basis upon which such ‘protection’ has been created is elusive. The foetus has no legal personality. Until it is born, it cannot be killed, yet the termination of pregnancy is a controlled activity, subject to criminal law. From 24 weeks' gestation until term, the foetus is not a person, but there is nonetheless no general right to seek a termination. If, as the law currently holds, late-term foetuses are not persons, the justification for the current statutory restriction of abortion is unclear. Yet the reality remains that the foetus is generally considered to merit ‘protection’ from destruction, and the law applicable in all the constituent jurisdictions of the UK reflects this.

Generally, criminal law is applicable to persons, property and ideas, but the foetus is not a person and having physical substance, it is not an idea, so is it property?¹⁶⁸ This was the way in which frozen embryos, *ex utero*, were considered in *Evans*, but the foetus (and embryo) *in utero* appear not to be considered in this way. However, a list of criteria which defines property does not exist, nor does agreement exist regarding what property really is.¹⁶⁹ Certainly, the foetus cannot be bought or sold, like most property. Even in a surrogacy arrangement, the foetus is not considered as ‘property’.¹⁷⁰ Provided she has capacity, a pregnant woman may elect to undergo all manner of medical and surgical procedures by reaching agreement with a physician or surgeon and giving her consent, but to terminate a pregnancy she requires the agreement of two physicians - she cannot ‘dispose of’ the foetus as though it was her own property. The notion of the foetus, *in utero*, as property does not sit comfortably nor does it reflect the applicable constraints

Over time, the balance between protecting the foetus and respecting the mother has changed. From abortion being illegal in England and Wales under (almost) any circumstances under the 1861 Act, within just over a century it had become permissible for

¹⁶⁸ Ford, M. (2005) A property model of pregnancy. *Int.J.Law Con.*, **1**, 261-293.

¹⁶⁹ Underkuffler, L.S. *The Idea of Property: Its Meaning and Power*. Oxford: OUP, 2003.

¹⁷⁰ Surrogacy Arrangements Act 1985.

the purpose of protecting the future health and well-being, including economic considerations, of the pregnant woman and her existing family, and in the case of foetal abnormalities which might become a serious handicap. Although the legislation perpetuated both the pregnant woman's primacy and a greater degree of protection to the more developed foetus, the previous, near-absolute protection of the foetus in this regard is now extensively qualified.

Advances in medical technology continue to create situations in which the law is unclear, and the foetus is no exception. Surgery can now be performed on the foetus *in utero* (which must entail surgery on the pregnant woman), and the prospect of maintaining an otherwise pre-viable foetus in an ectogenic environment is coming ever closer, raising a host of questions, the answers to which may significantly change our current perspective regarding foetal status.¹⁷¹ With the arrival of gene therapies, the possibility of conducting clinical trials in such a setting raises even more complications.

Arguably, participating in a clinical trial is a potentially risky procedure, although as explained in Chapter 1, given the dearth of information regarding the way in which pregnant women metabolise and excrete drugs, doing so may be safer than the normal medical practice of prescribing drugs in an uncontrolled environment. The fact that the foetus is considered as being of value indicates that additional care needs to be taken regarding it in a clinical trial setting. Given the intent will not be that of procuring an abortion, there seems no reason not to proceed with such trials based on the considerations arising from the criminal law described in this chapter.

¹⁷¹Alghrani, A., Brazier, M. (2009). What is it? Whose it? Re-positioning the foetus in the context of research? *C.L.J.*, **70**.51-82.

Chapter 3 *Postnatal* manifestation of *antenatal* injury

3.1 Introduction

The preceding chapter described the recognition and protection the law offers to the foetus *in utero* to prevent its intentional destruction. However, circumstances arising during pregnancy may affect the foetus, such that the child is born injured or harmed. These may lead to complex *trans-natal* issues arising from the distinction between the time before birth, when the foetus is not regarded as being a person in the eyes of the law, and its acquiring legal personhood at birth, when it may be affected by prior circumstances. This chapter will examine the ways in which the law has sought to address the issue of a duty of care being owed to an entity which at the time the injury is inflicted lacks legal status, and the approaches which have been taken regarding compensation. As described in the Introduction to this thesis, this was precisely the situation which arose with thalidomide. The chapter will start by considering the topic of succession because this is the area of the law which has long considered trans-natal issues, and provision for a child who may be born disadvantaged, although not through injury.

3.2 The Law Relating to Inheritance and the Foetus

The law has long recognised that a child born after the death of its father may inherit upon live birth. A widely-cited case from the 16th Century is that of the Earl of Bedford,¹⁷² whose brother and his children were beneficiaries of the Earl's will. The brother died, at which time his wife was pregnant and later she gave birth to a daughter. The court held that the child, though posthumous, should benefit under terms of the Earl's will, Chief Justice Eyre remarking that an infant *in ventre matris*, upon birth clearly came within the description of children living at the time of his father's death. Some two hundred years later, in *Thelluson v Woodford*,¹⁷³ the claim that a child *en ventre sa mère* was a non-entity was rejected by the Court. In *Wallis*,¹⁷⁴ the Lord Chancellor considered that "the plaintiff was *en ventre sa mere* at the time of her brother's death, and consequently a person *in rerum natura*, so that both by the rules of the Common and Civil Law she was to all intents and purposes a child as much as if born in the father's life-time". The Scottish Courts have

¹⁷² The English Reports, Vol. LXXVII King's Bench Division VI, containing Coke, parts 5 to 13. 7 Co. Rep. 7a-9b. Coke's Reports extend from 1572-1616, and are to be found in Vols. 76 and 77 of The English Reports. The reference Mich. 28 and 29 Elizabeth" establishes this case as occurring in the years 1586-1587.

¹⁷³ The English Reports, Vol. XXXI, Chancery XI, containing Vesey Junior, vols. 4-6

¹⁷⁴ *Wallis vs Hodson*. [1740] 27 E.R. 642.

a similarly long-standing construction which also can be traced back to the 16th century.¹⁷⁵ Both are illustrations of a *trans-natal* approach.

These are examples of the application of the *nasciturus* principle, a fiction developed in Civil Law jurisdictions based upon Roman law,¹⁷⁶ and which “concedes a benefit to which in strict law the child is not entitled”.¹⁷⁷ The essence of the principle is that a child *in utero*, if subsequently born alive,¹⁷⁸ is deemed as already born in respect of legal issues that arose due to events that occurred during the pregnancy if that would be to the child’s advantage. The rationale behind this is to ensure that the presumed intent of a deceased parent or other benefactor was effected, or at the least to avoid prejudicing an unborn child by denying it rights that would accrue to existing siblings.¹⁷⁹

Thus, the law relating to inheritance, from an early stage, sought to protect the future interests of the foetus, assuming a live birth. Even if the intent behind these constructions was primarily that of giving effect to the wishes of the parent or other benefactor, through this approach the law recognised foetal existence, and took steps to ensure that live born children’s interests were not denied by failing to take into account circumstances arising before birth - *trans-natal* thinking. The importance of this construction to the clinical trial setting is clear. The foetus lacks legal personality, and so, in theory, neither the mother nor those responsible for approving or conducting a clinical trial involving a pregnant woman need to have the foetus in their contemplation. However, adopting such an approach risks prejudicing the subsequent child, not just in the financial sense illustrated by the cases above (disabled people generally earn less and have higher living costs than non-disabled people¹⁸⁰), but also in the sense of physical and/or mental injury. This construction featured in the deliberations regarding one of the cases which proved a turning point in the

¹⁷⁵For a review of this aspect of succession rights, see Paisley, R.M.M. (2006). The succession rights of the unborn child. *Edin.L.R.*, **10**, 28-59.

¹⁷⁶Pace, P.J. (1977). Civil Liability for Pre-Natal Injuries. *Mod.L.Rev.*, **40**, 141-158.

¹⁷⁷Johnston, D. (1997). The renewal of the old. *C.L.J.*, **56**, 80-95.

¹⁷⁸The delivery of the foetal body, together with the existence of circulation or the taking of breath post-partum, is sufficient for a finding that the foetus was born alive; see *R. v Reeves* [1839] 173 E.R. 724; *Rance v Mid-Downs HA* [1991] 1 Q.B. 587; *A (Children) (Conjoined Twins: Medical Treatment) (No.1)*, *Re* [2001] Fam. 147.

¹⁷⁹Planiol, M. (1939). *Traité Élémentaire de Droit Civil*, 12th edn., vol 1, nos 366-367 (English translation by the Louisiana State Law Institute (1959)), cited in Paisley, R.M.M. (2006). The succession rights of the unborn child. *Edin.L.R.*, **10**, 28-59.

¹⁸⁰See, for example,

<http://www.papworthtrust.org.uk/sites/default/files/UK%20Disability%20facts%20and%20figures%20report%202014.pdf>, accessed 8th June, 2016; <http://www.poverty.org.uk/40/index.shtml>, accessed 8th June, 2016.

law relating to *postnatal* compensation for *antenatal* injury: *Montreal Tramways v Léveillé*, discussed in the next section.

3.3 *Antenatal* Conduct resulting in *Postnatal* Death

An illustration of the distinction between the time of the act or threat and the time at which the harm was or would be manifest arose in *R v Shephard*.¹⁸¹ The defendant had written to a pregnant woman, soliciting her to kill her child when it was born, and was charged under section 4 of the Offences Against the Person Act 1861, which relates to incitement or conspiracy to murder. The court held that for the purposes of section 4, the person whose murder was solicited did not need to be in existence at the time of the incitement; it was sufficient if he were in existence at the time when the act of murder was to be committed - another illustration of *trans-natal* thinking. A foetus could not be a subject of murder, but once the child was born alive, the *ante-mortem* incitement to murder constituted an incitement to murder a 'person' within the meaning of section 4 of the 1861 Act.

Section 16 of the 1861 Act imposes criminal liability for threatening to kill another person. In *R v Tait*,¹⁸² the defendant had threatened to kill a foetus *in utero*, the Court of Appeal specifically excluded the application of this section to threats to a foetus on the grounds that the foetus was not a separate entity from the mother and therefore could not, without straining the language of the section, be the 'person' contemplated by the statute; the proposed 'victim' would not be in existence at the time at which the deed was intended to be carried out.

Both of these situations exemplify threats being made to the life of the foetus; the position regarding sanction for injury to the foetus resulting in *postnatal* death was addressed by the *Attorney-General's Reference (No. 3 of 1994)*.¹⁸³ The case involved a pregnant woman who was stabbed and who later gave birth to a premature child which died some four months later. Although the foetus had been wounded in the stabbing, it could not be proved that the wound contributed to the death. The assailant was acquitted after it was held that, in such circumstances, he could not in law be convicted of murder or manslaughter, even if causation was proved. The Attorney General referred the case to the House of Lords under section 36 of the Criminal Justice Act 1972 for a ruling on whether

¹⁸¹ *R v Shephard* [1919] 2 K.B. 125.

¹⁸² *R v Tait* [1990] 1 Q.B. 290.

¹⁸³ *Attorney-General's Reference (No. 3 of 1994)* [1998] AC 245.

(1) murder or manslaughter could be committed where unlawful injury was deliberately inflicted on a mother carrying a child *in utero*, where the child was born alive but subsequently died and the injuries inflicted caused or contributed to death, and (2) liability for murder or manslaughter could be negated where death was caused solely as a result of injury to the mother, as opposed to direct injury to the foetus.

The House of Lords concluded that such an assailant could be convicted of manslaughter but not of murder; an intention to harm the mother could not be regarded as equivalent to intent to harm the foetus, since they were two distinct organisms albeit living symbiotically. Given the absence of intention to injure the foetus, although the defendant was aware that the woman was pregnant, there was no basis for extending the doctrine of transferred malice, and the *mens rea* for murder was not present.¹⁸⁴ However, the attacker could be held guilty of manslaughter resulting from an unlawful and dangerous act, for which it was unnecessary for that act to have been directed against the person who died, i.e., the child who died as a result of injuries caused to it while it was *in utero*. All that was required was proof that the assailant intentionally stabbed the mother, that the act caused the later death of the child and that reasonable people would have appreciated the risk that some harm to the foetus would result. In a case involving the *actus reus* of one offence (assaulting the mother) and the *mens rea* of a different offence (harming the foetus - which becomes an offence only if it results in injury following live birth), the principle of transferred malice may still apply as long as the *actus reus* and *mens rea* are of the same type (as they were in this case), and *mens rea* may be transferred from one offence to a lesser crime of the same kind¹⁸⁵ and so the defendant's intention may therefore be transferred from the mother to the baby. In fact, manslaughter could not be established in the this case due to the inability to prove that the attack caused the child's death, although it was suspected to be due to premature birth resulting from attack. However, on the point of legal principle, although the foetus was not a legal person at the time of the attack, it was not unreasonable on grounds of public policy to regard the foetus, when she became a legal person at live birth, as having been within the scope of the attacker's *mens rea* when he stabbed her mother since he was aware of the pregnancy, and the *actus reus* for

¹⁸⁴ Lord Mustill cited *R. v Latimer* [1886] 17 Q.B.D. 359 as authority, commenting that "This principle lacks any sound intellectual basis" but is "useful enough to yield rough justice". Simester and Sullivan (A.P. Simester, J.R. Spencer, G.R. Sullivan & G.J. Virgo, *Simester and Sullivan's Criminal Law: Theory and Doctrine*. 5th Edn. Hart Publishing, 2013) use the term transferred *mens rea*, which more accurately reflects that the principle may be applied in cases involving intention and those involving recklessness.

¹⁸⁵ Ashworth, A.J. Transferred Malice and Punishment for Unforeseen Consequences in Glazebrook, P.R. (ed), *Reshaping the Criminal Law - Essays in Honour of Glanville Williams*. Stevens & Sons, 1978.

manslaughter was completed when the child died. As will be discussed later, this construction was similar to one evolving in the civil courts, but this case again confirmed that, prior to birth, the foetus lacks legal personality, and so cannot be the subject of crimes or other wrongs which attach to 'live' victims. However, the constructions here are further examples of the *trans-natal* approach of considering the consequences for the child of acts committed before the child was in being.

3.4 *Antenatal Incident manifesting as Postnatal Injury*

The first reported case in the UK of a child seeking compensation for an injury sustained *in utero* was *Walker v Great Northern Railway Company of Ireland*,¹⁸⁶ (Ireland at that time was part of the UK) in which the claim for damages against the railway company for injuries inflicted in a railway accident was rejected. O'Brien CJ disallowed the claim on the grounds that no contract existed between the railway company and the plaintiff, and that the railway company did not have a duty towards the plaintiff merely from the fact that her mother was pregnant when she travelled as a passenger. He considered the child had no a right of action on the basis that at the time the injury was sustained the plaintiff had no legal existence; no authority or principle showed that a legal duty arose towards that which had only a fictitious existence in law, such that a negligent act breached that duty. The broader issue, that of the legal right of an unborn child to personal security, was discussed at some length, and the views of the Judges was against the recognition of the right; the Chief Justice, however, expressly stated that he would leave the question open, and based his judgment on the single ground that there were no facts set out in the statement of claim which resulted in the defendants bearing liability for breach of duty as carriers of passengers. The *nasciturus* principle does not appear to have been considered in this case, perhaps on the basis that this was not an Ecclesiastical or Admiralty matter, where the doctrine was more established, although the *trans-natal* aspect of the case was clearly considered. It seems highly likely that the case, if heard today, would result in a different verdict.

Nearly forty years later, broadly similar facts arose in Canada in *Montreal Tramways v Léveillé*,¹⁸⁷ a child having been born with club feet said to have been the result of her mother's involvement in a tramcar accident. The court rapidly dismissed the lack of a

¹⁸⁶ *Walker v Great Northern Railway Co. of Ireland* [1891] 28 LR (Ir) 69.

¹⁸⁷ *Montreal Tramways v Léveillé* [1933] 4 DLR 339.

contract between Montreal Tramways and the injured child as a defence. Three of the five judges were willing to apply the *nasciturus* doctrine to Article 1053 of the Quebec Civil Code which read: “Every person capable of discerning right from wrong is responsible for the damage caused by his fault to another.....”, and considered that the foetus fell within the definition of ‘another’. Although the doctrine was a fiction of the civil law which had been adopted in England by the Ecclesiastical and Admiralty Courts, and to some extent by the Court of Chancery, the common law courts had never recognised the fiction as applying such as to permit a child to obtain damages for *antenatal* injuries, which may explain this approach apparently not having been considered in *Walker*. The court noted Hardwicke LC’s comments in *Burnet v Mann*¹⁸⁸ (“The general rule is, that they (unborn children) are considered *in esse* for their benefit, not for their prejudice”), and in *Wallis*¹⁸⁹ cited previously.

However, Canon J, the fourth judge, while agreeing with the decision of these three fellow judges (the other judge dissenting), founded his *ratio* not on the fictional attribution of beneficial existence to the unborn child but on another, seemingly novel, construction: that it was unnecessary to consider the rights, if any, of the child at the time that the wrongful act occurred (before birth) but only from the day she suffered damage so a plaintiff could not make a claim until he or she suffered injury. Based upon this construction, the plaintiff’s right to compensation came into existence only when she was born with the disability from which she suffered. Before that time, when *in utero*, she suffered no injury, inconvenience or damage. In effect, her rights were born together with her, the injury ‘crystallising’ upon live birth. This was not a right to compensation the child had since being conceived, but one which commenced when she was born. The wrongful act in question should therefore be examined in relation to the cause of the injury to the child, and to that extent the foetus’ existence in relation to the mode of injury was recognised by the law.

This trial is widely considered as a turning-point in the civil law relating to foetal injury, conferring upon a child a right to seek compensation at birth for injuries inflicted during pregnancy. In reaching their decision, the Canadian judges had disregarded a slew of cases over the previous 30 years in the USA, although these were not binding upon them, which had consistently ruled that *antenatal* injury afforded no foundation for an action for

¹⁸⁸ *Burnet v Mann*, 1 Ves. Sen. 156, 27 E.R. 953.

¹⁸⁹ *Wallis vs Hodson*. 27 E.R. 642.

damages on the part of the child.¹⁹⁰ The construction offered by Canon J neatly avoided the need to resolve a range of questions relating to foetal status whilst providing a transportable rationale which was not dependent upon a particular interpretation of a local code.

Over the next 60 years, both approaches in *Montreal Tramways* were used in Scotland. In *Cohen v Shaw* [1991],¹⁹¹ concerning a child whose father had been killed in a road traffic accident before the birth of the child, the court held that there was no reason in principle why the fiction that a child injured before birth could be deemed to be a person should not apply to a reparation claim by a posthumous child arising out of the death of his parent, and that the word “child” in the Damages (Scotland) Act 1976 included a child who was *in utero* at the time of the negligent act but who was later born alive, and the child therefore had title to sue. In *Hamilton v Fife Health Board* [1993]¹⁹², concerning a child who died three days after birth due to injuries sustained *in utero* caused by negligent acts of the doctors attending the child's mother, the court held that once the child was born and became a person the necessary concurrence of *damnum* and *injuria* was established and the child acquired the right to sue the person whose breach of duty resulted in its injury. The extension of the *nasciturus* approach to the concept of foetal ‘future interests’ became prevalent only following an increased application of its use in property law *via* the doctrine of *stare decisis*.¹⁹³

In contrast, other jurisdictions more commonly adopted the tort construction, e.g., England (*Burton v Islington HA* [1993]; *De Martell v Merton And Sutton HA (No.1)* [1995]¹⁹⁴), Canada (*Duval v Seguin* [1972]¹⁹⁵) and Australia (*Watt v Rama* [1972]¹⁹⁶). A possible reason for the move away from the *nasciturus* approach is that there is no inherent concept of injury within the *nasciturus* doctrine; no ‘wrong’ needs to have occurred, and the child may suffer no physical injury. If *nasciturus* really does “concede a benefit to which in strict law the child is not entitled”¹⁹⁷ then its application to cases in which the child is born with an injury sustained *in utero* would seem likely to be seen as inconsistent, generating

¹⁹⁰ See Historic Trials: *Montreal Tramways v Leveille* [1933] 4 DLR 338. Hum.Repro. 2, 349-359, 1987.

¹⁹¹ *Cohen v Shaw* [1992] SLT 1045.

¹⁹² *Hamilton v Fife Health Board* [1993] SC 369.

¹⁹³ Thomson, E.A.C. (2005). *Nasciturus* and delict - born yesterday? S.L.T., 21, 121-126.

¹⁹⁴ *Burton v Islington Health Authority, De Martell v Merton and Sutton Health Authority* [1992] 3 All ER 833.

¹⁹⁵ *Duval v Seguin* [1972] 26 D.L.R. (3d) 418, Ont. HC.

¹⁹⁶ *Watt v Rama* [1972] V.R. 353.

¹⁹⁷ Johnston, D. (1997) The renewal of the old. C.L.J., 56, 80-95.

uncertainty regarding the doctrine's applicability to a range of circumstances. By adopting the tortious approach, the courts seem to be distinguishing unfortunate but isolated situations, such as the untimely death of a relative, due to which children would otherwise be deprived of a benefit, from those circumstances in which the child is born injured as a result of a potentially culpable act. In doing so the process generates precedent as part of the development of tort/delict; the long list of cases commonly cited, starting with *Montreal Tramways*, is witness to that. In most of the cases above, the relevant act was held to constitute negligence, the *damnum* and *injuria* coming together upon live birth. The *nasciturus* doctrine remains available as an approach to cases involving intractable moral or policy problems, or where technical issues or an anomaly in the law would result in the refusal of a remedy which would create an injustice. Tort, of course, relies upon the concept of a duty of care, and the challenge remains that before birth the foetus, lacking legal personality, is not a person to whom a duty of care can be owed.

Thus, in the United Kingdom and the Commonwealth jurisdictions, the legal position seems clear and consistent: a child, born alive, with a disadvantage resulting from an event which occurred whilst the child was *in utero*, has potential routes to recovery of damages. The law had now taken a new course: whilst there could be no liability until both *damnum* and *injuria* concurred, live birth resulted in such a concurrence, giving the newly born person, who now enjoyed legal personality, a right to sue the person whose breach of duty of care before birth caused the child's loss or injury.

Prior to clarification of the common law position, the perceived hiatus in the civil law approaches in England and Wales in the wake of thalidomide led the Law Commission¹⁹⁸ to recommend a legislative approach to permit the recovery of damages by a child born injured. Two years later, the **Congenital Disabilities (Civil Liability) Act 1976** (CDCLA 1976) came into force in England and Wales. The Act imposes liability for *antenatal* injury when a child is born alive and suffering from a disability caused by a wrongful act (S.1(1)) affecting either parent in his or her ability to have a healthy child (S.1(2)(a)), or affecting the mother in her pregnancy, or the mother or the child in the course of birth (S.1(2)(b)). The challenge that, before birth, the foetus is not a person to whom a duty of care can be owed was overcome by the construction in the CDCLA 1976 that the duty is derivative from a duty owed to the parents. Liability to the child is derivative, usually from

¹⁹⁸ Law Commission Report Injuries to Unborn Children 1974 (No. 60, Cmnd 5709).

the mother, for example if a physician negligently administered a teratogenic drug to a pregnant woman. The scope of the Act is sufficiently wide to embrace a claim derivative from a wrong done to the father too, e.g., damage to his sperm as a result of negligent exposure to toxic substances that resulted in fetal abnormality.¹⁹⁹ For the present, it is sufficient to note that legislative provision had now been created which was intended to enable children damaged *in utero* to seek compensation upon being born injured.

The legislative approach seems attractive for a variety of reasons, not least that it avoids the need to resolve the apparent contradiction of a duty of care being owed to a foetus which lacks legal personality, and indeed to a foetus whose existence may be unknown at the time the injury is suffered, e.g., during the first trimester when the foetus, technically at that stage an embryo, is at its most biologically vulnerable, growing from one cell to billions in a short period of time and the beginning of organogenesis.²⁰⁰ Although *Burton* and *DeMartell* were settled after the introduction of the CDCLA 1976, the injuries were sustained prior to the enactment of the legislation, and so the courts founded their decisions on the common law, relying upon “all relevant authorities including decisions, so far as helpful, of other Commonwealth jurisdictions”,²⁰¹ and particularly *Watt* and *Duval*.

3.5 The Maternal Exemption from Liability for Foetal Harm

In none of the cases so far considered was the harm to the foetus the result of the pregnant woman’s act or omission. Although a pregnant woman can open herself to criminal prosecution if she intentionally ends the life of her foetus other than by means of a legal abortion, pregnant women may - and do - undertake without fear of legal sanction many activities which have the potential to harm the foetus, varying from everyday actions such as driving a car to more extreme but still perfectly legal ones such as weightlifting.²⁰² Even activities which have clearly been shown to have detrimental consequences for foetal development and which become manifest at birth, such as smoking tobacco²⁰³ or

¹⁹⁹ The CDCLA 1976 and its application to a clinical trial setting will be discussed extensively in Chapter 7.

²⁰⁰ Green, M.A. *Bendectin and Birth Defects: The Challenges of Mass Toxic Tort Substances Litigation*. Philadelphia: University of Pennsylvania Press, 1995.

²⁰¹ ²⁰¹ *Burton v Islington Health Authority, De Martell v Merton and Sutton Health Authority* [1992] 3 All ER 833, *per* Dillon LJ at 232.

²⁰² Styles, R. Weightlifting mother is branded 'selfish' for carrying on extreme exercise routine at nine months pregnant. So, are the critics right or is her pre-natal lifting perfectly safe? 20th September, 2013, available at <http://www.dailymail.co.uk/femail/article-2425461/Mother-causes-social-media-storm-posting-pictures-weightlifting-EIGHT-months-pregnant.html> accessed 5th September, 2015.

²⁰³ Ekblad, M., Korkeila, J., Lehtonen, L. (2015). Smoking during pregnancy affects foetal brain development. *Acta Paediatrica*, **104**, 12-18; Mund, M., Louwen, F., Klingelhofer, D. *et al.* (2013). Smoking and pregnancy - a review on the first major environmental risk factor of the unborn. *Int.J.Envir.Res.Pub.*

excessively consuming alcohol,²⁰⁴ are not legally proscribed or punishable in the UK. The UK is a signatory to the Convention on the Rights of the Child, the preamble to which states (emphasis added) “the child, by reason of his physical and mental immaturity, needs special safeguards and care, including appropriate legal protection, *before* as well as after birth”,²⁰⁵ yet in *Criminal Injuries Compensation Authority v First-tier Tribunal (Social Entitlement Chamber)*,²⁰⁶ Lord Dyson MR expressed *obiter*, and without citing authority, the view that in English law a woman owed no duty in tort to her unborn child. The reasons behind this maternal exemption from liability are not immediately clear.

The original philosophy behind the maternal exemption given for such decisions in earlier cases in the USA²⁰⁷ may have been that if a child could sue his or her mother for injuries inflicted upon the child during gestation, this would disrupt family harmony and create an adversarial atmosphere between the two. The CDCLA 1976 contains an important qualification in section 1(1), excluding from liability the child’s own mother, unless (S.2) the injuries caused to the child are caused as a result of her negligent driving of a motor vehicle while pregnant; the reason for this exception to the qualification is that in such cases the claim would be met from insurance compensation, rather from the mother herself. The Law Commission’s 1979 report on injuries to unborn children highlighted the dilemma of balancing ethical and moral arguments against policy considerations and the application of the law, stating:

“We recognise that logic and principle dictate that if a mother’s negligent act or omission during or before pregnancy causes injury to a foetus, she should be liable to her child when born for the wrong done. But we have no doubt at all that in any system of law there are areas in which logic and principle ought to yield to social acceptability and natural sentiment and that this particular liability lies in such an area.”²⁰⁸

Health. **10**, 6485-6499; Adams, K.K., Beem, A., Diener, E. *et al.* (2012). Protecting the vulnerable: the importance of effective parental tobacco-dependence treatment during prenatal and newborn care. *Ped.Allergy Immunol.Pulmonol.*, **25**, 3-10.

²⁰⁴ Mukherjee, R. A. S., Turk, J. Hollins, S. (2006). Psychiatric comorbidity in fetal alcohol syndrome. *Psych. Bull.*, **30**, 194–195; McKnight, A., Merrett, D. (1987). Alcohol consumption in pregnancy: a health education problem. *J.Roy.Coll.Gen.Pract.*, **37**, 73–76.

²⁰⁵ United Nations Human Rights, Conventions on the Rights of the Child (20 November 1989), Office of the High Commissioner for Human Rights <<http://www.ohchr.org>>.

²⁰⁶ *Criminal Injuries Compensation Authority v First-tier Tribunal (Social Entitlement Chamber) [2014] EWCA Civ 1554* [2015] 2 W.L.R. 463.

²⁰⁷ See, for example, *Stanford v St Louis-San Francisco Ry* [1926] 214 Ala. 611.

²⁰⁸ Law Commission, Report on Injuries to Unborn Children, Report No. 60, Cmnd 5709 (1979) 5, [55].

Interestingly, family harmony is not so protected by the CDCLA 1976 that the father is similarly immune from liability.²⁰⁹ In addition, children may sue parents for *postnatal* injury, yet one might anticipate this would be just as disruptive to family harmony.

One alternative rationale for the maternal exclusion is that, but for such an exclusion, the pregnant woman's autonomy would be significantly impaired. As the unborn child has no legal personality, then considerations of maternal autonomy almost invariably take precedence in a legal sense, as many of the cases reviewed in the next section will illustrate. To do otherwise would be to create maternal-foetal conflict.²¹⁰ Imposing liability for *antenatal* negligence (which would depend upon the pregnant woman owing a duty of care to her foetus) would, in effect, create a unique gender-based tort. Conversely, the current position creates a gender-based immunity, as fathers may be held liable for injuries inflicted *in utero*. However, this situation is consistent with the now-established construction of respect for the pregnant woman's autonomy over foetal 'needs', which will be addressed further in the next section, although its complexion is rather different.

Another rationale for the maternal exemption may be that the threat of suit could encourage a pregnant woman to avoid liability completely by undergoing an (otherwise unnecessary) abortion. This argument seems less than compelling in a legal system in which there is no 'right' to an abortion, although termination, particularly in the early stages of pregnancy, is hardly rare in England and Wales.²¹¹ A stronger argument, perhaps, is that if the state becomes coercive in its treatment of pregnant women, it will discourage those who need help from seeking it for fear of the consequences if they do not conform to 'expected' norms - exactly the situation which now obtains in the USA,²¹² some cases having been decided on the basis that the state has a responsibility to intervene to protect a viable foetus,²¹³ if necessary at the expense of the autonomy,²¹⁴ possibly liberty²¹⁵ and, in an extreme case, the life of the woman carrying it.²¹⁶

²⁰⁹ The Royal Commission on Civil Liability and Compensation for Personal Injury, Cmnd 7054-I(1979) recommended that immunity be extended to fathers, but this has not been implemented.

²¹⁰ Mair, J. *Maternal/Foetal conflict: defined or defused?* In: McLean, S.A.M. (Ed.), *Contemporary Issues in Law, Medicine and Ethics*. Aldershot: Dartmouth Publishing, 1996.

²¹¹ The Report on abortion statistics in England and Wales for 2014, published 9th June, 2015, shows the number of terminations annually to be fairly stable at approximately 185,000; report available at <https://www.gov.uk/government/statistics/report-on-abortion-statistics-in-england-and-wales-for-2014> accessed 8th September, 2015. See also the discussion in Chapter 2.6.

²¹² Meredith, S. *Policing Pregnancy*, Ashgate, Farnham, 2005.

²¹³ For a comment by a judge in the USA, see Garcia, S.A. (1993). Maternal drug abuse: laws and ethics as agents of just balances and therapeutic interventions. *Int.J.Addiction*, **28**, 1311-1339.

The maternal exemption does not apply to criminal behaviour which results in foetal 'death', and women may be prosecuted under both the Offences Against the Person Act 1861²¹⁷ and the Infant Life Preservation Act 1929, although prosecutions under the latter are rare; procuring a miscarriage so as to kill a child capable of being born alive may contravene both the 1861 and 1929 Acts. However, the maternal exemption does apply to behaviour which results in foetal injury. Although calls continue to be made to change the interpretation of the law, such that women who drink alcohol during pregnancy sufficiently to result in their children being born with foetal alcohol syndrome should be regarded as having committed a criminal offence,²¹⁸ a recent case²¹⁹ held that excessive alcohol consumption by a pregnant woman in the knowledge that it would harm her unborn child did not amount to the criminal offence of inflicting grievous bodily harm by administering a noxious substance to any other person contrary to section 23 of the 1861 Act. The *actus reus* required the poison to be administered to another person; an unborn child does not constitute 'any other person' within section 23, (an interesting contrast with the majority ratio in *Montreal Tramways*) and hence the *actus reus* of this crime could not be committed by its mother.

This construction is consistent with the *Attorney General's Reference No 3 of 1994*.²²⁰ Given an absence of intention to injure the foetus, the pregnant woman lacks the *mens rea* for murder. If she is drinking alcohol to excess with the intent of terminating her pregnancy, then she could, arguably, be charged under section 58 of the 1861 Act. However, her excessive drinking is not criminal *per se* and so does not constitute an action which would support a manslaughter charge. However, should the pregnant woman's consumption of alcohol harm the foetus, and should that harm become apparent *postnatally*, then, conceptually, it seems no different from, for example, *Burton* or *DeMartell*, other than the fact that the pregnant woman has inflicted the harm. Under the CDCLA 1976, which would now be the conventional route to seek compensation for

²¹⁴ Laufer-Ukeles, P. (2011). Reproductive choices and informed consent: fetal interests, women's identity, and relational autonomy. *Am.J.Law Med.*, **37**, 567-623.

²¹⁵ Murphy, A.S. (2014). A survey of state fetal homicide laws and their potential applicability to pregnant women who harm their own foetuses. *Ind.Law J.*, **89**, 847-884; Cantor, J.D. (2012). Court-Ordered care - a complication of pregnancy to avoid. *N.Engl.J.Med.*, **366**, 2237-2240.

²¹⁶ *In Re A.C.* [1990] 573 A.2d 1235, 1240, 1246-1248, 1252.

²¹⁷ *R. v Catt (Sarah Louise)* [2014] 1 Cr. App. R. (S.) 35.

²¹⁸ Marsden, S. Drinking alcohol during pregnancy could be ruled a crime. 2nd February, 2014, available at <http://www.telegraph.co.uk/health/healthnews/10612818/Drinking-alcohol-during-pregnancy-could-be-ruled-a-crime.html>, accessed 8th September, 2015.

²¹⁹ *CP (A Child) v Criminal Injuries Compensation Authority* [2015] 2 W.L.R. 463.

²²⁰ *Attorney-General's Reference (No. 3 of 1994)* [1998] AC 245.

congenital injury, liability to the child is derivative from the duty owed to the parents, commonly the mother, but if the (formerly) pregnant woman is the defendant, then there would appear to be no basis upon which to bring the case. Prior to the CDCLA 1976, under the common law, there would seem to have been no barrier in such circumstances to an injured child seeking reparation from the mother, other than for reasons of public policy, although no such cases appear to have been reported. With the passing of the CDCLA 1976, that possibility has been removed, and the pregnant woman is indeed immune from civil liability in such circumstances.

The logic of the maternal exclusion has been challenged by Brazier²²¹ and Norrie,²²² but it remains the law in England and Wales. The CDCLA 1976 does not apply in Scotland, but the Scottish Law Commission Report on *Antenatal Injury*,²²³ noting the decision in *Young v Rankin*,²²⁴ concluded that “such actions are not excluded by any rule or doctrine in the law of Scotland”. This exemption also applies in Canada,²²⁵ and the matter is unresolved in Australia,²²⁶ and New Zealand, although in the latter matters are further complicated by the ‘no-fault’ system of compensation for injury. As will be discussed in the next section, in the UK, a pregnant woman is under no legal obligation to take any measures to protect the ‘health’ or ‘welfare’ of her foetus during pregnancy, although this alone would not exclude the possibility of being liable for damages if harm in fact arose.

One manoeuvre to control the behaviour of a pregnant woman considered as being potentially injurious to her foetus - that of making the foetus a ward of court - was explored in *in re F*.²²⁷ The court held that it lacked the jurisdiction to make a foetus a ward of court. Citing *Paton*, since a foetus has no existence independent of its mother regardless of its stage of development, the court could not exercise the rights, powers and duties of a parent over the foetus without controlling the mother's actions. Accordingly, the court could not extend its wardship jurisdiction over minors to a jurisdiction over a pregnant

²²¹ Brazier, M. Parental Responsibilities, Foetal Welfare and Children’s Health. In: Family Law Towards the Millenium: Essays for PM Bromley, Bridge, C. (ed). London: Butterworths, 1997, at pp.263-293.

²²² Norrie, K.M. Protecting the Unborn Child from its Drug or Alcohol Abusing Mother. Freeman, M., Lewis, A. (Eds.) Law and Medicine (Current Legal Issues, Vol.3, 2000) at pp.223-244.

²²³ Scottish Law Commission Report No. 30; Liability for Antenatal Injury, Cmnd 5371, available at <http://www.scotlawcom.gov.uk/files/5112/7989/6877/rep30.pdf> accessed 8th September, 2015.

²²⁴ *Young v Rankin* [1934] S.C. 499; [1934] S.L.T. 445.

²²⁵ In Canada, *Dobson v Dobson* [1999] 174 D.L.R. (4th) 1 (Sup Ct (Can)).

²²⁶ Do, C., Mapulanga-Hulston, J. The ethical and legal conundrum: should a mother owe a duty of care to her unborn child? Available at http://business.curtin.edu.au/local/docs/Do_Mapulanga-Hulston_Duty_of_Care.pdf, accessed 8th September, 2015.

²²⁷ *In re F (in utero)* [1988] Fam 122.

woman for the protection of an unborn child, which had no legal rights or existence. Thus, the courts in the UK set a clear distinction between a course of action which could be followed after live birth, such as immediately taking a newborn child into care, and one which was not applicable in an *antenatal* setting.

The position in the USA has followed a somewhat different path to that in the UK and the European Union regarding the pregnant woman's primacy. In the USA, the activities of pregnant women have been said to have been increasingly restricted with the professed intent of 'protecting' the foetus.²²⁸ Legislation in many states now seems to permit the imprisonment of women to prevent their undertaking activities which are considered to pose a risk to the foetus, and the majority of states in the USA have now enacted legislation which render as criminal activities which could endanger foetal survival or development.²²⁹ Clearly, in such circumstances, the autonomy of a pregnant woman may be significantly compromised, and effectively subordinated to the foetus which she carries.²³⁰ Children born injured as a result of pregnant women's acts or omissions have successfully sued their mothers,²³¹ but the right to do so varies across states and with the circumstances.²³² A recent review identified hundreds of cases in which foetuses had been made wards of court (in contrast to the position in the UK described above), newly-born children had been removed from parental care, and pregnant women had been subjected to court-ordered Caesarean surgery or blood transfusions.²³³ In some cases, these actions had been taken long before the foetus had attained viability. In many cases in which the authors could identify the underlying legal basis for these actions, it was similar to that promoted by the proponents of foetal personhood; the fertilized egg, embryo, or foetus should be treated as if it was legally separate from the pregnant woman. Legal authority for their actions came directly or indirectly from foeticide statutes which considered the

²²⁸ See Meredith, S. *Policing Pregnancy*, Ashgate, Farnham, 2005. Also Paltrow, L.M., Flavin, J. (2013). Arrests of and forced interventions on pregnant women in the United States, 1973-2005: implications for women's legal status and public health. *J.Health Politics Policy Law*, **38**, 299- 343.

²²⁹ Murphy, A.S. (2014). A survey of state fetal homicide laws and their potential applicability to pregnant women who harm their own foetuses. *Ind.L.J.*, **89**, 847-884; Cantor, J.D. (2012). Court-Ordered care - a complication of pregnancy to avoid. *N.Engl.J.Med.*, **366**, 2237-2240.

²³⁰ Laufer-Ukeles, P. (2011). Reproductive choices and informed consent: fetal interests, women's identity, and relational autonomy. *Am.J.Law Med.*, **37**, 567-623.

²³¹ See, for example, *Grodin v Grodin* [1981] 102 Mich. App. 396, 301 N.W. 2d 869.

²³² American Civil Liberties Union. What's Wrong with Fetal Rights, available at <https://www.aclu.org/whats-wrong-fetal-rights> accessed 8th September, 2015.

²³³ Paltrow, L.M., Flavin, J. (2013). Arrests of and forced interventions on pregnant women in the United States, 1973-2005: implications for women's legal status and public health. *J.Health Politics Policy Law*, **38**, 299- 343; see also Matevosyan, N.R. (2012). Court-visited obstetrical and fertility procedures. *Arch.Gynecol.Obstet.*, **285**, 1195-1203.

unborn as legally separate from pregnant women, from state abortion laws that included language similar to personhood measures, the uncritical application of legislation and procedures originally intended to be applied to children post-birth, and a misrepresentation of the judgment in *Roe v Wade* that, once the foetus attained viability, the foetus and the pregnant woman could be treated as separate persons.²³⁴ However, these initial decisions were often overturned in appellate courts, illustrating that the legal basis for the decision was at best debatable, and in many cases amounted to unlawful interventions in the constitutional and other legal rights of the woman. The survey highlighted some worrying disparities: 71% of the pregnant women involved were sufficiently poor to qualify for indigent defence and nearly 60% were women whose ethnic origin was not Caucasian. The American Medical Association, the American Academy of Pediatrics, and the American College of Obstetricians and Gynecologists had long concluded that the potential for arrest and punishment deterred many women from seeking care and from speaking openly with their doctors,²³⁵ precisely the concern raised earlier in this section. Paltrow's survey suggests the risk is still real in the USA 20 years after these medical bodies raised concerns, perhaps supporting the reason advanced earlier for the maternal exemption under the CDCLA 1976.

Obviously, in a clinical trial setting, the risk of injury to the foetus is present, and the pregnant woman's consent to participate in the trial would unavoidably commit the foetus to the same trial. This raises issues regarding the extent to which that consent might affect the rights of a child born injured to seek compensation. Moreover, the public policy implications of permitting children to sue their mothers for injuries arising in such trials would be considerable.²³⁶ The potential implications of the maternal exclusion in a clinical trial setting will be addressed in Chapter 7.

²³⁴ Paltrow, L.M., Flavin, J. (2013). Arrests of and forced interventions on pregnant women in the United States, 1973-2005: implications for women's legal status and public health. *J.Health Politics Policy Law*, **38**, 299-343.

²³⁵ Cole, H.M. (1990). Law and Medicine/Board of Trustees Report: Legal interventions during pregnancy: court-ordered medical treatments and legal penalties for potentially harmful behavior by pregnant women. *J.Am.Med.Ass.*, **264**, 2663-2670; American Academy of Pediatrics Committee on Substance Abuse. (1990). Drug-Exposed Infants. *Pediatrics* **86**, 639-642.

²³⁶ Clayton, E.W. Liability exposure when offspring are injured because of their parents' participation in clinical trials. In: *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Vol. 2. Workshop and Commissioned Papers. Mastroianni, A.C., Faden, R., Federman, D (Eds). Washington D.C.: National Academy Press, 1994, pp103-112.

3.6 Conclusions

Notwithstanding the developments of the last 150 years and the clear concern of the courts to acknowledge, recognise and, in certain circumstances, protect the developed, possibly-viable, foetus, the fact remains that, under the law in the UK, the foetus lacks legal personality, has no ‘rights’ which can be asserted on its behalf until it is born alive, and as a result enjoys relatively little legal ‘protection’ from harm before birth. The results of cases considered by the European Commission for Human Rights suggest this position is unlikely to be successfully challenged using human rights law. Nonetheless, the law does ‘protect the foetus’ by recognising future interests in the event of live birth following injury *in utero*.

Future foetal ‘interests’ (or the *antenatal* interests of the child) have become increasingly protected. The situation in inheritance law is well-established, and the position regarding compensation for injury inflicted *in utero* manifesting upon live birth has been progressively developed through the *nasciturus* doctrine, criminal, civil and common law. Taken together, these developments place a child born injured in a much better position to recover compensation than his counterpart of only 50 years ago.

However, gaps and contradictions remain. For example, a foetus which suffers avoidable injuries which are ‘fatal’ before birth enjoys no ‘rights’; as the case of *Vo* illustrated, the perpetrator may be answerable in civil law to the woman who was carrying the foetus, but the foetus itself is not recognised as having been a person who has been unlawfully killed, and the same appears to be the case under common law in the UK. In contrast, the perpetrator of an act causing injury *in utero* or precipitating premature labour, which results in the death of a child following live birth, may be pursued by the law in respect of the death caused. The outcome is, effectively, the same, yet the liability differs. Under the common law approach adopted in *Montreal Tramways* and subsequently, the foetus is considered as ‘another’, however under the criminal law, and specifically section 23 of the Offences against the Person Act 1861, that is not the case.

A pregnant woman is entitled to refuse treatment *in utero* for her unborn child but, once delivered, that child can receive treatment in the face of parental opposition should a court sanction it,²³⁷ although *antenatal* treatment may be necessary to ensure a safe delivery or

²³⁷ *In Re C. (A Minor) (Wardship: Medical Treatment)*, [1990] Fam 26; *An NHS Trust v D*, [2000] 2 F.L.R. 677; *Re J (A Minor) (Child in Care: Medical Treatment)*, [1993] Fam 15.

even a live birth. From a legal perspective, it is therefore to a child's advantage to be born prematurely rather than at term, since from that moment the child's life and rights are protected by law, whereas the foetus *in utero* has no 'rights' that can be exercised on its behalf, other than the qualified and indirect protection offered by restrictions on abortion. Yet it is rarely in the child's best medical interests to be born prematurely. The contradiction from the perspective of foetal protection is clear.

The courts cannot exercise wardship over a foetus (*in Re F*), and a pregnant woman can act as she pleases (other than attempting to procure a miscarriage) with scant regard for the risks to foetal survival and development. However, once born, the courts may intervene if the pregnant woman's behaviour constitutes a risk to the survival or development of the child, but by then the damage may have been done.

Within a clinical trial setting (see Chapter 6), the risk, however small, is always present that the investigational drug will injure the foetus, or it may induce premature labour. It seems highly unlikely that participation in a properly-approved clinical trial would be considered as behaviour likely to induce the courts to issue a protection order for the resulting child. A pregnant woman not enrolled in a clinical trial may similarly make a decision not to accept foetal treatment *in utero*. There seems no basis upon which to believe the response of the courts would be different in these two settings, and there is no precedent in the UK for a refusal to accept foetal treatment *in utero* to be grounds for the issuance of a protection order on behalf of the foetus.

Chapter 4 Foetal Moral Status and Maternal-Foetal Models

4.1 Introduction

The previous chapter addressed the extent to which UK law has sought to recognise the foetus and its future interests, and the relevance of that to the clinical trial setting. The debates and discussions which preceded the creation of legislation and common law were often founded upon a range of perspectives regarding moral considerations relating to the foetus, the common theme being that of safeguarding the foetus *in utero*, and the future interests of the child it would become. In conventional medicine, treatment is administered because it is necessary for the health of the patient, and so the benefit:risk ratio is held to be acceptably high. That is not the case in medical research, as explained earlier,²³⁸ and so engaging people in research involves the making of a decision regarding taking an avoidable risk. It therefore is appropriate to consider the foetus' moral standing with respect to clinical research, and in particular to clinical trials in which the foetus is not the anticipated beneficiary.

In the wake of a number of scandals, a plethora of guidelines has been constructed regarding the ethical conduct of clinical trials in humans,²³⁹ none of which has explicitly considered pregnant women as a target population, nor the foetus. This is not surprising, given the historical background described in Chapter 1. Whilst deliberation regarding the foetus' moral standing has continued for millenia, the discussion relating to the foetus in a clinical trial setting is a little over 20 years old, following the lifting of the FDA embargo²⁴⁰ described previously. These discussions raised many questions, one of which was: should the foetus be regarded as a research subject? This chapter will address this question, beginning with a description of the main models which have been developed to describe the relationship between the pregnant woman and the foetus.

4.2 The Autonomy of Pregnant Women

In the USA, from the 1980s, some authors detected the apparent personalisation of the foetus. When the pregnancy was intended to go to term, the foetus became increasingly viewed as a patient in its own right, and when conflicts developed between the pregnant

²³⁸ See discussion in Chapter 1.2.

²³⁹ Emanuel, E.J., Wendler, S., Grady, C. An ethical framework for biomedical research. In: Emanuel, E.J., Crouch, R.A., Arras, J.D., Moreno, J.D. Grady, C., eds. Ethics and regulatory aspects of clinical research – readings and commentary. Baltimore: Johns Hopkins University Press; 2003. Chapter 11, 123-135.

²⁴⁰ Explained in Chapter 1.5

woman's medical needs and those of the foetus, foetal needs were sometimes prioritised by the physician;²⁴¹ this was perhaps more marked in the USA than the UK. The Polkinghorne Report, published in 1989, stipulated that: "The written consent of the mother must be obtained before any research or therapy involving the foetus or foetal tissue takes place", thereby affirming that decision-making responsibility remained exclusively with the pregnant woman.²⁴²

In 1992, in *re S*,²⁴³ Sir Stephen Brown P held, without giving explanation or justification, that in a situation where the lives of both mother and child would be at risk unless an operation was performed, the court could make a declaration that it could be performed despite the mother's refusal of consent. Earlier in the same year, in *re T (adult: refusal of treatment)*,²⁴⁴ a hospital had been authorised to administer a transfusion with the intention of saving the life of a pregnant woman injured in a road traffic accident who had refused a blood transfusion, Ward J considering that the circumstances constituted an emergency situation in which the woman could not express a competent view and that it would be proper for the doctors to treat her as they felt was in her best interests and in accordance with appropriate professional practice. The Court of Appeal in upholding the decision raised one possible exception to the right of a competent individual to refuse treatment: "the only possible qualification is a case in which the choice may lead to the death of a viable foetus...and, if and when it arises, the courts will be faced with a novel problem of considerable legal and ethical complexity."²⁴⁵ This was precisely the situation which had arisen in *re S*, the key distinction between the cases being that Mrs S's competence was not in question. *Re S* remains the only UK case in which the decision to authorise treatment of a pregnant woman against her wishes has not rested upon the court's assessment that the patient lacked the competence to validly refuse treatment.

In the 1990s, judicial opinion in the UK seemed to be moving toward a more formal recognition of foetal status. In 1993, in *Hamilton v Fife Health Board*,²⁴⁶ Lord Mccluskey commented "it is perfectly common in ordinary speech to refer to the child in the womb as "him" or "her".... It was this child who sustained injuries to his person and who died in

²⁴¹ See Robertson, J.A. *Freedom and the New Reproductive Technologies*. New Jersey: Princeton University Press, 1994, at p.174; *St George's Healthcare NHS Trust v S* [1998] 3 W.L.R. 936.; *In re Unborn Child* [1998] 683 NYS S.2d 366 (New York Family Court).

²⁴² See discussion in Chapter 1.3

²⁴³ *Re S (Adult: Refusal of Treatment)* [1992] 4 All E.R. 671.

²⁴⁴ *Re T (Adult: Refusal of Treatment)* [1992] 4 All E.R. 649.

²⁴⁵ *In Re T. (Adult: Refusal of Treatment)* [1993]. Fam. 95 at 102.

²⁴⁶ *Hamilton v Fife Health Board* [1993] S.C. 369.

consequence of injuries sustained by him”. Thus, the courts seemed to be placing an increasing weight on the notion of viability: if the foetus was viable, preventing its ‘death’ (accepting that legally it was not alive, in that it had not been born) might suggest a justification for instigating treatment despite the pregnant woman’s dissent. The outcome the following year of *Attorney-General’s Reference (No.3 of 1994)*, discussed in the previous chapter, the House of Lords considering that injury to a foetus inflicted *in utero* by a third party which resulted in *postnatal* death could attract criminal liability, was perhaps another manifestation of this change in thinking.

However, in 1997, in *re MB (medical treatment)*,²⁴⁷ the Court of Appeal developed guidelines for future cases of court involvement in emergency Caesarean surgery cases, Butler-Sloss LJ, referring to *re S* in her judgment as “a decision, the correctness of which, we must now call in doubt”.²⁴⁸ In 1998, in *St George’s Healthcare N.H.S. Trust v S.*,²⁴⁹ the Court of Appeal commented that “... a 36-week old foetus is not nothing; if viable it is not lifeless and it is certainly human”. However, the Court of Appeal held that the emergency Caesarean surgery which had been performed upon the competent Mrs. S. against her will constituted a trespass. Thus, the higher courts ‘drew a line in the sand’; the foetal ‘interests’ – however these might be construed – did not override the autonomy of the competent pregnant woman. However, as the following section will illustrate, the legal position in the UK is not universally-held.

4.3 Maternal-Foetal Models

For many decades, physicians were trained to assess the foetus indirectly by examination of the pregnant woman and to treat suspected foetal conditions by managing the maternal environment. Unable to interact with the foetus directly, physicians viewed the maternal-foetal ‘dyad’ as one complex patient, the gravid female, of which the foetus was an integral part, physically and morally.²⁵⁰ During the 1970s and 1980s obstetric medicine was transformed by the development of high-resolution ultrasound techniques which enabled progressively clearer foetal visualisation *in utero*.²⁵¹ Routine scans are now often

²⁴⁷ *Re MB (Medical Treatment)*, [1997] 2 F.L.R. 426.

²⁴⁸ Cited in Jackson, E. *Medical Law: Text Cases and Materials*. Oxford: OUP, 2013, at p.218

²⁴⁹ *St George’s Healthcare N.H.S. Trust v S.* [1998]; *R. v Collins and Others.*, *ex p S* [1999] Fam 26, at s.45.

²⁵⁰ Mattingly, S.S. (1992). The maternal-fetal ‘dyad’: exploring the ‘two-patient’ obstetric model. *Hast.Cent. Rep.*, **22**, 13-18.

²⁵¹ See Nicolson, M., Fleming, J.E.E. *Imaging and Imagining the Foetus: The Development of Obstetric Ultrasound*. Baltimore: Johns Hopkins University Press; 2013.

perceived as an opportunity for the pregnant woman and her partner to ‘see’ the future baby and to obtain a first image for the family album.²⁵² The increasing clarity of such images has led to a growing ‘personification’ of the foetus by both pregnant women and physicians²⁵³ to the point that they now are the cause of some ethical challenges when seeking to balance maternal and foetal health interests.²⁵⁴ This has resulted in a significant re-conceptualisation of the foetus as part of a ‘two-patient’ obstetric model,²⁵⁵ with the foetus being accorded a variable degree of moral standing of its own.²⁵⁶

Conceptually, of course, a ‘one-patient’ model may also exist, which takes no account of the foetus or the effects which illness and its treatment have on the foetus, provided it has no impact on the pregnant woman’s health.²⁵⁷ Under this model, the foetus is morally (and physically) indistinct from any other part of the pregnant woman. This model was originally advanced as a response to the perceived threats to the liberty and autonomy of pregnant women, following a number of court-ordered obstetric interventions in the USA,²⁵⁸ and rapidly was criticised as being too inflexible for clinical purposes,²⁵⁹ but has largely fallen out of favour now.

Thus, broadly, the maternal-foetal relationship may be described by three models, and the following terminology will be used throughout this thesis:

²⁵² Bricker, L., Garcia, J., Henderson, J. *et al.* (2000). Ultrasound screening in pregnancy: a systematic review of the clinical effectiveness, cost-effectiveness and women's views. *Health Tech.Assess.*, **4**, 1-193; Garcia, J., Bricker, L., Henderson, J., *et al.*(2002). Women's views of pregnancy ultrasound: a systematic review. *Birth*, **29**, 225–50.

²⁵³ McLean, S. (1998). The moral and legal boundaries of fetal intervention: whose right/whose duty. *Sem. Neonatol.*, **3**, 249–254; McNay, M.B., Fleming, J.E. (1999). Forty years of obstetric ultrasound 1957-1997: from A-scope to three dimensions. *Ultrasound Med.Biol.*, **25**, 3–56.

²⁵⁴ Edvardsson, K., Small, R., Lalos, A. *et al.* (2015). Ultrasound’s ‘window on the womb’ brings ethical challenges for balancing maternal and fetal health interests: obstetricians’ experiences in Australia. *J.Med. Ethics*, **16**, 31-48.

²⁵⁵ Burrows, J. (2001). The parturient woman: can there be room for more than ‘one person with full and equal rights inside a single human skin’? *J.Adv.Nurs.*,**33**, 689–95; Mattingly, S.S. (1992). The maternal-fetal ‘dyad’: exploring the ‘two-patient’ obstetric model. *Hast.Cent.Rep.*, **22**, 13-18; McLean, S. *Old Law, New Medicine*. London: River Orams Press, 1999.

²⁵⁶ Petchesky, R.P. (1987). Fetal images. The power of visual culture in the politics of reproduction. *Fem. Studies*, **13**, 263-292.

²⁵⁷ Annas, G.J. (1988). Protecting the liberty of pregnant patients. *N.Engl.J.Med.*, **316**,1213-1214.

²⁵⁸ Johnsen, D. (1987). A new threat to pregnant women’s autonomy. *Hast.Cent.Rep.*, **17**, 33-40; Nelson, L.J.; Milliken, N. (1988). Compelled medical-treatment of pregnant women - life, liberty, and law in conflict. *J.Am.Med.Ass.*, **259**, 1060-1066.

²⁵⁹ Strong, C. (1991). Court-ordered treatment in obstetrics - the ethical views and legal framework. *Obs.Gyn.*, **78**, 861-868.

- the ‘single-patient’ model, in which no account is taken of the existence of the foetus, or its ‘welfare’, with medical treatment being considered as it would be for any adult female;
- the maternal-foetal ‘dyad’, in which the pregnant woman and the foetus are considered holistically;
- the ‘two-patient’ model, in which the pregnant woman and the foetus are considered as separate entities.

In the UK, as discussed in Chapter 3, provided she is legally competent, the pregnant woman’s autonomy is such that the decision-making prerogative lies with her alone. That said, in either the ‘dyad’ or ‘one-patient’ model, should the pregnant woman’s response to an investigational drug result in potential harm to the foetus, then the resulting net burden to the pregnant woman may become excessive, and so it seems likely that the foetus would still be in the contemplation of a clinical investigator who was a proponent of either the ‘dyad’ or ‘one-patient’ model.

Clearly, although the foetus and pregnant woman may be considered philosophically as two separate patients, they are not separate in fact: they are intimately linked, with one, the foetus, dependent upon the other either through necessity (prior to viability) or choice (after viability), although whose choice this is may vary on a case-by-case basis.²⁶⁰ In the UK, we have adopted the legal position that the life, health and liberty of a pregnant woman prevail over foetal interests, unless the pregnant woman herself decides otherwise. She may elect to risk or even sacrifice her life, health or liberty by exercising an autonomous choice to embark upon a course of action which will benefit the foetus or the child it will become, but she is not legally required to do so, although the publicity surrounding a recent foetal alcohol syndrome disorder case suggests that the legal position may not entirely reflect the moral view within the UK.²⁶¹

In reality, in most cases, the ‘dyad’ model probably most closely approximates to everyday situations. Most women take account of their pregnancy, and elect to modify behaviours to an extent they decide for themselves based upon their own holistic assessments of what

²⁶⁰ Lyerly, A.D., Mahowald, M.B. (2003). Maternal-fetal surgery for treatment of myelomeningocele. *Clin. Perinatol.*, **31**, 155–165.

²⁶¹ *CP (A Child) v Criminal Injuries Compensation Authority* [2015] 2 W.L.R. 463.

matters to them. Effectively, this is a form of ‘relational autonomy’, the pregnant woman entering into an evolving relationship with her foetus.²⁶²

The intention of medical research in pregnant women of the type the Agencies are requesting is to gain more information on the pharmacokinetics of and response to drugs in pregnant women. The intention is not to benefit the foetus, but the conduct of medical research on pregnant women unavoidably carries the risk of foetal harm. Is the moral standing of the foetus such that these risks can justifiably be engaged in a research setting? The following section will explore a range of arguments regarding this, and will then seek to relate the moral standing of the foetus in a research setting.

4.4 The Moral Justification for Research in Pregnant Women

Some authors, basing their arguments on a platform of fairness and distributive justice, contend that the risks and burdens of participating in research should be borne by all in society, or by that part of society which will benefit from research.²⁶³ Given the almost complete absence of information relating to the appropriate use of drugs in pregnant women, the section of society which will benefit most from this type of research will be pregnant women and, consequently, the foetuses they carry. Interestingly, none of the commentators advancing this view appear to have contemplated this population, although the information the Agencies are seeking will fall squarely into the category of research which will benefit others. In the absence of acceptable alternatives - and continuing as we are now is arguably not acceptable - the demands of fairness within society and distributive justice are best satisfied by the conduct of carefully-controlled clinical trials in pregnant women which will in future benefit the same two populations.

Conversely, others have argued that if doing so does not generate a high personal cost, the pregnant woman has the duty to prevent harm to the foetus.²⁶⁴ In opposition, proponents of maternal autonomy argue that no one but the pregnant woman can make such intimate

²⁶² For a more extensive discussion, see McLean, S.A.M. *Autonomy, Consent and the Law*, Routledge-Cavendish, Oxford 2010, pp128-155.

²⁶³ De Melo-Martin, I. (2008). A duty to participate in research; does social; context matter? *Am.J.Bioethics*, **8**, 28-36; Christensen, E. (2012). The re-emergence of the liberal-communitarian debate in bioethics: exercising self-determination and participation in biomedical research. *J.Med.Phil.*, **37**, 255-276; Harris, J. (2005). Scientific research is a moral duty. *J.Med.Ethics*, **31**, 242-248

²⁶⁴ Schucklenk, U., Kleinsmidt, A. (2007). Rethinking mandatory HIV testing during pregnancy in areas with high HIV prevalence rates: ethical and policy issues. *Am.J.Public Health*, **97**, 1179–1183.

decisions.²⁶⁵ If we adhere to the notion of consent, which is entirely voluntary in nature, then the duty argument must fail; doing something because others perceive it as a duty surely vitiates the essence of consent.

A consequentialist approach - that a morally right act is one that will produce a good outcome or consequence - also seems applicable in this setting; there would seem to be no reasonable doubt that being able to provide better treatment to pregnant women and thereby protect or minimise harm to the foetus is a good thing, although the extreme manifestation of this approach - that the ends justify the means - is unlikely to be acceptable to all, or possibly even a majority, in the UK. To an extent, the utilitarian views of Bentham²⁶⁶ and Mill²⁶⁷ are relevant here too. In the absence of relevant information in this population, we will continue to provide potentially sub-optimal treatment to pregnant women, and in the process increase the risks to the foetus of both the disease condition and unnecessary exposure to drugs. However, utilitarianism permits the causing of harm to innocent victims if doing so would be likely to deliver benefits to others greater than the harm to the victims, and this would not be ethically acceptable in the conduct of clinical trials.

The more fundamental question of whether a moral duty can be owed to an entity without independent moral status - the foetus - has been addressed by a number of authors. For example, Campbell and McKay,²⁶⁸ Harris²⁶⁹ and Feinberg²⁷⁰ all conclude that a moral duty can be owed to a foetus which lacks independent moral status, and that duty can be breached if the pregnant woman takes actions which result in the birth of an injured child. This is the same premise upon which common law allows compensation for *in utero* injury manifesting *postnatally*,²⁷¹ demonstrating that an expectation exists that the foetus should have been in the contemplation of those whose actions and decisions affected it, accepting

²⁶⁵ Johnsen, D.E. (1986). The creation of "fetal rights": conflicts with women's constitutional rights to liberty, privacy, and equal protection. *Yale Law J.*, **99**, 599-625; Perry, C. (2011). Unacceptable risk in pregnancy: whose choice and responsibility? *Am.J.Bioethics*, **11**, 64-65; Laufer-Ukeles, P. (2011). Reproductive choices and informed consent: fetal interests, women's identity, and relational autonomy. *Am.J.Law Med.*, **37**, 567-623.

²⁶⁶ Bentham, J.S. (1781). *An Introduction to the Principles of Morals and Legislation*, reprinted by Batoche Books, Ontario, Canada, available at <http://socserv.mcmaster.ca/econ/ugcm/3ll3/bentham/morals.pdf> accessed on 11th September, 2015.

²⁶⁷ Mill, J.S. (1861) *Utilitarianism*, reprinted by Batoche Books, Ontario, Canada, available at <http://socserv.mcmaster.ca/econ/ugcm/3ll3/mill/utilitarianism.pdf>, accessed 11th September, 2015.

²⁶⁸ Campbell, T.D., McKay, A.J.M. (1978). Antenatal injury and the rights of the foetus. *Phil. Q.*, **28**, 17-30.

²⁶⁹ Harris, J. (1990). The wrong of wrongful life. *J.Law Soc.*, **17**, 90-105.

²⁷⁰ Feinberg, J. (1986). Wrongful life and the counterfactual element in harming. *Soc.Phil.Policy*, **4**, 145-178.

²⁷¹ This is discussed extensively in Chapter 3

the maternal exemption described in Chapter 3.5 and which will be addressed further in Chapter 7. It seems clear that any duty to/concerning the foetus is qualified in both a temporal sense (the duty becoming legally actionable only upon live birth) and a relative sense, in that the duty to each individual may be subordinated to the duty to others, if that dictates a course of action which leads to a ‘least detrimental option’, as was taken in *In Re A (Children) (Conjoined Twins: Surgical Separation)*.²⁷²

4.4.1 The Steinbock-Robertson-Gillon Proposition

Following the revision of the FDA’s prohibition of the inclusion of women in clinical trials described in Chapter 1, the academic and medical communities began to consider the conduct of research in pregnant women, with the echoes of thalidomide and diethylstilboestrol still ringing. In 1993, a workshop convened by the Institute of Medicine in the USA considered the potential issues arising from the inclusion of pregnant women in research. Two American speakers, John Robertson and Bonnie Steinbock, addressed the ethics of conducting such research. Without stating clear reasons, Robertson held that a pregnant woman was “not free to sacrifice the interests of expected offspring by her interests in serving the needs of science or of other women”, predicated upon the assumption that the foetus would be carried to term.²⁷³ Steinbock considered that ethical issues of conducting such research did not arise when the intention was to terminate the pregnancy, but concurred regarding a lack of entitlement to expose a foetus intended to be carried to term to risks associated with non-therapeutic research, i.e., research which did not have the potential to confer benefit to participants.²⁷⁴ Neither Robertson nor Steinbock described the foetus as a ‘participant’ in a clinical trial, and both seemed to assume maternal consent was acceptable. Following the publication of the Polkinghorne Report, the question was raised whether a pregnant woman who has elected for an abortion, and gave proxy consent for foetal research, could still be considered as having the ‘child’s’

²⁷² *In Re A (Children) (Conjoined Twins: Surgical Separation)* [2001] Fam. 147, per Ward LJ, at 1006D-E.

²⁷³ Robertson, J. Ethical issues related to the inclusion of pregnant women in clinical trials (I). In: *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Vol. 2. Workshop and Commissioned Papers. Mastroianni, A.C., Faden, R., Federman, D (Eds). Washington D.C.: National Academy Press, 1994, pp18-22.

²⁷⁴ Steinbock, B. Ethical issues related to the inclusion of pregnant women in clinical trials (II). In: *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Vol. 2. Workshop and Commissioned Papers. Mastroianni, A.C., Faden, R., Federman, D (Eds). Washington D.C.: National Academy Press, 1994, pp 23-28.

(foetus') bests interests at heart,²⁷⁵ but if the pregnant woman's consent is inappropriate, then the alternative is not obvious.

Steinbock proposed prohibiting pregnant women entering trials which did not have the potential to benefit foetuses as a class - precisely the type of research described previously which led to the discovery that one of the recommendations regarding the treatment of anthrax in pregnant women was valueless.²⁷⁶ She also agreed with Thomson²⁷⁷ that a pregnant woman was not morally required to sacrifice her own life or health to sustain the life of the foetus, and refusal of treatment which might harm the foetus was not morally required. However, she did not express a view on the morality of a pregnant woman seeking experimental treatment for herself if the progression of her condition would foreseeably harm the foetus. Thus both of these (American) authors shared the view that the foetus intended to be carried to term enjoyed a moral status such as to restrict, in this respect, the pregnant woman's freedom to participate in a perfectly lawful activity - at best the 'dyad model' but perhaps closer to the 'two-patient' one.

These constructions of the moral status of the foetus were similar to that previously proposed by Gillon, who suggested that foetuses have an attenuated moral status compared to persons - so attenuated that it is permissible to kill them when doing so benefits persons,²⁷⁸ i.e., not only to save the pregnant woman's life or protect the health, but also when the termination results in an advantage to the pregnant woman, and so potentially consistent with Kamm's 'Principle of Permissible Harm' theory.²⁷⁹ The crux of Gillon's argument is that a human person is someone who has been born, that human persons constitute a subset of human lives, the latter encompassing those humans who do not, or are not allowed to, develop sufficiently to become human persons, and that our moral and ethical obligations are to human persons. On this premise, once a decision is made to terminate a pregnancy, the choice is also made that the life of the foetus will be completed at the point of termination; it will not become a human person, and so it is not owed a moral or ethical obligation. Should the decision be made to continue the pregnancy, since all human persons occupy the same biological spatio-temporal continuance that they did as

²⁷⁵ Keown, J. (1993). The Polkinghorne Report on Fetal Research: nice recommendations, shame about the reasoning. *J.Med.Ethics*, **19**, 114-120.

²⁷⁶ Andrew MA, Easterling TR, Carr DB, *et al.* (2007). Amoxicillin pharmacokinetics in pregnant women: modeling and simulations of dosage strategies. *Clin.Pharmacol.Ther.*, **81**, 547-56.

²⁷⁷ Thomson, J.J. (1971) Defence of abortion. *Phil.Public Aff.*, **1**, 47-66.

²⁷⁸ Gillon R. (1988). Pregnancy, obstetrics, and the moral status of the foetus. *J.Med.Ethics*, **14**, 3-4.

²⁷⁹ Kamm, F.M. *Intricate Ethics: Rights, Responsibilities and Permissible Harm*. Oxford: OUP, 2007.

embryos and as fetuses, then – Gillon’s argument goes – it follows that we have a moral obligation not to harm those embryos and fetuses destined to become persons, a construction similar to those described by Campbell, Harris and Feinberg above. In essence, this is the same position proposed by Steinbock and Robertson, and conveys a utilitarian dimension: once the decision is made that a foetus is to be terminated, then it becomes a candidate for research it has no independent moral standing as a result of the woman’s decision to terminate the pregnancy. However, Gillon’s position is not quite asexclusionary as his American counterparts; if the foetus intended for survival has the same moral status as a person, then surely the possibility must exist of conducting clinical trials involving the foetus which are governed in the same way as trials in human persons.

Much of Steinbock’s and Robertson’s argument on the moral status of the foetus seems to reflect their location (the USA) where there has been a steady progression of foetal protection legislation, such that 38 of the 50 states now have some form of legislative provision regarding ‘foetal homicide’.²⁸⁰ In contrast, in the UK, the courts and Parliament continue to draw a ‘bright line’ between the legal recognition of the foetus and those who have actually been born, as described in Chapter 2.²⁸¹

With the progressive lowering of the legal gestation limit for abortion, the constructions of Steinbock, Robertson and, perhaps to a lesser extent, Gillon would potentially undermine the intent of the EMA and FDA by restricting ethical non-therapeutic clinical research to pregnant women who have elected to pursue a termination. The most recent published data for England and Wales (2013) show that 91% of terminations were carried out before 13 weeks’ gestation,²⁸² with similar figures reported for Scotland²⁸³ and the USA.²⁸⁴ At this early stage of pregnancy, the impact of the foetus on the pregnant woman’s biochemistry and physiology is relatively minor,²⁸⁵ and the relevance of results from clinical trials in this group is uncertain for women who are closer to term. The foetus is certainly vulnerable to the teratogenic effects of drugs during both the first and second

²⁸⁰ See <http://www.ncsl.org/research/health/fetal-homicide-state-laws.aspx> accessed 14th September, 2015.

²⁸¹ Burin, A.K. (2014). Beyond pragmatism: defending the ‘bright line’ of birth. *Med.L.Rev.*, **22**, 494-525.

²⁸² Department of Health, Abortion Statistics, England and Wales: 2013, June, 2014, available at https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/319460/Abortion_Statistics_England_and_Wales_2013.pdf, accessed 14th September, 2015.

²⁸³ NHS National Services Scotland, Information Services Division, Abortion Statistics, 2012, May 2013. Available at <http://www.isdscotland.org/Health-Topics/Sexual-Health/Publications/2013-05-28/2013-05-28-Abortions-Report.pdf>, accessed 14th September, 2015.

²⁸⁴ Guttmacher Institute, website: <https://www.guttmacher.org/media/presskits/abortion-US/statsandfacts.html>, accessed 14th September, 2015.

²⁸⁵ Datta, S., Kodali, B.S., Segal, S. *Obstetric Anesthesia Handbook*, 5th Edn., New York: Springer, 2010.

trimesters, but pre-approval studies are unlikely to be able to investigate this,²⁸⁶ so consideration of teratogenesis is a moot point. The proposed restriction that pregnant women who intend to carry a foetus to term cannot morally participate in research which is non-therapeutic for the foetus would significantly reduce the potential value of the information generated as well as the freedom of choice of pregnant women to participate in such studies - precisely the same criticisms of the FDA's earlier decision to exclude all women from clinical trials.²⁸⁷

4.4.2 The 'Waiver Theory'

Earlier American authors had formulated the 'waiver theory': if a woman had waived the opportunity of a legal abortion, she was thereafter duty bound to do whatever was required to protect and promote the foetus' best interests,²⁸⁸ even at the expense of her own rights.²⁸⁹ The basis for this position derives from the moral status of the human person the embryo is intended to become and the belief that the duty of care a mother has towards her child can be extended into the *antenatal* setting, although most authors restrict its application to injuries which are reasonably foreseeable.²⁹⁰ One of the drivers for this theory was the potential impact of uncontrolled behaviours, such as substance abuse, on the foetus.²⁹¹ This approach seems the apogee of the 'two-patient' model, the foetus exerting dominion over its 'carrier' and relying on 'life support' until it is capable of being supported by others in a post-delivery setting, and surely represents the surrender of autonomy.²⁹² The 'waiver theory' relies on the extension to an *antenatal* setting of the duty of care owed by a mother to her child which seems a particularly American construction, consistent with the progressive erosion in the USA of parental immunity

²⁸⁶ Adam, M.P., Polifka, J.E., Friedman, J.M. (2011). Evolving knowledge of the teratogenicity of medications in human pregnancy. *Am.J.Med.Gen, Part C*, **157**, 175-182; see also Chapter 1.6.

²⁸⁷ Merton, V. (1993). The exclusion of pregnant, pregnable, and once-pregnable people (aka women) from biomedical-research. *Am.J.Law Med.*, **19**, 369-451.

²⁸⁸ Robertson, J.A. (1983). Procreative liberty and the control of conception, pregnancy, and childbirth. *VA.Law Rev.*, **69**, 405-464; for a contrasting view, see Nocon, J. (1999). Panel on maternal-fetal conflict. *Tex.J. Women Law*, **8**, 261-266.

²⁸⁹ Balisy, S.S. (1987). Maternal substance abuse: the need to provide legal protection for the foetus. *So.Cal. Law Rev.*, **60**, 1209-1238.

²⁹⁰ See, for example, Robertson, H. (1979). Toward rational boundaries of tort liability for injury to the unborn: prenatal injuries, preconception injuries and wrongful life. *Duke Law.J.* **6**, 1401-1457.

²⁹¹ See, for example, Peak, K; Delpapa, F.S., (1993). Criminal-Justice Enters The Womb - Enforcing The Right To Be Born Drug-Free. *J.Crim.Just.*, **21**, 245-263.

²⁹² Paltrow, L.M., Flavin, J. (2013). Arrests of and forced interventions on pregnant women in the United States, 1973-2005: implications for women's legal status and public health. *J.Health Politics Policy Law*, **38**, 299-343.

from prosecution,²⁹³ and specifically rebutted in a legal sense in the UK.²⁹⁴ The intention of clinical trials of the types the Agencies are requesting is not to harm the foetus (or indeed the pregnant woman), far less terminate the pregnancy. Arguably, the foetus' best interests may be served by participation in carefully controlled clinical trials, carried out in specially-selected medical institutions under the oversight of physicians, rather than leaving untreated conditions which may impact the foetus, or managing them by using drugs which have not been studied in the pregnant population. Accordingly, the relevance of the waiver theory and of issues relating to pregnancy termination to clinical trials is at best limited.

4.4.3 The Chervenak-McCullough Model

Over the past 20 years, Americans Frank Chervenak, a Professor of Obstetrics, and Laurence McCullough, a medical ethicist, have progressively developed a 'two-entity' model under which physicians incur beneficence-based obligations to the foetus when they consider the foetus *to be* a patient and contemplate treating the foetus *as* a patient in its own right,²⁹⁵ rather than endowing the foetus with an intrinsic moral standing based on other criteria. Like most other authors, their approach is based upon protecting the child which the foetus will become, rather than ascribing a moral status to the foetus *per se*.

The concept of the foetal patient had been advanced earlier,²⁹⁶ reflecting the reality that the foetus was becoming progressively more treatable directly, although access, of course, was possible only *via* the pregnant woman.²⁹⁷

Their model would apply to situations in which a physician considered instituting some form of direct foetal therapy, or treatment for the pregnant woman with the primary purpose of benefitting the foetus, and where the foetus was expected subsequently to achieve independent moral status by becoming a child. This combination of

²⁹³ Anonymous(1981). The child's right to "life, liberty, and the pursuit of happiness": suits by children against parents for abuse, neglect and abandonment. *Rutgers L.Rev.*, **34**, 154-188.

²⁹⁴ *CP (A Child) v Criminal Injuries Compensation Authority [2015] 2 W.L.R.* 463.

²⁹⁵ McCullough L.B., Chervenak, F.A. *Ethics in Obstetrics And Gynecology*. New York, OUP, 1994.

²⁹⁶ See, for example, Fletcher J.C. (1981) The foetus as patient; ethical issues. *J.Am.Med.Ass.*, **246**, 772-773; Mahoney, M.J. (1989). The foetus as patient. *West.J.Med.* **150**, 459-460; Murray, T.H. (1987). Moral obligations to the not-yet born: the foetus as patient. *Clin.Perinatology*, **14**, 329-343.

²⁹⁷ Lenow, J.L. (1983) The foetus as a patient: emerging rights as a person? *Am.J.Law Med.*, **9**, 1-29; American College of Obstetricians and Gynecologists. Committee on Ethics. *Patient Choice: Maternal-Fetal Conflict*. Washington, D.C. American College of Obstetricians and Gynecologists, 1987; American Academy of Pediatrics Committee on Bioethics. (1988). Fetal therapy: ethical considerations. *Pediatrics*, **81**, 898-899.

circumstances, they argued, created a dependent moral status of the foetus - dependent upon the pregnant woman's intent to deliver a child. Chervenak and McCullough went further: "The physician will sometimes have beneficence-based obligations to the fetal patient that will require recommendations of clinical management that puts the pregnant woman's health at risk".²⁹⁸ Despite repeated assertions regarding the autonomy of the pregnant patient, they also comment that "conflict between the physician's recommendation and a pregnant woman's autonomous decision to the contrary..... is best managed preventively through informed consent as an ongoing dialogue throughout the pregnancy, augmented as necessary by negotiation and respectful persuasion".²⁹⁹ The last phrase is reminiscent of the 'waiver theory' and carries an undertone of 'doctor knows best' in its wording, perhaps reflecting an earlier article by the same authors.³⁰⁰ Therefore, in this model, the foetus becomes the primary consideration, possibly at the pregnant woman's expense - another construction of Kamm's theory. Chervenak and McCullough have not attempted to apply their model to a planned abortion setting; presumably, the foetus in such cases would not be the intended beneficiary of any medical intervention.

The original model was constructed to apply to the practice of medicine. Subsequently, they developed the model,³⁰¹ defining additional criteria applicable to clinical trials of potential new drugs during pregnancy, which, when satisfied, would not violate the beneficence-based obligations they had proposed were owed to the foetal patient. These criteria were:

- a) That the investigational drug was reliably predicted to alter the course of the condition for which the pregnant woman sought treatment.
- b) That previous animal or human studies did not report "documented death or documented serious, far-reaching, and irreversible injury of any major organ system".
- c) The third set out the same requirement as b) for the foetus.

²⁹⁸ McCullough, L. B., Chervenak, F.A. (2008). Response to commentaries on "A critical analysis of the concept and discourse of 'unborn child.'" *Am.J.Bioethics*, **8**, W4-W6.

²⁹⁹ Chervenak, F.A., McCullough, L.B. (1995) What is obstetric ethics? *J.Perinat.Med.*, **23**, 331-341 at p335.

³⁰⁰ Chervenak, F.A., McCullough, L.B. (1991) Legal intervention during pregnancy. *J.Am.Med.Ass.*, **265**, 1953-1953.

³⁰¹ McCullough, L.B. Coverdale, J.H. Chervenak, F.A. (2005) A comprehensive ethical framework for responsibly designing and conducting pharmacologic research that involves pregnant women. *Am.J.Obs.Gyn.*, **193**, 901-907.

- d) That previous animal and/or human studies reported no or very low documented risk of less serious injury to the foetal patient.

Whilst appearing to be a reasonable, cautious approach which seeks to set standards of protection for the foetus - which the last three criteria will in part achieve - the extension of the model to clinical trials is open to a number of criticisms.

The first criterion in the model is at variance with the requirement for clinical equipoise inherent in all clinical trials; if a drug can reliably change a condition, then the trial is not required, and so is ethically unjustifiable. This criterion also precludes one of the types of studies which will generate the information the EMA and FDA are seeking - non-therapeutic pharmacokinetic studies - which will provide the societal benefit which ethically justifies their conduct. Whilst the drug may reliably change the condition for which the pregnant woman sought treatment in non-pregnant adults, including women, the research question is whether it also does so in pregnant women despite the pregnancy-related changes in renal, hepatic and other functions. A second question, regardless of the answer to the first but which cannot be disconnected from it, relates to the impact of the drug on the foetus. The first criterion is, therefore, not attainable.

Although ostensibly attractive, the reliance of the other three criteria on animal studies may be misleading. Whilst, with one exception, every drug since thalidomide which has been found to be teratogenic in humans has caused similar teratogenic effects in animals, the converse is not true. The literature contains many examples of drugs which express teratogenic effects in animals exposed to high doses but which are not teratogenic at clinically-relevant doses in humans, or in animals exposed to doses producing plasma concentrations which are therapeutic in humans.³⁰² The criteria disregard the impact of untreated disease morbidity on maternal and, critically here, foetal safety.³⁰³ Viewing the first three criteria, but considering the disease rather than the investigational drug, the underlying disease may be known to alter the course of a pregnant woman's condition to the detriment of the foetus, previous animal or human studies of the disease may have reported "documented death or documented serious, far-reaching, and irreversible injury of any major organ system to the pregnant woman", or, indeed, the foetus, and the disease may be foetotoxic. If the risks to pregnant woman and foetus associated with the disease

³⁰² Koren, G; Pastuszak, A; Ito, S. (1998). Drugs in pregnancy. *N.Engl.J.Med.*, **338**, 1128-1137.

³⁰³ Shivakumar, G., Inrig, S., Sadler, J.Z. (2011). Community, constituency, and morbidity: applying Chervenak and McCullough's criteria. *Am.J.Bioethics*, **11**, 57-60.

are minimal, then perhaps the ethical arguments for exposing the foetus to an investigational drug need to be more compelling than those associated with an illness which may have catastrophic consequences for either. The model makes no allowance for such considerations.

The reference to human safety data may also be deceptive. Congenital defects may occur in 5% of all births, and defects attributable to drug therapy represent about 1% of congenital defects of known aetiology.³⁰⁴ Based on these figures, a drug-related congenital abnormality will arise in 1 in 2,000 births. Thus, if a drug has been taken by a large number of pregnant women, a small number of reports of abnormalities may reflect the spontaneous occurrence of malformations in the general population, whereas if a drug has been taken by a small number of women, a low-incidence teratogenic effect may not have been recognised. Given the Agencies' requests for such data prior to first approval, it seems unlikely that sufficient information can be accrued clinically to satisfy this criterion.

4.4.4 Criticisms of the 'two-patient' Models

The 'two-patient' models seem to increase foetal protection by according a level of moral standing which may equal or exceed that of the woman carrying it.³⁰⁵ The proponents of these models appear to believe that the maximisation of the prospect of healthy children being born is achieved when the primary responsibility for foetal care is removed from pregnant women and replaced by appropriate medical and legal interventions. No doubt, in some cases, this will be correct.

However, all 'two-patient' models are open to criticism. The most obvious are that the foetus is not an independent patient in practice since the foetus cannot be treated without the pregnant woman's body being affected,³⁰⁶ and that the model fails to recognise the autonomy-based freedom she has to decide upon alternative courses of treatment based on her own values and beliefs.³⁰⁷ Annas has commented that 'two-patient' models risk treating the pregnant woman as a "fetal container, a nonperson without rights to bodily

³⁰⁴ De Santis, M., Straface, G., Carducci, B., *et al*(2004). Risk of drug-induced congenital defects.

Eur.J.Obs.Gyn.Repro.Biol., **117**,10–19.

³⁰⁵ Lyerly, A. D., Little, M.O., Faden, R. (2008) A critique of the foetus as patient. *Am.J.Bioethics* **8**, 42–44.

³⁰⁶ Dickens, B.M., Cook, R.J. (2003). Ethical and legal approaches to 'the fetal patient'. *Int.J.Gyn.Obs.*, **83**, 85–91.

³⁰⁷ Oduncu, F.S., Kimmig, R., Hepp, H., *et al.* (2003). Cancer in pregnancy: maternal-fetal conflict. *J.Cancer Res.Clin.Oncol.*, **129**, 133-146.

integrity”.³⁰⁸ Strong,³⁰⁹ citing Warren,³¹⁰ argues that while role-related obligations that physicians have toward their patients are special obligations, this does not require the ascription of moral status to the foetus; actions that would unjustifiably harm a future child should be avoided on the basis of the ethical obligations owed to the future child - a position which aligns with Gillon’s arguments 25 years earlier. Whilst the majority of the proponents of ‘two patient’ models have been American, the American medical community takes a different view: the American College of Obstetricians and Gynecologists has advocated the development of a “framework that instead defines the professional ethical obligations with a deep sensitivity to relationships of interdependency (which) may help to avoid the distorting influence of the ‘two-patient’ model as traditionally understood”,³¹¹ but has yet to propose such a framework.

The reliance upon access *via* the woman’s body where she has decided not to seek a termination of pregnancy is surely a reflection of the foetus’ dependent status; if its continued survival depends on treatment, the foetus remains dependent upon the pregnant woman granting such access. The logical consequence of viewing the foetus as an independent ‘patient’ is a reduction, possibly a complete loss, of the pregnant woman’s autonomy, the same point raised by Annas. In addition, all of these authors overlook the morally and legally important distinction between patients and research participants, to whom practitioners and researchers have different obligations; this will be discussed more extensively in Chapter 5.

Wild has suggested that the concept of a maternal-foetal ‘double unit’, i.e., ‘dyad’, as proposed by Mattingley and others, means it is inappropriate to individualise the foetus, as that focusses on potential foetal harm whilst neglecting the harmful consequences the intervention, or lack thereof, may have for the pregnant woman.³¹² She invokes MacKenzie’s argument that, having elected to assume parental responsibility for the foetus’s future well-being by not aborting it, the foetus thereby gains moral significance by virtue of its relationship with the pregnant woman and that it is the researchers’ duty to

³⁰⁸ Annas, G. J. (1987). Protecting the liberty of pregnant patients. *N.Engl.J.Med.*, **316**, 1213–1214.

³⁰⁹ Strong, C. (2011). Moral status and the fetus: continuation of a dialogue. *Am.J.Bioethics*, **11**, 52-54.

³¹⁰ Warren, M.A. *Moral status: Obligations to persons and other living things*. New York, OUP, 1997.

³¹¹ American College of Obstetricians and Gynecologists. (2005). Maternal decision making, ethics, and the law. ACOG Committee Opinion No. 321. *Obs.Gyn.*, **106**, 1127–1137.

³¹² Wild, V. (2007). How are pregnant women vulnerable research participants? *Int.J.Fem.App.Bioethics*, **5**, 82-104.

respect this and to care for the foetus's well-being.³¹³ Wild proposes that investigators in trials involving pregnant women must consider them in this way, i.e., neither only as a woman nor only as a foetus, nor as two separate units, as an adverse impact of the trial on one party will, inevitably, have an adverse impact, albeit possibly of a different type, on the other. Based upon this approach, arguably, the act of participating in clinical research results in an expanded medical obligation to care for the foetus.

4.5 The Limited Relevance of the Abortion Debate

Much of the debate regarding the legislation and in the literature regarding the moral standing of the foetus is, of course, linked to the issue of abortion, and the moral basis, if any, upon which a foetus (or an embryo) can be 'killed'.³¹⁴ Despite the continually-expanding theological and philosophical literature on this subject, that debate is now deadlocked and seems likely to remain so; resolution would require an agreement on spiritual and philosophical values acceptable to all, which seems highly unlikely. As a simple illustration, even in those countries which have relatively conservative laws regarding abortion, most - but not all - make an exception in the case of pregnancy arising from rape or incest.³¹⁵ However, the foetus' 'right' to life is arguably independent of the circumstances in which it was conceived. Kaposy contends that the protagonists on both sides of the debate base their arguments on intuitions and analogies; as the latter rely on a shared standard of measurement for moral views which can be employed to develop consensus, an agreement, or even a compromise, seems highly unlikely because the different intuitions which lie behind any shared standards still exist. As a consequence, the extent of genuinely shared values in the abortion debate may be overstated.³¹⁶ Those who hold strong views seem likely to find challenging an impartial consideration of arguments relating to abortion, since such views are commonly connected to a range of other, central beliefs, and a contrary view, in a sense, threatens that wider base.³¹⁷ As Tooley captures

³¹³ Mackenzie, C. (1992). Abortion and embodiment. *Aust.J.Phil.* **70**, 136-155.

³¹⁴ See, for example, Tooley, M. (2013). Philosophy, critical thinking and 'after-birth abortion: why should the baby live?' *J.Med.Ethics*, **39**, 266-272; Harris J. *The Value of Life*. London: Routledge, 1985; Cox, D.R.A. (2014). The problems with utilitarian conceptions of personhood in the abortion debate. *J.Med. Ethics*, **37**, 318-320.

³¹⁵ Center for Reproductive Rights Factsheet *The World's Abortion Laws Map 2013 Update*, available at http://www.reproductiverights.org/sites/crr.civicactions.net/files/documents/AbortionMap_Factsheet_2013.pdf accessed 14th September, 2015.

³¹⁶ Kaposy, C. (2012) Two stalemates in the philosophical debate about abortion and why they cannot be resolved using analogical arguments. *Bioethics*, **26**, 84-92.

³¹⁷ Tooley, M. (2013). Philosophy, critical thinking and 'after-birth' abortion: why should the baby live?' *J.Med.Ethics*, **39**, 266-272.

the situation: if the moral standing of the foetus is such that abortion is wrong, but society considers that it is not, the result will be the unjustified killing of many innocent potential persons; conversely, if the moral standing of the foetus is such that abortion is not morally wrong, but society believes that it is and legislates accordingly, the result will be considerable suffering, and the deaths of many women. Thus, the potential impact of following a mistaken belief to its logical conclusion is high, which makes finding agreement across society even more challenging. Accordingly, whether foetuses have a moral standing which entitles them to protection in the sense of security from abortion has been neither convincingly established nor refuted. As a consequence, the debate regarding the morality of abortion is of limited relevance to the debate regarding the moral status of the foetus in other settings, although one might take the position that the apparent acceptance by many of the morality of abortion would suggest that the morality of involving pregnant women in clinical trials is less contentious.

The distinction in context is, however, a relevant one: there is a significant moral and legal difference between embarking upon a course of action with the intent of taking a life, such as deliberately driving a car at an individual, and taking action which results in taking life but without intending to do so, such as accidentally hitting an individual with a car as he steps from between parked vehicles. For some who hold 'pro-life' views, the former might be analogous to abortion, whereas the latter, perhaps, is more comparable to a clinical trial, in that an individual freely follows a course of action which creates a risk of causing death or injury, but where this is not the intention. The actions in the latter situation may be regarded as more or less morally (and legally) culpable depending on a number of factors such as the degree of avoidability of the injury, the utility of the activity causing injury and the rights and interests of others. So, in an attempt to 'benchmark' the moral status of the foetus in a clinical trial setting, a foetus at an early stage of gestation destined for abortion is not the most relevant selection, as the intent in such trials would be to avoid such a situation.

4.6 The Foetus and the Neonate as a Moral Continuum

By analogy with the normal development paradigm for new medicines in children (initial trials in adolescents, progressing to pre-teenage children, then to infants and lastly to

neonates, following a path from least to greatest risk),³¹⁸ it would seem likely that such trials might involve, initially, women in the third trimester of pregnancy - the same gestational age for the vast majority of premature neonates,³¹⁹ and so, broadly, of comparable viability, and, some will argue, of similar moral standing. A number of concepts, parameters and considerations have been explored or proposed as criteria upon which to establish the relative moral standing of the foetus and the neonate. The neonate certainly enjoys legal personality and few would contest it has significant moral standing. Clinical trials involving neonates are considered morally acceptable, and so a comparison of the moral standing of the neonate and, initially, the late-stage foetus is relevant.

Strong and Anderson³²⁰ have argued that the near-term foetus should be regarded as having the same moral status as persons, on the premise that the foetus and the neonate constitute a continuum, especially during the third trimester. At this stage of development the foetus is in most cases 'viable', i.e., capable of being supported technologically to the point of physiological independence (as defined in *C v S*³²¹), just like many newborn, particularly premature, infants.³²²: "The infant...has the same characteristics...as a foetus shortly before birth; the same size, shape, internal constitution, species membership, capacities, level of consciousness and so forth".³²³ However, if the (late-stage) foetus and the neonate represent a continuum, then the same is arguably true for the late-stage and the early-stage foetus:³²⁴ the same entity in the same location, and dependent for nourishment upon, and can be accessed for medical purposes only *via*, the pregnant woman. If viability is the key element underlying the claim for moral equivalence, the survival, albeit exceptionally, of a 22-week neonate³²⁵ surely suggests that the non-late-stage foetus may also be able to lay claim to the moral status of 'person'.

³¹⁸ See Mulberg, AE., Murphy, D., Dunne, J. *Pediatric Drug Development: Concepts and Applications*, 2nd Edition. Chichester, John Wiley & Sons Ltd, 2013

³¹⁹ 87% of premature births occur after week 32 of pregnancy; see Davidoff, M.J., Dias, T., Damus, K. (2006). Changes in the gestational age distribution among US. singleton births: impact on rates of late preterm birth, 1992 to 2002. *Sem.Perinatol.*, **30**,8-15.

³²⁰ Anderson, G., Strong, C. (1988). The premature breech: caesarean section or trial of labour? *J.Med.Ethics*, **14**, 18-24; Strong, C., Anderson, G. (1989). The moral status of the near-term foetus. *J.Med.Ethics*, **15**, 25-27.

³²¹ *C v S* [1988] 1 QB 135.

³²² Strong, C., Anderson, G. (1989). The moral status of the near-term foetus. *J.Med.Ethics*, **15**, 25-27.

³²³ Sumner, L.W. *Abortion and Moral Theory* New Jersey, Princeton University Press, 1981 at p.53.

³²⁴ See Eberl, J.T. (2008). The moral status of 'unborn children' without rights. *Am.J.Bioethics*, **8**, 44-46.

³²⁵ Cable, A. The tiniest survivor: How the 'miracle' baby born two weeks before the legal abortion limit clung to life against all odds. 22nd May, 2008. Available at <http://www.dailymail.co.uk/femail/article-1021034/The-tiniest-survivor-How-miracle-baby-born-weeks-legal-abortion-limit-clung-life-odds.html>, accessed 14th September, 2015.

Jensen,³²⁶ arguing that viability is the relevant criterion upon which to bestow moral status to the foetus, dismisses the fact of birth as relatively arbitrary, and contends that the extent of social responsiveness (one aspect of ‘personhood’) is so minimal as to lack sufficient moral relevance to distinguish the foetus from a newborn, suggesting that these two entities should enjoy the same moral status. Inevitably, a number of authors have contrasting views. Bermudez,³²⁷ for example, cites studies showing that, in contrast to foetuses, newborns possess primitive forms of self-awareness and self-knowledge sufficient to create a moral distinction; this he describes as his ‘Principle of Derived Moral Significance’, under which if a particular characteristic is a basis upon which to confer moral significance to a life, then a primitive form of that same characteristic also confers moral significance. Neonates obviously display features characteristic of basic consciousness but still need considerable maturation to reach the level of infant cognizance.³²⁸ Levy³²⁹ argues that newborns are capable of interacting with carers shortly after birth, a capacity not shared by the foetus. Perhaps the behavioural continuum between an infant and a neonate does, in fact, extend back into the womb, but we have yet to develop the techniques to detect it, although developing evidence suggests the foetus is able to show responses indicative of its capacity to experience pleasure and pain from around 18 weeks’ gestational age.³³⁰ In essence, these authors disagree upon the level of relevance which should be attached to the extent of interaction which a newborn can display, rather than attributing an intrinsic worth or value to it.

Gillon³³¹ criticises viability as a differentiator on the basis that it is reliant upon the skills and resources of others, contrasting foetal viability in a Third World village with that in a First World neonatal intensive care unit, and so cannot constitute a characteristic upon which to base the intrinsic moral status of the foetus; similar comments might be made regarding the actual time of birth as a differentiator. The vagaries of medical practice are also relevant here. As Gross captures the situation: “The same moderately malformed 25

³²⁶ Jensen, D. (2015). Birth, meaningful viability and abortion. *J.Med.Ethics*, **41**, 460–463.

³²⁷ Bermúdez, J.L. (1996). The moral significance of birth. *Ethics*, **106**, 378–403.

³²⁸ Lagercrantz, H., Changeux, J.P. (2009). The emergence of human consciousness: from fetal to neonatal life. *Ped.Res.*, **65**, 255-260.

³²⁹ Levy, N. (2013). The moral significance of being born. *J.Med.Ethics*, **39**, 326–329.

³³⁰ Bellieni, C.V., Buonocore, G. (2012). Is fetal pain a real evidence? *J.Matern.Fetal Neonatal Med.*, **25**,1203–1208; Glover, V., Fisk, N.M. (1999). Fetal pain: implications for research and practice. *Br.J.Obs.Gyn.*, **106**, 881–886; Anand, K.J.S. (2006). Fetal pain? *Pain Clin.Updates*, **14**, 1–7; Fisk, N.M., Gitau, R., Teixeira, *et al.* (2001). Effect of direct fetal opioid analgesia on fetal hormonal and hemodynamic stress response to intrauterine needling. *Anesthesiology*, **95**,828–835.

³³¹ Gillon R. (2001). Is there a ‘new ethics of abortion’? *J.Med.Ethics*, **27**, 5–9.

week old foetus might be aborted in Israel, delivered but not necessarily resuscitated in Denmark, resuscitated but not always treated aggressively in the UK and treated aggressively in the USA.”³³²

The descriptions of neonatal behaviours by Jensen, Bermudez and Levy lead to the concept of personhood, commonly associated with notions such as soul, mind, spirit or physical body³³³ and generally considered to require a variety of capacities together with a moral or normative status dependent on those capacities.³³⁴ It also includes the attributes of self-awareness, recognition and belief, i.e., the manner in which someone is treated by others is part of their being a person.³³⁵ This recognition can be both external and internal and can arise in a variety of ways, such as discourse, performance, context or relationships with other persons.³³⁶ Essentially, personhood entails how I am to myself, how I am to you/them/it and how you/them/it are to me - it is a description of multi-level interaction and recognition which entails sensory experience.³³⁷ If an individual has the moral status of personhood, then all moral agents have a *prima facie* obligation not to cause harm to that individual,³³⁸ although there are some clear legal exceptions to this.³³⁹ From a moral perspective, if the foetus is held to lack personhood, then its termination or injury in a clinical trial or otherwise cannot normally be described in terms of self-defence.³⁴⁰

Is the fact of birth itself morally relevant? Warren holds that birth is morally significant in that it marks the end of the totally-dependent relationship the foetus has upon the pregnant woman carrying it.³⁴¹ Technically, of course, she is correct that the newborn child is dependent for survival upon the assistance of others in a way which cannot be replicated

³³² Gross, M.L. (2002) Abortion and neonaticide: Ethics, practice and policy in four nations. *Bioethics*, **16**, 202-230.

³³³ For a thorough discussion of the concept of personhood, see Steinbock, B. *Life Before Birth*, 2nd Edn, Ney York, OUP, 2011.

³³⁴ Taylor, C. (1985) *Human Agency and Language: Philosophical Papers Vol. 1*. Cambridge: Cambridge University Press.

³³⁵ Dennet, D.C. *Conditions of Personhood*, in *Brainstorms: Philosophical Essays on Mind and Psychology*. Brighton: Harvester Press, 1981, pp.267-85; Laitinen, A, Ikaheimo, H. *Dimensions of Personhood*. Exeter: Imprint Academic, 2007.

³³⁶ Fowler, C. *The Archaeology of Personhood*. London: Routledge, 2004.

³³⁷ Harre, R. *The Singular Self*. London: Sage Publications, 1998.

³³⁸ Strong, C. (2011) Moral status and the foetus: continuation of a dialogue. *Am.J.Bioethics*, **11**, 52-54.

³³⁹ The common law has long held that one may use reasonable force to defend oneself. The Criminal Law Act 1967 confirmed reasonable force could be used in the prevention of crime. The Criminal Justice and Immigration Act 2008 effectively codified the law of self-defence. See also Kelly, G. (2006). Killing me softly: medical ethics and the death penalty in the United States. *MLJI*, **12**, 22-30.

³⁴⁰ An interesting construction of *quasi*-self-defence was developed in the tragic case of *In Re A (Children) (Conjoined Twins: Surgical Separation)* [2001] Fam. 147.

³⁴¹ Warren M.A. (1989). The moral significance of birth. *Hypatia*, **4**, 46-65.

whilst the foetus is *in utero*; witness the tragic case in Ireland in 2014, in which, despite all efforts to sustain the physiological functions of a brain-dead pregnant woman, the foetus could not be maintained to the point of viability.³⁴² However, some remarkable contrasting cases have been reported.³⁴³ Like Gillon, Warren's view seems to rely upon a technical, practical distinction rather than a moral one, which will vary according to the resources and skills available. However, she does, indirectly identify a break in the foetal-newborn continuum. Should a foetus sustain an injury, including within a clinical trial setting, then it can recover damages only upon live birth, when it becomes a neonate; legally, there is a break in the continuum at the point of live birth.

In one way, the seeming lack of a morally-relevant difference between neonates and the late-stage foetus is already accepted in the UK. The law recognises that, exceptionally, it is not in the best interests of a severely handicapped neonate to receive futile or burdensome treatment, and so treatment may be withdrawn or withheld, and the neonate allowed to die 'naturally',³⁴⁴ a situation somewhat analogous to the legally-permissible abortion of a late-stage foetus if there is a substantial risk that the resulting child would be seriously handicapped. Recent articles and newspaper coverage report the practice of not feeding severely disabled neonates.³⁴⁵ Once again, a certain moral equivalence is being created between a late-stage foetus and a neonate, although there is a significant legal difference between such a neonate being 'allowed to die' and a termination actively being conducted. Some will argue, following *Bland*,³⁴⁶ that such cases involve an omission – the omission to continue (i.e., withdrawal of) life-sustaining action, rather than an act – and so are distinguishable. This distinction is firmly embedded in the laws of the UK. As a generality, an act which causes the death of a person in being, and with the requisite intent, will constitute murder, whereas an omission to act will not,³⁴⁷ although this depends upon whether there is a duty to act. However, it is unlikely that clinical trials would be

³⁴² McDonald, H. Brain-dead pregnant woman's life support can be switched off, Irish court rules, 26th December, 2014. Available at <http://www.theguardian.com/world/2014/dec/26/ireland-court-rules-brain-dead-pregnant-womans-life-support-switched-off> accessed 14th September, 2015.

³⁴³ Bernstein, I.M., Watson, M., Simmonds, G.M. (1989). Maternal brain death and prolonged fetal survival. *Obs.Gyn.*, **74**, 434-437.

³⁴⁴ *Re C (a minor) (wardship: medical treatment)* [1989] All ER 782; *Re J (a minor) (wardship: medical treatment)* [1990] All ER 930.

³⁴⁵ See, for example, Hellmann, J., Williams, C, Ives-Baine, L., *et al.* (2013). Withdrawal of artificial nutrition and hydration in the Neonatal Intensive Care Unit: parental perspectives. *Arch.Dis.Child Fetal Neonatal Edn.*, **98**, F21–5; 11 Anonymous. (2012). How it feels to withdraw feeding from newborn babies. *Br.Med.J.*, **345**, e7319.

³⁴⁶ *Airedale NHS Trust v Bland* [1993] A.C. 789, [1993] 1 All ER 821.

³⁴⁷ *R v Reeves* [1839] 9 C.&P, 25.

considered ethically acceptable in severely handicapped neonates or in pregnant women known to be carrying foetuses at such risk. The fundamental principle of research, that of generating generalisable knowledge, seems unlikely to be realised in entities with an almost unlimited range of such conditions.

The existence of a universally-accepted moral distinction between the foetus and the neonate sufficient to influence the decision on the ethical standing of the foetus in clinical trials in pregnant women therefore remains elusive. The diversity of clinical practice and the variety of factors, including birth, held to be definitive by various authors means that, as is the case with abortion, attempts to define the moral standing of the foetus in relation to the neonate cannot be cogently defended or refuted to the satisfaction of all, and so seem of little help when seeking to establish a position regarding the acceptability of such trials.

However, none of these authors has argued that the moral status of the foetus is in any way greater than that of the neonate. The regulation of clinical trials will be discussed more extensively in Chapters 6 and 7, but for the present purpose it seems appropriate to touch on the topic here. Non-therapeutic trials in neonates are permissible if, using the language of the MHU Regulations 2004, the class of patients represented by the participant - other neonates - would be expected to derive benefit from the knowledge gained,³⁴⁸ i.e., a utilitarian approach, and it is not the intent of trials in pregnant women to confer a direct benefit to the foetus. Therefore, as far as the foetus is concerned, all of these trials should be regarded as non-therapeutic in nature and the question becomes one of whether foetuses as a class would benefit from the information generated. As mentioned earlier, improved control of maternal conditions can confer benefit to the foetus, and the anthrax example also resulted in the generation of information with the same potential. Provided the purpose of the trial in pregnant women is to generate generalisable knowledge which will benefit other foetuses, then subject to the usual safeguards and provisions for injury, there seems no reason not to consider such trials as being equally morally-acceptable in foetuses and neonates..

Despite our attempts to find a basis upon which to make a distinction, the words of the judge in an otherwise unremarkable case from New Zealand echo loud when he said

³⁴⁸ The Medicines for Human Use (Clinical Trials) Regulations 2004 (S.I. 1031), Part 4, paras 9, 10.

“[T]he rule according legal rights at birth is in modern times one founded on convenience. It does not rest on medical or moral principle”.³⁴⁹

4.7 The Foetus as a ‘Concomitant Condition’

In the studies of the types the Agencies have requested, the foetus is not the ‘subject’; the intent of the trial is not to assess the efficacy, safety or pharmacokinetics of the investigational drug for treatment or prevention of a condition affecting foetuses. The pregnant woman is the trial subject - the primary generator of the data sought - and the information generated is intended to be applicable to the treatment of the same conditions in other pregnant women in the future. Conceptually, such studies are similar to those carried out in patients with other co-existing conditions which may affect the properties of the investigational drug, such as those with renal or hepatic impairment; the investigational drug will not treat the condition, and the point of the study is to establish how the condition affects the properties of the drug. In other words, pregnancy may be regarded as a concomitant condition with the potential to affect the way in which the drug works upon the trial subject. To adopt a different level of risk acceptance in pregnant women as opposed to other adults based upon the existence of the foetus, not because it is an additional factor that might affect the action of the drug in pregnant women, but based upon its possible effects upon the foetus, would reflect the ‘two-patient’ model discussed previously. This is discussed further in Chapter 6.3.5.

That said, the review conducted by the REC should ensure that the risks of any trial are acceptable in the proposed target population, and the RECs would be failing in their responsibilities were they to approve a trial in pregnant women involving a drug believed to have foetotoxic or teratogenic effect - just as they would were they to approve a trial in neonates of a drug believed to carry a particular risk to that subject population.³⁵⁰

4.8 An Enduring Obligation to the Foetus in Research?

If the foetus is a ‘participant’, when do the resulting moral obligations cease? Some contend that researchers have an enduring duty to anticipate and prepare for emerging disclosure obligations to the mature person that the foetus is likely to become, for example,

³⁴⁹ *Harrild v Director of Proceedings* [2003] 3 NZLR 289

³⁵⁰ The classic example of this occurring is in “grey baby syndrome” seen with chloramphenicol; see Weiss, C.F.; Glazko, A.J.; Weston, J.K. (1960). Chloramphenicol in the newborn infant, *N.Engl.J.Med.*, **262**, 787–794. The REC and its processes are discussed more fully in Chapter 6.

emerging evidence that *in utero* exposure is associated with the development of a condition many years in the future (the diethylstilboestrol scenario) or, in these days of genetic testing, that later analyses of retained biological samples uncover the presence of a potentially fatal abnormality. In conventional medicine, approaches have been developed for dealing with such sensitive matters, and it would seem reasonable for the investigators' responsibilities to endure regarding the pregnant woman. After all, but for her autonomous decision to enter a clinical trial for which she received no payment, the trial sponsors would not have gained information which was potentially useful to them. However, the various maternal-foetal models and regulations are silent on this matter,³⁵¹ and the question of whether an individual can employ Freedom of Information legislation to recover information gathered when he was *in utero* has yet to come before the courts.

4.9 Conclusions

Most academic writers hold that the foetus *per se* has no intrinsic moral status - its moral status derives from the child, the person, it will become - but that we have moral duties *concerning* the foetus. These duties include a moral requirement not to harm the foetus intended for survival to term, hence the limitations of the applications of utilitarianism, consequentialism and Kamm's 'Principle of Permissible Harm'³⁵² to the conduct of clinical trials in pregnant women. Those same duties, in the views of most writers, do not extend to the foetus destined for abortion, and so the pregnant woman's autonomy to make such a decision is preserved. Even the proponents of the waiver theory restrict its application to the foetus intended for survival.

The strength of the claim by the foetus, and particularly the late-stage foetus, to enjoy 'moral standing' is, in many ways, as compelling as that of the neonate. With gestation periods extending from 153³⁵³ to over 300 days³⁵⁴ that leaves a period of approximately six months during which a potentially-viable foetus may remain *in utero*. While, of course, each case must be judged individually, it seems difficult to argue that two entities of

³⁵¹ Kipnis, K. (2011). Emergent obligations to the former fetal research subject. *Am.J.Bioethics*, **11**, 54-56.

³⁵² Kamm, F.M. *Intricate Ethics: Rights, Responsibilities and Permissible Harm*. Oxford: OUP, 2007.

Chapter 5: Toward the Essence of Nonconsequentialist Constraints on Harming.

³⁵³ Cable, A. The tiniest survivor: How the 'miracle' baby born two weeks before the legal abortion limit clung to life against all odds. 22nd May, 2008. Available at <http://www.dailymail.co.uk/femail/article-1021034/The-tiniest-survivor-How-miracle-baby-born-weeks-legal-abortion-limit-clung-life-odds.html>, accessed 14th September, 2015.

³⁵⁴ Groskop, V. I was pregnant for 10 months 1st October, 2010, available at <http://www.theguardian.com/lifeandstyle/2010/oct/01/pregnant-for-10-months> accessed 14th September, 2015.

precisely the same gestational age should be considered to be morally, as opposed to legally, different because one is delivered and the other is not, if the reason for that difference is not intrinsic, e.g., related to foetal maturation, but extrinsic, e.g., related to the level and availability of technical support at one hospital compared to the other.

The factors which influence the thinking of pregnant women, like everyone else, are many and varied. As a consequence, two pregnant women in ostensibly similar situations may make diametrically-opposed decisions upon whether to grant a foetus of a given gestational age a particular moral status. The moral status of the foetus is, therefore, not a constant, but has become an uncontrolled, and possibly uncontrollable, variable. However, if the pregnant woman is not to be the arbiter of moral status for her own foetus, and thus assume moral responsibility for its welfare, then who will be?

Although they may be unable to demonstrate the notions and concepts of personhood in ways we can understand and recognise, we can 'bestow' personhood upon foetuses or neonates by the way in which we interact with them, in much the same way that a pregnant woman bestows moral value to a foetus by her decision to continue, rather than terminate, her pregnancy. Accepting that a foetus has personhood would mean that its 'rights' and interests merit protection, and it could therefore be suggested that the pregnant woman's autonomy regarding medical intervention must be "subject to the interests of others (i.e., the foetus) whose needs those decisions directly impinge upon?".³⁵⁵ The exercise of autonomy is not unfettered; under the neighbour principle laid down in *Donoghue v Stevenson*,³⁵⁶ we can all be held liable for the consequences of negligent acts or omissions which adversely affect those whom we ought to have in our contemplation, and as explained above, those conducting clinical research (or medical treatment) in pregnant women ought to have the foetus in contemplation. This does not, however, mean that the 'needs' of the foetus outweigh those of the pregnant woman.

Medical research often involves risk which is undertaken for the benefit of others and clinical trials in pregnant women not intended to benefit the foetus will be categorised as non-therapeutic for the foetus. Under the MHU Regulations 2004, non-therapeutic clinical trials are acceptable in incompetent adults and minors as a carefully-controlled, risk-minimised method to accrue information which will help others in the future, provided the

³⁵⁵ Fovargue, S., Miola, J. (1998) Policing pregnancy: implications of the Attorney-General's Reference (No.3 of 1994). *Med.L.Rev.*, 6, 265-296.

³⁵⁶ *Donoghue v Stevenson* [1932] A.C. 562.

same information cannot be acquired from different populations *and* the trial will produce some benefit for the populations represented by the incompetent adult or minor.³⁵⁷ Proxy consent is acceptable in these circumstances. So, if the foetus was to be considered morally, rather than legally, as *incapax* or an extreme minor, given these same conditions, with the pregnant woman giving proxy permission, that would not be different to the current positions regarding the *incapax* and minors, assuming the appropriate prior deliberations of the REC. The information gained in these trials will be used to better manage maternal illnesses, some of which have the potential to harm the foetus. Defining an alternative study population from which the data would be as applicable is extremely challenging, as pregnancy is a unique condition.

Based on the arguments above, the conduct of clinical studies in pregnant women has many parallels to the conduct of studies in neonates, and, subject to the appropriate approvals, the latter is already considered morally acceptable. It seems difficult to identify a basis upon which to construct an argument that, morally, a pregnant woman cannot participate in a clinical trial, but a mother may give her permission for her newly-born child to do so. The majority of the medicines used in neonates, like pregnant women, have never formally been assessed in that population, and are employed ‘off-label’, i.e., at doses and for indications for which formal approval is lacking, and may never have been sought.³⁵⁸ Thus, non-therapeutic studies, to assess the pharmacokinetics of investigational drugs in pregnant women would be morally-justifiable, knowing that these parameters are often affected by the pregnant state.

Conceptually, the ‘one-patient’, ‘dyad’ and ‘two-patient’ models can all be contemplated within a clinical trial setting. Advocates of the ‘waiver theory’ would seem unlikely to volunteer for clinical trials; why would they subject the foetus to the unavoidable risk, unless they interpret the theory at a population level, i.e., the obligation is to avoid risk to the population of fetuses, rather than the specific foetus being carried? Similarly, proponents of the ‘two-patient’ model may be less likely to participate in the absence of assurance regarding benefit, or at best the absence of harm, to the foetus, which a properly-conducted consent process should manage. The decision and legal authority to participate

³⁵⁷ Statutory Instrument 1031, 2004; The Medicines for Human Use (Clinical Trials) Regulations, Part 4, ss.9-11

³⁵⁸ Laughon, M.M, Avant, D, Tripathi, N., *et al.* (2014). Drug labeling and exposure in neonates. *J.Am. Med.Assoc.Pediatrics*, **168**, 130-136; Allegaert, K., van den Anker, J.N. (2014). Clinical pharmacology in neonates: small size, huge variability. *Neonatology* **105**, 344-349.

in a trial rests entirely with the pregnant woman and her assessment of the risk:benefit ratio for herself and the foetus, which in turn is influenced by the degree of moral standing she imparts to the foetus. The assessment of the moral considerations regarding the trial *per se* will already have been undertaken by the REC, and the REC approval constitutes permission for the Investigator to ask potential subjects to apply their own judgement, including a moral assessment, to the trial in question. The Investigator, whilst not acting as a physician, remains under an obligation to minimise harm to trial subjects.³⁵⁹ One might reasonably construe that foetal harm would result in distress and anxiety for the pregnant woman, and so it seems likely that the Investigator would have the foetus in contemplation when considering the trial. The REC would presumably take into account any particular risks associated with gestational age in their conditional approval of the trial. One might speculate, for example, that a lower risk might be tolerated for a trial enrolling subjects in the first or second trimesters, as various drugs have demonstrated teratogenic activity in humans during these periods. However, identifying subsets of the target population at particular risk in this setting is no different to the deliberations of the REC for all trials, and the same is true of the Investigator's obligation.

Should a clinical trial proceed uneventfully, then, in effect, maternal-foetal model becomes a moot point; by consenting, the pregnant woman has made her decision for both herself and her foetus, and no reason has arisen to question that decision. In the event that an investigational drug elicited a response which put the foetus at risk, it seems likely that the 'stopping rules' included in all protocols would be invoked; trial subjects cannot insist upon continuing in a trial in violation of the protocol and/or contrary to the Investigator's medical judgment. If the trial subject is a proponent of the 'one-patient' model, having given her consent to the study, she may, of course, decline treatment to manage the emerging situation. Trial subjects whose beliefs are consistent with the 'dyad' model are in the same position, although it seems unlikely they would attempt to insist upon the trial continuing. Supporters of the 'two-patient' model may be more inclined towards foetal preference should an adverse event arise, but should have anticipated the situation as part of the consent process.

It seems unlikely that any form of clinical research involving pregnant women which disregarded the existence of the foetus would be considered as ethically-acceptable: a strict

³⁵⁹ The distinctions between the actions and responsibilities of an physician and an investigator are discussed in Chapter 5.

‘one-patient’ model is too far from current medical and ethical thinking, effectively categorising the foetus as ‘expendable’. Given the legal decisions reached after many decades regarding the ‘interests’ of the foetus and the child it will become, all of which were based on ethical considerations, such a model would not be morally-acceptable. So far as clinical trials of the types the Agencies have requested are concerned, given the intent is not to harm the foetus, it is implicit the foetus will be in the contemplation of all those involved.

The ‘two-patient’ model, taken to the point of two patients viewed as independent and equal also seems a poor model. The two patients clearly are not independent, nor are they ‘equal’, in the sense that, unless she is legally-incompetent, the pregnant woman’s permission is always required for any intervention to herself and her foetus, and no permission is required from the foetus. If the decision-maker is not to be the pregnant woman, then who would that be, and on what basis could another party make such decisions? Before consent can be sought, the REC and the regulatory authority, will already have approved the research protocol. Given the requirement for ‘special expertise’ within the REC specified in the new EU Regulation 536, approval means that specific consideration will already have been given to this population.³⁶⁰ Such approval allows Investigators, who cannot be compelled to conduct research with which they do not agree, to approach potential subjects to explore whether they wish to participate. Thus, four separate agreements (REC, regulatory authority, Investigator, subject) are already required before a pregnant woman may enrol into any form of medical research. Short of adopting a position that all research involving pregnant women is unethical and therefore not permissible, i.e., a return to the pre-1993 situation, it is not clear how a greater level of protection could be accorded to the foetus within the ‘two-patient’ model. While the latter position may protect an individual foetus from potential harm related to the research, the loss of the data such research would yield increases the risk to every foetus of harm resulting from inadequate treatment of the condition in pregnant women.

For medical research in general, including clinical trials of the types under consideration, the maternal-foetal ‘dyad’ - the one complex gravid female patient - seems the most appropriate model from a moral perspective at present. In this model, a balance is struck between the pregnant woman’s needs and interests (which could legitimately include

³⁶⁰ EU Regulation 536 is reviewed in Chapter 6.3.

considerations in addition to the foetus) and those of the foetus, with the fully-informed pregnant woman making the final choice. As explained above, the four agreements which need to be reached prior to enrolment of a pregnant woman into any clinical trial provide safeguards for the foetus which match those for any other trial participant. The consent process, discussed extensively in Chapter 6.4, allows the pregnant woman to decide whether to engage the degree of risk the REC, the regulatory authority and the Investigator have already considered as being acceptable, having taken into account the trial subjects being pregnant women. Should an adverse event occur, the Investigator would be obliged to seek the pregnant woman's permission before making an intervention directed at protecting the foetus, just as would be the case in conventional medical practice; unless the participant had given her permission prior to the trial, the Investigator may be restricted regarding the actions necessary to protect the foetus, regardless of the consequences for the pregnant woman.

Thus, the moral standing of the foetus is not compromised by the involvement of pregnant women in clinical trials, but quite the reverse: it is the moral status we have accorded to the foetus which requires us to conduct the appropriate clinical trials to ensure better treatment for both pregnant women and the foetus in the future.

Chapter 5 The Investigator-Subject Relationship

5.1 Introduction

In most clinical trials in the UK, with the exception of Phase I studies in healthy volunteers, the Investigator often is also the physician who is treating the patient for whichever condition she has that requires treatment. That means that the Investigator is using information he gained whilst acting as a physician to assess whether the patient is a candidate to become a clinical trial subject. If that assessment is positive, then he will approach the patient, most likely in a 'Doctor-Patient' setting, to discuss the trial. If the patient agrees to participate, he will then take her consent in an 'Investigator-Subject' setting. This suggests that the Doctor-Investigator status, like that of Patient-Subject, is a continuum; specific acts may fall within the purview of one part of the continuum, but are based upon information and circumstances drawn from across the whole continuum.³⁶¹ From this type of transaction, it is not clear whether the patient recognises that her status will change, as will that of the 'doctor', nor is it clear that the patient is told, or understands, the consequences of the changed relationship. The purpose of this chapter is to explore the nature of the Investigator-Subject relationship, as a prelude to discussing its significance for the prevention of harm (Chapter 6) or the recovery of compensation by the child in the event of congenital injury (Chapter 7).

5.2 A Contractual Relationship?

In the UK, it would be unusual for a formal contract to exist between trial subjects and the sponsor or Investigator, although this may in theory arise if the participant is a private patient of the Investigator. However, in a recent Scottish case - a rare example of a legal matter relating to a clinical trial being addressed in open court and reported - the court held that the Investigator-subject relationship may be contractual.³⁶² The patient information sheet constituted an offer, the signed consent form was the acceptance, and both parties enjoyed capacity to contract. The consent form described obligations to which the Investigator and the trial subject were each prepared to be bound, which taken together, amounted to sufficient certainty of terms (given that research is an inherently uncertain undertaking) and constituted consideration. The court appears not to have considered

³⁶¹ Habiba, M., Evans, M. (2002) The inter-role confidentiality conflict in recruitment for clinical research. *J.Med.Phil.*, 25:565-587.

³⁶² *Wylie v Grosset*, [2011] S.L.T. 609.

whether the parties intended to create a contractual relationship, nor the fact that the consent form will have contained a withdrawal clause, mandated by the MHU Regulations 2004, under which the subject was freely able to withdraw from the study at any time and without penalty, in effect making this a unilateral contract. As a lower-court case, this decision is not binding on any other courts, and may prove to be of historical interest only.

The term ‘contract’ was widely employed in clinical research until the development of the doctrine of ‘informed consent’. The concept of the document we now know as the ‘consent form’ was until then captured by the terms contracts, releases or waivers, perhaps indicating that such documents were intended more to protect the researchers than to protect or inform the participants. Capron has speculated that the term ‘contract’ may have served to relieve the researcher of liability when proceeding with what might have become unjustified research.³⁶³ With present-day trial approval processes, one would think that unjustified research would no longer be possible, at least in the UK. The legal status of the consent documents has been reviewed recently from a predominantly UK perspective, the conclusion being that consent is better seen as a continuing relational process rather than a contractual one.³⁶⁴ Thus, it would appear that subjects enrolled to clinical trials do not enjoy the protection of a formal contract, and, of course, the foetus lacks the capacity to enter into a contract.

5.3 A Fiduciary Relationship?

In the UK, the physician-patient relationship was long-held to be fiduciary:

“... according to the textbook writers, the physician-patient relationship remained an epitome of the fiduciary relationship well into this century.”³⁶⁵

This seems obvious: the physician has superior knowledge upon which the patient is dependent, and by attending appointments and accepting treatment, prescribed with the intent of alleviating illness in that particular patient, the patient is expressing confidence and trust in the physician. However, Lord Scarman’s comment in *Sidaway* indicates otherwise:

³⁶³ Capron, A.M. Legal and Regulatory Standards of Informed Consent in Research. In: The Oxford Textbook of Clinical Research Ethics. Ezekiel J. Emanuel, E.J., Grady, C.C., Crouch, R.A., Lie, R.K., Miller, F.G., Wendler, D.D. (Eds), Oxford, OUP, 2008, pp. 613-632

³⁶⁴ Laurie, G., Postan, E. (2013). Rhetoric or reality: what is the legal status of the consent form in health-related research? *Med.L.Rev.*, **21**, 371-414.

³⁶⁵ See Bartlett, P. (1997) Physicians as fiduciaries: equitable regulation of the physician-patient relationship. *Med.L.Rev.* **5**: 193-224.

“... there is no comparison to be made between the relationship of physician and patient with that of solicitor and client, trustee and *cestui qui* trust or other relationships treated in equity as of a fiduciary character.”³⁶⁶

Others have challenged this view. Brazier, for example, has questioned whether equity is too rigid to expand to fill the gaps resulting from the inflexibility of tort in the common law.³⁶⁷ In the absence of a fiduciary relationship, a subject inadequately informed regarding a clinical procedure but suffering no injury has (almost) no grounds for any form of recovery. Bartlett notes that physicians already owe their patients certain obligations of a *quasi*-fiduciary nature, confidentiality perhaps being the most obvious of these,³⁶⁸ and which have arisen because equity has recognised the dependency which exists within the doctor-patient relationship. As matters stand at present, in the UK the relationship between patient and physician is held not to be fiduciary in nature. In clinical research, there is even less agreement, and no applicable legal precedent in the UK, if one accepts that the doctor-patient relationship is different to that of Investigator-Subject. The basis for the differences between the relationships will be explained shortly.

Elsewhere in the Commonwealth, Australian law has recognised that the doctor-patient relationship has fiduciary aspects.³⁶⁹ In Canada, in *McInerney v MacDonald*,³⁷⁰ LaForest J. emphasised that fiduciary obligations are shaped by the demands of the situation (in this case the patient's right of access to the physician's medical notes, which had been denied on the basis of therapeutic privilege) and the presence of trust and loyalty were essential. Thus, we have little guidance from Commonwealth jurisdictions. Accordingly, it would appear that subjects enrolled to clinical trials in the UK do not enjoy the protection which would arise from a fiduciary relationship.

³⁶⁶ *Sidaway v Board of Governors of the Bethlem Royal Hospital* [1985] AC 871 at §884.

³⁶⁷ Brazier, M. (1987). Patient autonomy and consent to treatment: the role of the law? *Leg.Studies*, **7**, 169-193.

³⁶⁸ Bartlett, P. (1997). Doctors as fiduciaries: equitable regulation of the doctor-patient relationship. *Med.L.Rev.*, **5**, 193-224.

³⁶⁹ Faunce, T.A., Bolsin, S.N. (2005) Fiduciary disclosure of medical mistakes: the duty to promptly notify patients of adverse health care events. *J.Law Med.*, **12**: 478-482.

³⁷⁰ *McInerney v MacDonald* [1992] 93 D.L.R. (4th) 415, S.C.C.

Even in the USA, where the doctor-patient relationship is held to be fiduciary in law, the courts have commented that the concepts inherent in fiduciary relationships do not fit the research setting, and attempting to impose this would “pose a host of vexing issues”.³⁷¹

5.4 The Physician’s Duty to Minimise Harm?

In the UK, the GMC lists the first duty of a physician as that of making “the care of your patient your first concern”,³⁷² consistent with the Declaration of Helsinki, which includes the sentence “The health of my patient will be my first consideration”,³⁷³ and the ethical obligations of the Hippocratic Oath which include beneficence and non-maleficence.³⁷⁴ The GMC document advises the physician to “take prompt action if you think that patient safety, dignity or comfort is being compromised”. In a conventional medical setting, that will include providing the best treatment possible, tailoring the treatment regimen to the responses of, and discussing the course of treatment with, the patient.³⁷⁵

If the physician is also acting as the Investigator, some of these may be not possible. In a single-blind study, the treatment allocation is not known to the subject, and in a double-blind study, neither the subject nor the Investigator is aware of the treatment allocation. The protocol will normally stipulate the dose of the experimental medication, and the identity and dose of any active comparator, and may also require that the dose regimens for other medications are held constant throughout the trial. In such circumstances, the Investigator cannot ascertain that the best treatment possible is being provided or that the treatment is tailored to the subject’s responses, and is clearly limited regarding the extent of discussion which is possible, since neither party knows which treatment the subject is receiving. Indeed, in a double-blind trial, the Investigator may be prevented from reviewing any data generated which could result in unblinding, such as a particular change

³⁷¹ See Morreim, E.H. (2004) Litigation in clinical research: malpractice doctrines versus research realities. *J.Law Med.Ethics*, **32**, 474-484; *Suthers v Amgen*, [2005] WL 1349450 (S.D., NY, 2005) (denying preliminary injunction).

³⁷² General Medical Council. Duties of a Doctor, available at http://www.gmc-uk.org/mobile/duties_of_a_doctor, accessed 28th September, 2015.

³⁷³ World Medical Association’s Declaration of Helsinki. Ethical principles for medical research involving human subjects. Adopted by the 18th World Medical Assembly (WMA), Helsinki, Finland, June 1964, amended in 1975, 1983, 1898, 1996, 2000, 2002, 2004, 2008. See <http://www.wma.net/e/policy/pdf/17c.pdf>, for the current revision, accessed . 28th September, 2015.

³⁷⁴ Encyclopaedia Britannica, Hippocratic oath, available at <http://www.britannica.com/topic/Hippocratic-oath> , accessed 28th September, 2015: “I will follow that system of regimen which, according to my ability and judgement, I consider for the benefit of my patients, and abstain from whatever is deleterious and mischievous.”

³⁷⁵ General Medical Council. Duties of a Doctor, available at http://www.gmc-uk.org/mobile/duties_of_a_doctor, accessed 28th September, 2015.

in clinical chemistry, or the electrocardiogram. It seems difficult to reconcile such trial designs with the ‘best interest and ‘primary consideration’ stipulations in these two codes, and where the subject is necessarily exposed to possibly unquantifiable risks, as noted earlier, it seems difficult to see this as being with in a framework of best interests. Morreim,³⁷⁶ argues that the constraints on clinical freedom imposed by adhering to a protocol deprives the Investigator of the opportunity to ‘advise’ – an essential element of a fiduciary relationship in the USA, and relevant to recovery of damages in the UK.³⁷⁷ Moreover, since research, by definition, is not designed to benefit the individual participant, the Investigator cannot be considered as benefiting the patient by enrolling her into a research study.

But what are the patient’s ‘best interests’? As Wendler indicates, these may not be the best ‘medical’ interests, but a more holistic appreciation of the patient’s autonomy, e.g., by respecting the right of a Jehovah’s Witness to decline a blood transfusion,³⁷⁸ or the right of a pregnant woman to accept or decline a particular course of treatment based upon her appreciation of the potential impact on the foetus. The patient’s ability to exercise the right to self-determination is based upon a combination of personal beliefs and values and the information provided. The concept of therapeutic exception seems, potentially, to compromise the respect of autonomy, but as described above, information is also withheld in randomised clinical trials - a situation some have described as unethical.³⁷⁹ As discussed in the previous chapter, in the two-patient maternal-foetal model, the obligation to act in the ‘best interests’ of each patient individually will inevitably lead to conflict, and the need to choose which patient has primacy; as Wendler demonstrates, this is not a new situation for physicians - such choices are required in many settings.

Given that the option always exists for the subject to withdraw consent, or for the Investigator to discontinue the subject should the Investigator consider that to be medically-necessary, then the risk of harm is arguably under control. Provided the subject has given valid consent, and was aware that the response to the investigational drug could not be foreseen, the Investigator seems unlikely to stand accused of failing in his duties

³⁷⁶ Morreim, E.H. (2005). The clinical Investigator as fiduciary: discarding a misguided idea. *J.Law Med.Ethics*, **33**, 586-598.

³⁷⁷ This is discussed in Chapter 7.8.3

³⁷⁸ Wendler, D. (2010). Are physicians obligated always to act in the patient’s best interests? *J.Med.Ethics*, **36**, 66-70.

³⁷⁹ Rothman, K.J., Michels, K.B. (1994). The continuing unethical use of placebos. *N.Engl.J.Med.*, **331**, 394-398; Enkin, M.W. (2000). For and Against: Clinical equipoise and not the uncertainty principle is the moral underpinning of the randomized controlled trial: against. *BrMedJ.*, **321**, 757-8.

towards a patient. However, the constraints of a clinical trial are such that the Investigator is effectively precluded from discharging the ‘first concern’ or ‘first consideration’ behaviours defined in the GMC Guidelines and the Declaration of Helsinki, respectively.

Miller has argued that the differences between the aims of the researcher and the treating physician do not have sufficient significance to justify deviating from the physician’s duty to act in the best interests of the patient.³⁸⁰ He also posits that,

“... patients enter relationships with physicians with the reasonable expectation that their physicians’ recommendations always will be consistent with, and indeed intended to promote, their best interests”.³⁸¹

Veatch goes further, suggesting that the duties of physicians of the future will be required to promote the ‘best interests’ of the patient as the patient, rather than the physician, sees these, due to the increasing ethical demands of patient’s rights including the right to the truth and to have autonomy respected.³⁸² The courts have wrestled with similar situations.³⁸³

The Code of Ethics of the American Medical Association states that “Within the patient-physician relationship, a physician is ethically required to use sound medical judgment, holding the best interests of the patient as paramount”.³⁸⁴ The Code also advises that “when a physician has treated or continues to treat a patient who is eligible to enrol as a subject in a clinical trial that the physician is conducting, the informed consent process must differentiate between the physician’s roles as clinician and investigator”,³⁸⁵ a construction which suggests that, although information may be drawn from a continuum, the response to it may be categorical.

³⁸⁰ Lemmens, T., Miller, P.B. (2002). Avoiding a Jekyll-and-Hyde approach to the ethics of clinical research and practice. *Am.J.Bioethics*, **2**, 14-17.

³⁸¹ Miller, P.B., Weijer, C. (2003). Rehabilitating equipoise. *Kennedy Inst.Ethics J.*, **13**, 93-118, at 110-11.

³⁸² Veatch, R.M. (2000). Doctor does not know best: Why in the new century physicians must stop trying to benefit patients. *J.Med.Phil.*, **25**, 701-725.

³⁸³ For a case in which the Court had to consider the question of treatment being against someone's best interests while that person at once lacks capacity but is fully aware of her situation. see Coggon, J. (2014). Anorexia nervosa, best interests, and the patient's human right to 'a wholesale overwhelming of her autonomy'. *A Local Authority v E* [2012] H.R.L.R. 29 Official Transcript.

³⁸⁴ American Medical Association Code of Medical Ethics, Opinion 10.015 - The Patient-Physician Relationship, available at <http://www.ama-assn.org/ama/pub/physician-resources/medical-ethics/code-medical-ethics/opinion10015.page>? accessed 28th September, 2015.

³⁸⁵ American Medical Association Code of Medical Ethics, Opinion 8.0315 - Managing Conflicts of Interest in the Conduct of Clinical Trials, available at <http://www.ama-assn.org/ama/pub/physician-resources/medical-ethics/code-medical-ethics/opinion80315.page> accessed 28th September, 2015.

5.5 Conclusions

If the relationship between the trial subject and the Investigator is neither contractual nor fiduciary, what is it? Is clinical research, including clinical trials, a largely utilitarian exercise, in which the investigational subjects are merely a means to an end? Early research ethics philosophers such as Jonas³⁸⁶ and Donagan³⁸⁷ disputed such views of clinical research. Jonas did not accept that the justification for clinical research lay in its capacity to advance the common good of the community, or that risks which were not offset by benefits to individual trial participants were reasonable only if they were sufficiently offset by wider gains in knowledge.³⁸⁸ Kant held an essentially similar view: because humans are rational beings, each human deserves respect - which means being able to set his own goals and being treated as an end in and of himself, and not merely a means toward fulfilling others' goals.³⁸⁹

The current position in the UK appears to be that the subjects in clinical trials have neither fiduciary nor contractual relationships upon which to base their relationship with anyone. The only relationship which they seem to have is a common law one with the Investigator.

In the event that the Investigator is not the subject's physician, e.g., in a Phase I trial, the Investigator's primary responsibility remains that of conducting research that contributes to generalisable knowledge while protecting the rights and welfare of human participants.³⁹⁰ The subject is not the Investigator's patient, and therefore the Investigator does not bear the responsibilities of the physician responsible for the patient's care. In that circumstance, the Investigator's responsibility is that of minimising risk to trial subjects, and informing the physicians responsible for the subjects' care of any study emergent findings which may require further medical investigation.

Overall, this seems somewhat unsatisfactory. These patients are exposing themselves to risk, from which they may receive no advantage, for the benefit of other, future patients, the Investigator and his employer (who will be paid by the trial sponsor for the work done

³⁸⁶ Jonas, H. (1969). Philosophical reflections on experimenting with human subjects. *Daedalus*, **98**, 219–247.

³⁸⁷ Donagan, A. (1977). Informed consent in therapy and experimentation. *J.Med.Phil.*, **2**, 318–329, cited in London, A.J. (2007). Two dogmas of research ethics and the integrative approach to human-subjects research. *J.Med.Phil.*, **32**, 99–116.

³⁸⁸ Jonas, H. Philosophical Reflections on Human Experimentation. In: Freund, P.A. *Experimentation with Human Subjects*. London: George Allen and Unwin; 1972, at p3.

³⁸⁹ Kant, I. *Groundwork of the metaphysics of morals*. Cambridge: Cambridge University Press. 1997..

³⁹⁰ International Conference on Harmonisation, Good Clinical Practice (ICH GCP), para 1.34.

in support of the trial), and the sponsor (who may reap the rewards of the investment made in the development programme should the investigational drug prove successful). The question of a moral duty to participate in research was explored in Chapter 4.4. However, it is unclear whether patients enrolled as trial subjects are aware that the obligation towards them, and their foetuses, has moved from that of providing the best care during the trial, for one, all or both, depending on the maternal-foetal model, to one of producing generalizable information. This change of relationship may be implicit in the consent process, but to ensure trial subjects truly understand the implications, perhaps a requirement to make this explicit is required. It is also unclear whether patients are made aware of the potential impacts on the scope for recovery of compensation by a child born injured (Chapter 7). Again, an explicit description as part of the consent process may be required.

Chapter 6 Foetal Protection within the Trial Approval Processes

6.1 Introduction

A key aspect of all clinical trials is that of avoiding harm to the participants. As outlined previously, the protection of participants in the clinical trial setting broadly falls into two categories, and the overarching question is: to what extent does and should the clinical trial process recognise the foetus and provide the same or similar protection? The first category to be considered, and the subject of this chapter, relates to preventing injury to the foetus. This concerns the processes which precede the administration of an investigational product to a pregnant woman within a clinical trial setting. It is perhaps more accurately expressed as reduction of risk to the foetus as complete prevention is probably unattainable. The second category, which will be addressed in the next chapter, relates to the mechanisms by which a child born injured following such a trial might recover damages.

In trials involving pregnant women, potentially two entities will be exposed to an investigational drug. As discussed in Chapter 4, as a society, we have moral duties *concerning* the foetus, and moral duties *to* the children they will become, such that future children should be in our contemplation. The law has recognised that children born injured as a result of harm inflicted *in utero* have a right to recover compensation, thereby recognising that a wrong has been done, and this was addressed in Chapter 2. The specific issue of whether the foetus should be considered as a trial participant is addressed in Chapter 6.3.1 and the processes relating to the recovery of compensation in the event of trial-related injury will be considered in Chapter 7. The processes by which clinical trials in pregnant women are approved take account of the existence of and minimise the risk of harm to the foetus are the subject of this chapter.

The prevention of harm comprises a number of elements: the review and approval process for proposed trials, the pregnant woman's consent and the implications which arise from that, and the legal nature of the Investigator-Subject relationship. Each of these will be considered in turn.

6.2 The Current Clinical Trial Review and Approval Process

In the UK, as in most countries, mutually-contingent and independent approvals of clinical trials from ethical and technical perspectives are required prior to the commencement of any trial-related activities. The series of conventions developed by countries, regions and

regulatory bodies from the late 1980s and intended to set standards for the conduct of pharmaceutical clinical trials is generally referred to as Good Clinical Practice (GCP). There are several GCP standards around the world, but specific standards evolved in Europe,³⁹¹ which culminated in the International Congress on Harmonisation (ICH) Guidelines. These have been in use since 1997, and were developed by European, US and Japanese regulators and industries.³⁹² The ICH Guidelines define the ethical and scientific quality standards for clinical trials,³⁹³ including chemical stability for the investigational drug, preclinical information, and the conduct and reporting of the trials themselves. ICH Guideline E6, which defines GCP, is particularly relevant, having been codified, and other Guidelines will be considered in Chapter 6.2.1.

A common legal framework for conducting clinical trials in the EU and providing a legal basis for compliance with GCP was established in 2001 *via* the Clinical Trials Directive (CTD).³⁹⁴ transposed into UK law as the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031; MHU Regulations).³⁹⁵ The CTD will be replaced by Regulation (EU) No 536/2014,³⁹⁶ now due to come into effect in 2018.

The current clinical trial approval process within the UK, like the CTD, stipulates no additional requirements regarding the conduct of clinical trials in pregnant women. This is in contrast to Regulation 536, which introduces requirements regarding trials in pregnant women; these will be discussed shortly.

The CTD created a legal requirement for pharmaceutical clinical trials to be designed, conducted, recorded and reported in accordance with GCP.³⁹⁷ Although not specifically

³⁹¹ See, for example Association of the British Pharmaceutical Industry. Guidelines on Good Clinical Research Practice. ABPI, 1988; Nordic Council on Medicine. Good Clinical Trial Practice: Nordic Guidelines. Nordic Council on Medicine, December 1989. (NLN Publication No 28); see also Good Clinical Practice for Trials on Medicinal Products in the European Community (III/3976/88), adopted May 1990, and Good Clinical Practice Directive 75/318/EEC as amended, available at http://ec.europa.eu/health/files/eudralex/vol-10/3cc1aen_en.pdf, accessed 19th September, 2015.

³⁹² ICH guideline: adopted in the EU by the CPMP (now CHMP) 135/95/EEC.

³⁹³ Directive 2001/20/EC of the European Parliament and of the Council Of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. Official Journal of the European Union. L 121, 1 May 2001, pp. 34-52.

³⁹⁴ Directive 2001/20/EC of the European Parliament and of the Council.

³⁹⁵ SI 2004/1031 as amended.

³⁹⁶ European Union. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. Official Journal of the European Union. L158, Vol. 57, 27 May 2014, pp. 1-76.

³⁹⁷ Directive 2001/20/EC, Article 1(2).

defined as the GCP standard within the CTD, the obvious standard for European clinical trials is ICH Guideline E6.³⁹⁸

A number of additional Directives affecting clinical trials have been introduced by the European Commission following the CTD. The most relevant one to this thesis is the Good Clinical Practice (GCP) Directive 2005/28/EC codified by Statutory Instrument 2006/1928, which strengthens the legal basis for requiring Member States to comply with the principles set out in the ICH E6 Guideline. The GCP Directive also stipulates retention periods for specific documents after trial completion by the Ethics Committees, sponsors and investigators. This has particular relevance for clinical trials in pregnant women, where iatrogenic injury to the foetus may not manifest in the child for a substantial period following the trial, and will be discussed in Chapters 7.2 and 7.3.

The GCP Directive also requires that all clinical trials must be conducted in accordance with the 1996 version of the Declaration of Helsinki, the set of ethical principles regarding human experimentation developed for the medical community by the World Medical Association. Although devoid of legal authority, the Declaration of Helsinki is widely regarded as the cornerstone document on human research ethics.³⁹⁹ This version of the Declaration distinguishes between research with potential for therapeutic effect in the subjects enrolled and research conducted for the greater good (i.e., the expansion of knowledge without the expectation of direct benefit to the subjects enrolled), which is also pertinent to the types of trials the regulatory authorities have requested be conducted in pregnant women.⁴⁰⁰ Thus, all clinical trials in the UK must be conducted according to the ICH E6 Guideline and the Declaration of Helsinki.

The approval procedure for clinical trials entails review by the relevant regulatory authority (RA) and by a Research Ethics Committee (REC), in both cases appertaining to the country in which the trial is intended to be conducted. Thus, multinational clinical trials require both REC and RA approvals from each country under consideration, and the roles of these bodies in the UK will next be considered.

³⁹⁸European Medicines Agency ICH Topic E 6 (R1) Guideline for Good Clinical Practice, available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002874.pdf accessed 15th September, 2015.

³⁹⁹World Medical Association Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects, available at <http://www.wma.net/en/30publications/10policies/b3/>, accessed 19th September, 2015.

⁴⁰⁰World Medical Association Declaration of Helsinki (amended 1975, 1983, 1989, 1996, 2000, 2002 and 2004). Ferney - Voltaire, France: World Medicinal Association.

6.2.1 Regulatory Approval

The RA for the UK is the Medicines and Healthcare products Regulatory Agency (MHRA). RA approval is currently required if the test article:

- a) is a substance or combination of substances presented as having properties for treating or preventing disease in human beings, or
- b) functions as a medicine, i.e., can it be administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action or to making a medical diagnosis, or
- c) is otherwise administered for a medicinal purpose.⁴⁰¹

Based upon these criteria, clinical trials of new drugs in pregnant women will invariably require MHRA approval. The MHRA assessment is limited to confirmation that the technical requirements have been met with regard to the duration of preclinical toxicology necessary to underwrite the proposed duration of treatment in humans, and that the analytical and stability data for the investigational substance meet the required standards.⁴⁰²

The MHRA is charged with undertaking a risk-benefit assessment according to the ICH guidelines.⁴⁰³ These guidelines, sixty in number, define the quality, safety and efficacy requirements for investigational medicinal products. A number of these guidelines specifically address reproductive toxicology,⁴⁰⁴ which is particularly relevant to the conduct of clinical trials in pregnant women. Guideline ICH M3 (R2) states (§11.4) “Before the inclusion of pregnant women in clinical trials, all female reproduction toxicity

⁴⁰¹ Medicines and Healthcare products Regulatory Agency. Clinical trials for medicines: apply for authorisation in the UK. 18 December 2014. Available at <https://www.gov.uk/guidance/clinical-trials-for-medicines-apply-for-authorisation-in-the-uk> accessed 19th September, 2015.

⁴⁰² Medicines and Healthcare products Regulatory Agency. Clinical trials for medicines: apply for authorisation in the UK. 18 December 2014. Available at <https://www.gov.uk/guidance/clinical-trials-for-medicines-apply-for-authorisation-in-the-uk> accessed 19th September, 2015.

⁴⁰³ International Conference on Harmonisation (ICH) Work Products ICH Guidelines, available at <http://www.ich.org/products/guidelines.html> accessed 19th September, 2015. adopted in the EU by the CPMP (now CHMP) 135/95/EEC.

⁴⁰⁴ ICH M3 (R2): Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals; June 2009; ICH S5 (R2) Guideline: Detection of toxicity to reproduction for medicinal products and toxicity to male fertility; June 1993; ICH S2B Guideline: Genotoxicity: a standard battery for genotoxicity testing for pharmaceuticals; July 1997. All of these are available on the ICH Website: <http://www.ich.org/home.html>, accessed 15th September, 2015.

studies [defined in Guideline ICH S5 (R2)] and the standard battery of genotoxicity tests [defined in Guideline ICH S2B] should be conducted. In addition, safety data from previous human exposure should be evaluated”.

The note to Guideline ICH S5 (R2) states (§1.1) states: “These guidelines are not mandatory rules; they are a starting point rather than an end point”. In fact, this is the status of all the ICH Guidelines, with the exception of ICH E6, which was codified by the MHU Regulations 2004.

The non-mandatory nature of ICH was highlighted by Gøtzsche, from his personal experience.⁴⁰⁵ He had requested to know the results of carcinogenicity studies relating to a long-term trial in which he was participating; it emerged these studies were being undertaken in parallel with the clinical trial of which he was part, and were not available when the request was made. The trial enrolled over 28,000 subjects with a planned treatment duration of at least three years before the results of the long term safety studies in animals were available. The sponsor explained that the decision had been taken with full agreement by global regulatory agencies based on the toxicology information available at that time, despite ICH Guideline S1A recommending that carcinogenicity studies should be performed for any pharmaceutical whose expected clinical use was continuous for at least six months.⁴⁰⁶

Thus, it would appear that the MHRA may not be obligated to require sponsors to execute the studies defined in the ICH Guidelines prior to approving proposed studies in pregnant women if the authority is of the opinion that the risk-benefit assessment is considered acceptable, and that such a decision need not be made known to potential trial subjects. If this is correct, it seems to connote potential risks to the foetus: the absence of this information, apparently, need not be made known to the pregnant woman, who is giving consent for her foetus to be exposed to an investigational drug. In the absence of a duty to provide such information, the failure to do so does not constitute a statutory breach, which may affect the recovery of compensation in the event a child is born injured. However, given the apparent challenges associated with establishing legal liability of the MHRA, which will be described in Chapter 7.7, an injured child’s prospects for recovery of

⁴⁰⁵ Gøtzsche, P.C. (2014). “Human guinea pig” asks for animal studies. *Br.Med.J.*, **349**, g6714.

⁴⁰⁶ International Conference on Harmonisation. Harmonised tripartite guideline. Need for carcinogenicity studies of pharmaceuticals S1A. 1995, available at www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S1A/Step4/S1A_Guideline.pdf accessed 15th September, 2015.

compensation do not appear high. Few potential subjects would be aware of these Guidelines, and if this information is not offered, most subjects would have no reason to request it.

The Authorities have the advantage of access to information not in the public domain which is contained within requests to conduct clinical trials relating to investigational drugs from many sponsors. Although the chemical structure of an investigational drug is normally patented, chemical structures normally comprise a variety of units, or moieties, and these moieties are commonly found across a wide range of drugs. Certain moieties within the structure of an investigational drug may have a suspected association with teratogenic or foetotoxic effect when they were contained within the structures of other investigational drugs. Should a new investigational drug contain such a moiety, it is unclear whether the RA is under an obligation to disclose such information to sponsors. It seems likely the authority would take such steps as were necessary to minimise the risk, either by requesting additional information, or suggesting to the sponsor additional tests which the authority considered to be pertinent (these may be the tests conducted by other sponsors which disclosed the suspected problem). However, should the authority fail to do this, it is unclear whether, in the event of a child being born injured, the RA would be held to have owed a duty to such a child upon which to base an action, because of the lack of a duty to disclose such information.

The reasons the MHRA has for not requiring the conduct of preclinical reproductive toxicology studies prior to approving a trial will be based upon a thorough, scientific risk:benefit analysis. This analysis may not be readily amenable to simplification sufficient for comprehension by an 'average' trial subject. So the inclusion these reasons may be of little relevance to the consent process, which will be discussed later in the chapter. However, consideration may be given to a system whereby the MHRA is required to document those reasons as part of a Registry of clinical trials in this population, which will be explained in Chapter 8.

The MHRA website contains reference to seven teratogenic substances, all widely-known from the published literature.⁴⁰⁷ The reproductive toxicology reports submitted by manufacturers within the Marketing Authorisation Application for a new drug contain a plethora of additional information which, being commercially-sensitive, is not normally

⁴⁰⁷ See <https://www.gov.uk/search?q=teratogen%2A&q=teratogenic> , accessed 15th September, 2015.

available under freedom of information legislation. Consideration should be given to a requirement for manufacturers to identify the moiety within the structure, rather than the structure itself, suspected of being the cause of such effects, and for those moieties to be assembled by the European Medicines Agency (see Chapter 1.1) into a publically-accessible database. Again, this is unlikely to be of direct relevance to potential study participants as part of the consent process, but the construction and maintenance of such a database may guide approvals for future investigational drugs, and be relevant in claims for damages.

6.2.2 Ethics Approval - the Research Ethics Committees

Currently over 80 RECs operate in the UK, comprising up to 18 members, one-third of whom are lay.⁴⁰⁸ National approval from a single REC is applicable to the whole of the UK, with additional approvals from NHS Research and Development (R&D) Committees at either a hospital or district level throughout the UK.⁴⁰⁹ Thus, a degree of local control is still exercised which should ensure that hospitals involved in clinical trials have the appropriate levels of resource to ensure subject safety and that resources are not preferentially diverted from non-study patients.

Historical examples demonstrate both the need for some means of ensuring that research participants are not mistreated and that regulatory frameworks alone do not always achieve this.⁴¹⁰ The best known illustrations are the Nazi⁴¹¹ and Japanese⁴¹² experiments during World War II; the Nuremberg Code of 1947⁴¹³ resulted from the Nazi atrocities. Post-war examples are generally less well-known and mostly involve the USA,⁴¹⁴ although reports

⁴⁰⁸ Health Research Authority National Health Service Research Ethics Committees, available at <http://www.hra.nhs.uk/about-the-hra/our-committees/research-ethics-committees-recs/> accessed 19th September, 2015.

⁴⁰⁹ National Institute for Health Research. Clinical Trials Toolkit. R&D Submission available at <http://www.ct-toolkit.ac.uk/routemap/r-and-d-submission> accessed 28th September, 2015.

⁴¹⁰ Vollman, J., Winnau, R. (1996). Informed consent in human experimentation before the Nuremberg Code. *Br.Med.J.*, **313**, 1445e7.

⁴¹¹ United States Holocaust Memorial Museum. The Doctors Trial: The Medical Case of the Subsequent Nuremberg Proceedings, available at <http://www.ushmm.org/research/physicians> accessed 28th September, 2015.

⁴¹² See, for example, McNeill, P.M. *The Ethics and Politics of Human Experimentation*. New York: Cambridge University Press; 1993, pp. 22-26.

⁴¹³ *Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No.10*: 181-182. Washington, D.C.: U.S Government Printing; 1949, available at https://www.loc.gov/rr/frd/Military_Law/pdf/NT_war-criminals_Vol-II.pdf accessed 28th September, 2015

⁴¹⁴ For examples from the USA, see Beecher, H.K. *Research and the Individual: Human Studies*. Boston: Little, Brown and Company; 1970, pp. 122-127 (Willowbrook State School, New York); Supreme Court of New York, Special Term, Kings County 42 Misc. 2d 427; 248 N.Y.S. 2d 245; 1964 (Jewish Chronic Disease Hospital, New York); The Center for Disease Control and Prevention, Tuskegee site:

suggest that unethical trials may still be conducted in many, particularly third-world, countries.⁴¹⁵ In the UK, few examples of clinical trials subsequently considered as ethically questionable have emerged, although the conduct of clinical research more broadly has been criticised.⁴¹⁶ The behaviour of a small number of Investigators has resulted in appearances before the Disciplinary Committee of the General Medical Council (GMC), but these arguably represent individual failings rather than any attempt to execute an ‘improper’ clinical trial.⁴¹⁷

In the UK, the MHU Regulations 2004 placed RECs in the UK on a statutory basis for the first time. In common with many other member states in the EU, prior to the implementation of the MHU Regulations 2004, as a matter of law, it was not a legal requirement that all clinical research should be subject to prior ethical review. The role of the RECs in the UK is not to consider the quality of the science underlying the proposed trial (the province of the MHRA), nor of enforcing legislative compliance, but of ensuring that the proposed trial is ethically sound, safeguarding the rights, safety, dignity and well-being of research participants (independently of research sponsors), and assessing the balance between individual risks and benefits.⁴¹⁸ In short, the primary duty of RECs is to ensure that unavoidable risks are reasonable.⁴¹⁹

As part of the assessment of the ethical aspects of any clinical trial, the REC will wish to review all patient-oriented materials, including the information provided, the consent form, and any diaries or questionnaires which will be used. Consideration had previously been given to information disclosure and consent concerning research involving the foetus in the Polkinghorne Report (see Chapter 1.3), which stated: “The written consent of the mother must be obtained before any research or therapy involving the foetus or foetal tissue takes

<http://www.cdc.gov/nchstp/od/tuskegee/index.html> , accessed 28th September, 2015 (Tuskegee Experiment, Alabama); Fact Sheet on the 1946-1948 U.S. Public Health Service Sexually Transmitted Diseases (STD). Inoculation Study. United States Department of Health and Human Services. Accessed 28th September, 2015 (syphilis experiments conducted in Guatemala).

⁴¹⁵ See http://somo.nl/html/paginas/pdf/Examples_of_unethical_trials_nov_2006_NL.pdf, accessed....

⁴¹⁶ For a review, see Hazelgrove, J. (2002). The old faith and the new science. *Soc.Social Hist.Med.*, **15**, 109-135.

⁴¹⁷ For example, Gornall, J. (2008). Three physicians and a GMC prosecution. *Br.Med.J.*, **337**, a907; Dyer, C. (1996). GP struck off for fraud in drug trials. *Br.Med.J.* **312**, 798. See also Lock, S., Wells, F. (Eds). *Fraud and misconduct in medical research*. London: Br.Med.J., 1993.

⁴¹⁸ Savulescu, J., Hope, T. *Ethics of Research*. In: Skorupski, J. (Ed) *The Routledge Companion to Ethics*. Abingdon: Routledge, 2010, pp.781–95.

⁴¹⁹ Savulescu, J. (2002). Two deaths and two lessons: is it time to review the structure and function of Research Ethics Committees? *J.Med.Ethics*, **28**, 1–2.

place. Sufficient explanation should be offered to make the act of consent valid”.⁴²⁰ In the event that no data, either preclinical or clinical in nature, is available regarding experience of the investigational drug in pregnancy, that fact would routinely be included in both the information provided and the consent document. Whether a REC would consider approving a clinical trial in pregnant women in the absence of preclinical information is open to question, but there appears to be no legal impediment to the REC doing so. Analogous to the situation described above regarding the MHRA approval of clinical trials in the absence of ICH-specified information, this again suggests potential risk to the foetus; how many potential trial participants would be aware that the conduct of such studies was described in these Guidelines, and the relevance of the absence of such information? Given the apparent immunity to suit of the RECs which will be described in the next chapter, an injured child’s prospects for recovery of compensation do not appear high here either.

The REC will require assurance that the trial sponsor holds appropriate levels of insurance to meet the potential need to compensate subjects for trial-related injury. This will be affected by the introduction of Regulation 536, which requires the creation of a national system for providing compensation in the event of trial-related injury.⁴²¹ The REC is also required to ensure that payments to Investigators and NHS Trusts are reasonable and proportionate to the work involved,⁴²² which should ensure that resources are not diverted inappropriately from non-trial subjects, therefore ensuring that distributive justice is done.

Thus, the regulatory and ethics requirements provide complementary approaches intended to protect the interests of subjects recruited for clinical research purposes, and those of society by ensuring that investigational drugs are developed in a manner which supports reliance on trial data to establish whether such drugs merit approval. It would appear that both bodies may approve trials in the absence of information called for in relevant Guidelines without documenting their reasons for doing so. As will be discussed in Chapter 7, neither appears to owe a duty of care to trial participants which would allow injured subjects to recover compensation in the event of injury. This situation applies to all

⁴²⁰ Review of the Guidance on the Research Use of Foetuses and Foetal Material (Cmnd. 762) (Polkinghorne Committee Review) 1989, at para. 4.1.

⁴²¹ Regulation (EU) No 536/2014 of the European Parliament and of the Council, Chapter X11, Article 76, S.I., available at <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0536&from=EN>

⁴²² The Medicines for Human Use (Clinical Trials) Regulations 2004, S.I. 1031/2004, Part 3 §15(5)(j), Schedule 3, Part 1, §1(g)(4) and (5).

trial subjects, of course, but the implications which arise from this situation in trials involving pregnant women are clearly somewhat different.

6.3 The Future Ethics Process: Regulation (EU) No 536/2014

The CTD has been much-criticised,⁴²³ and following consultation the European Parliament Council enacted Regulation 536, which will replace the CTD. This includes a number of specific requirements relating to the REC assessment of clinical studies in pregnant women.⁴²⁴ The first, contained in the introductory part of Regulation 536 sets out a number of requirements, including: the need for specialist expertise in the assessment of clinical trials by the REC (§19), for specific protection measures (§27), and for specific provisions for the protection of pregnant and breastfeeding women participating in clinical trials and in particular when the clinical trial does not have the potential to produce results of direct benefit to her or to her embryo, foetus or child after birth (§34). These sections stipulate the same requirements for minors and incapacitated subjects.

Article 10 (Specific considerations for vulnerable populations) and Annex 1B7 (administrative requirements) also groups together the same three populations (paediatric; incapacitated; pregnant or breastfeeding women).

Article 33 is devoted entirely to clinical trials involving pregnant or breastfeeding women, and stipulates:

“A clinical trial on pregnant or breastfeeding women may be conducted only where
.... the following conditions are met:

(a) the clinical trial has the potential to produce a direct benefit for the pregnant or breastfeeding woman concerned, or her embryo, foetus or child after birth, outweighing the risks and burdens involved; or

(b) if such a clinical trial has no direct benefit for the pregnant or breastfeeding woman concerned, or her embryo, foetus or child after birth, it can be conducted only if:

⁴²³ See, for example, Cressey, D. (2009). European clinical trial rules under fire. *Nature*, doi:10.1038/news.2009.163, accessed 18th September, 2015.

⁴²⁴ See <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0536&from=EN> accessed 28th September, 2015.

- (i) a clinical trial of comparable effectiveness cannot be carried out on women who are not pregnant or breastfeeding;
 - (ii) the clinical trial contributes to the attainment of results capable of benefitting pregnant or breastfeeding women or other women in relation to reproduction or other embryos, fetuses or children; and
 - (iii) the clinical trial poses a minimal risk to, and imposes a minimal burden on, the pregnant or breastfeeding woman concerned, her embryo, foetus or child after birth;
- (c) where research is undertaken on breastfeeding women, particular care is taken to avoid any adverse impact on the health of the child; and
- (d) no incentives or financial inducements are given to the subject except for compensation for expenses and loss of earnings directly related to the participation in the clinical trial.”

The new EU Regulation should also address concerns regarding the adequacy of insurance coverage, as it charges member states with ensuring “...systems for compensation for any damage suffered by a subject resulting from participation in a clinical trial conducted on their territory are in place in the form of insurance, a guarantee, or a similar arrangement...”.⁴²⁵ Member states will be required to demonstrate proof of insurance cover or indemnification,⁴²⁶ by, for example, making clinical trials a compulsory class of insurance or by setting up a national insurance pool. The method of funding this provision is not specified, but a system of user fees might be the most equitable approach, with sponsors who conduct more trials and so, perhaps, creating the greater risk making greater contributions to the ‘pot’. However, the response to this requirement in Spain (see Chapter 8.4.1) suggests some countries may be concerned by the potential costs of such a scheme.

Following a 50-year period during which the intentional testing of potential new medicines in this population was practically unknown, and given the aims of both the major Agencies to collect data in this population (see Chapter 1.1), the specific recognition of this group is to be welcomed. The essence of the argument presented in Chapter 4 is that the holistic,

⁴²⁵ Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, Chapter XII, Article 76.

⁴²⁶ Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC Annex 1, o, 68.

maternal-foetal dyad is the most appropriate model to apply in the clinical trial setting, with the pregnant woman making decisions regarding accepting or declining treatment, which inevitably impact the foetus. The additional requirements for approval of studies in pregnant women introduced by Regulation 536 create a greater level of protection for the foetus than was the case previously, but also raise a number of issues concerning foetal status and the pregnant woman's rights which warrant further consideration.

6.3.1 Who is/are the Research Subject(s)?

Article 33(a) requires “direct benefit for the pregnant or breastfeeding woman concerned, or her embryo, foetus or child after birth”, which might be taken to imply that the research subject could be one or more of the entities listed, although the use of the possessive ‘her’ might suggest that the embryo, foetus and child after birth are not considered to be research subjects in their own right, but derivatively from the pregnant woman. The research subject has generally been considered in a one-patient model as the individual to whom the investigational drug is administered, and from whom data are collected. In most circumstances this would be the case, but as discussed in Chapter 4, a ‘one-patient’ model is not easily applicable to trials in pregnant women which may result in foetal exposure to the drug or its effects; even if the drug cannot cross the placenta, the pharmacological effects produced in the pregnant woman may indirectly affect the foetus. Although the requests from the Agencies relate to the way in which investigational drugs are handled within the bodies of pregnant women, the evaluation of the effects on the foetus would seem likely to be a secondary objective of all such trials; for example, it is not easy to conceive of trials in which the monitoring of foetal heart rate or the progression of pregnancy, to establish safety information, would not be standard. Given that the foetus will be exposed to the investigational drug or its effects, its potential harm but also benefit, and will provide information which will be relevant to the drug under investigation, why would the foetus not be considered as a trial participant?

The definition of a subject proposed in cluster randomised trials, in which the identity of the trial subject may vary depending on the study design, population, or intervention under investigation,⁴²⁷ seems apposite (emphasis added): “an individual **whose interests may be compromised** as a result of interventions in a research study”. This terminology is similar

⁴²⁷ See, for example, McRae, A.D., Weijer, C., Binik, A. *et al.* (2011). Who is the research subject in cluster randomized trials in health research? *Trials*, **12**, 183 -194.

to that used by Steinbock when considering the moral standing of the foetus (see Chapter 4.4.1). Although the foetus may not be considered as an ‘individual’, it is certainly conceivable that its interests may be ‘set back’ as a consequence of any drug given to a pregnant woman, regardless of whether or not she is participating in a clinical trial, which, in the absence of an intent to terminate the pregnancy, would, in the view of some commentators, confer a greater moral standing upon the foetus.

Of course, not all investigational drugs will cross the placenta, and the pharmacological action on the mother may not impact the foetus indirectly, therefore the foetus may not be exposed to the investigational drug, or its effects. However, data are likely still to be collected from and regarding the foetus, even if just to prove those points. If the foetus appears to be responding adversely to or following the investigational drug, it seems likely that the Investigator would take steps, or discuss with the pregnant woman the need to take steps, to manage the situation - just as would happen in any other clinical trial.

Taken together, the potential foetal exposure to the investigational drug or its effects on the pregnant woman, systematic data collection and medical response to adverse reaction are all suggestive of the foetus being *de facto* a trial participant.

6.3.2 The Requirement for Specific Expertise

The purpose of the ‘specific expertise’, which broadly requires scrutiny of the trial as part of the approval process by experts with some specific knowledge of the population, is not explained in the Regulation, and no guidance appears to have been issued regarding this. Article 10 (Specific Considerations for Vulnerable Populations) defines the basis upon which applications to conduct trials in these populations are to be assessed:

- pediatrics: “... paediatric expertise or after taking advice on clinical, ethical and psychosocial problems in the field of paediatrics”;
- the incapacitated: “... expertise in the relevant disease and the patient population concerned or after taking advice on clinical, ethical and psychosocial questions in the field of the relevant disease and the patient population concerned”;
- pregnant women: “... expertise in the relevant condition and the population represented by the subject concerned”.

The last is a less structured definition than the other categories. The expertise relates to the condition, but is that the condition from which the pregnant woman suffers or is it the condition of being pregnant? Does the subject represent the population of pregnant women, or pregnant women with the target disease, or those with the target disease regardless of pregnancy? If the trial under consideration is a Phase I pharmacokinetic study, one might consider expertise in clinical pharmacology rather than pregnancy to be the more useful expertise from one perspective, but the assessment of foetal safety may require obstetric expertise. Nevertheless, as we embark upon systematic studies in pregnant women for the first time, the requirement for specific expertise, however that may be construed, is to be welcomed, as it would be for any other patient group in the same situation.

The requirement for specific expertise indicates the presence of additional factors or considerations relating to these populations which differentiate them from the typical adult trial subject, i.e., that these are departures from the norm that justify special consideration. The next section will consider the extent to which additional factors are, or might be present, to justify clinical trials in pregnant women requiring additional consideration to those with the general population.

6.3.3 Pregnant women and fetuses as ‘vulnerable populations’

§§19 and 27, Article 10 and Annex 1B7 all identify the same populations - minors, the incapacitated and pregnant women - to be subject to additional conditions for conducting trials. As Table 1 illustrates, the specific articles dealing with these populations define identical conditions.

The reference to pregnant women as a vulnerable population under Article 10 is perplexing. The only other reference to a ‘vulnerable population’ in the Regulation appears in §15, which gives the examples of “frail or older people, people suffering from multiple chronic conditions, and people affected by mental health disorders”, but does not include minors, the incapacitated or pregnant women. Yet these three groups are categorised as special - and, under Article 10, vulnerable - populations. The Regulation thus lacks consistency in its reference to and categorisation of vulnerable populations

Table 1: Specific considerations in Regulation (EU) No 536/2014 for the conduct of clinical trials in pregnant women, minors and the incapacitated adults.

Population →	Pregnant Women	Minors	Incapacitated Adults
Additional Conditions ↓	Art. 33	Art. 32	Art. 31
Direct potential benefit to subject	(a)	1(g)(1)	1(g)(1)
Clinical trial of comparable effectiveness cannot be carried out on those not in this population	(b)(i)	1(e)	1(e)
No direct benefit to subjects, but potential benefit to others from the same population	(b)(ii)	1(f)	1(g)(ii)
Study imposes minimal risk and minimal burden	(b)(iii)	1(g)(i)	1(g)(ii)
No incentives or financial inducements are given to the subject	(d)	1(g)(ii)	1(d)

A common denominator for the three groups defined as ‘special populations’ is not obvious. It is not a lack of capacity to consent; the Regulation contains a stipulation for consent from the legally designated representative of minor and incapacitated subjects, but does not do so for pregnant women, confirming that pregnant women as a population are considered to have capacity to consent. If the rationale relates to the prospect that drugs will be handled differently by the body, that would potentially include the “frail or older people, people suffering from multiple chronic conditions” listed in §15, much of the paediatric population, and, as explained in Chapter 1.4, pregnant women, but would not generally apply to the incapacitated (Article 31) or “people affected by mental health disorders” (§15), and many other conditions will alter the pharmacokinetics of drugs in addition to the ones listed here.

One possibility is that the Regulation is bringing together, albeit imperfectly, those groups of patients who are considered as being vulnerable to exploitation, which would certainly include the *incapax*, minors, the frail and elderly, and - potentially - pregnant women

(discussed later in Chapter 6.4.3).⁴²⁸ The FDA considers all pregnant women as vulnerable.⁴²⁹ CIOMS⁴³⁰ describes the vulnerable are “Those who are relatively (or absolutely) incapable of protecting their own interests” as a result of “insufficient power, intelligence, education, resources, strength or other needed attributes.” This may, of course, be the case for some, but clearly not for all, pregnant women; the CIOMS Guideline explicitly supports the inclusion of pregnant women in clinical research, and does not categorise them as a vulnerable group.⁴³¹ This is consistent with the position taken by Beauchamp and Childress in their standard work: pregnant women as a class are not vulnerable, although some members of that class may be.⁴³² This interpretation is shared by others,⁴³³ one author describing the portrayal of pregnant women as vulnerable as ‘stereotyping and insulting’.⁴³⁴ In the UK, the legal definition of ‘vulnerable’ varies with circumstances; the Safeguarding Vulnerable Groups Act 2006, for example, defines a vulnerable adult in section 59(1)(d) as someone who is receiving any form of health care, which, arguably, could encompass all clinical trial participants..

However, if exploitation is the unifying concept amongst all the groups of patients identified in this regard in Regulation 536, the reason for including pregnant women may lie elsewhere: trials in pregnant women may be deemed to benefit from specific expertise as part of protecting the (future) interests of the foetus. As explained in Chapter 4, although lacking legal personality, the foetus is regarded as having ‘interests’ which

⁴²⁸ American College of Obstetrics and Gynecology. *Ethics in Obstetrics and Gynecology*, 2nd edn. Washington, DC: American College of Obstetrics and Gynecology, 2004; Hundley, V., Cheyne, H. (2004) The trials and tribulations of intrapartum studies. *Midwifery*, **20**, 27–36.

⁴²⁹ American College of Obstetrics and Gynecology. *Ethics in Obstetrics and Gynecology*, 2nd ed. Washington, DC: American College of Obstetrics and Gynecology, 2004; Hundley, V., Cheyne, H. (2004) The trials and tribulations of intrapartum studies. *Midwifery*, **20**, 27–36; U.S. Department of Health and Human Services. 21 CFR Parts 56 §107(a); §111(a)(3); §111(b)

⁴³⁰ The Council for International Organizations of Medical Sciences (CIOMS) - an international, non-governmental, non-profit organization established jointly by WHO and UNESCO in 1949

⁴³¹ CIOMS. *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. Geneva, 2002, available at http://www.cioms.ch/publications/layout_guide2002.pdf, Commentary on Guideline 16, accessed 28th September, 2015.

⁴³² B Beauchamp, T.L., Childress, J.F. *Principles of Biomedical Ethics*, 7th Edn. New York: OUP, 2013, pp.267-268.

⁴³³ See, for example, Schonfeld, T. (2013). The perils of protection: vulnerability and women in clinical research. *Theor.Med.Bioeth.*, **34**,189-206; , Kipnis, K. (2006). Vulnerability in research subjects: A bioethical taxonomy (research involving human participants V2). Online Ethics Center for Engineering and Science, National Academy of Engineering. Available at <http://www.onlineethics.org/CMS/research/resref/nbacindex/nbachindex/hkipnis.aspx> accessed 28th September, 2015; Luna, F. (2009). Elucidating the concept of vulnerability: Layers not labels. *Int.J.Fem.App.Bioethics*, **2**, 121-139; Coleman, C.H. (2009). Vulnerability as a regulatory category in human subject research. *J.Law Med.Ethics*, **37**, 12–18.

⁴³⁴ Hurst, S.A. (2008). Vulnerability in research and health care; describing the elephant in the room? *Bioethics*, **22**, 191-202;

become vested at birth,⁴³⁵ one of which is being born uninjured. Like minors and incapacitated adults, the foetus cannot represent its own present and future interests. The foetus is, so far as we know, unable to form an opinion, and so the decision to participate cannot be made on the same basis, i.e., presumed will, as would be the case for minors or the *incapax*. The Regulation creates provision for minors and incapacitated adults to be ‘represented’ by a relative or a close friend,⁴³⁶ as did the CTD.⁴³⁷ In the absence of a similar provision, it can be inferred that the ‘representative’ for the foetus must be intended to be the pregnant woman. This would seem reasonable; who else could it be, unless the pregnant woman is a minor or incapacitated, in which case alternate provisions would take effect? If this interpretation is correct, the Regulation is, arguably, creating a consistency across populations, including the foetus, unable to represent themselves, by requiring specific expertise to be brought to bear during the approval process. As a corollary, this would denote an implicit ‘two-patient’ model within Regulation 536.

The risks to the foetus may constitute an additional consideration regarding the overall safety of the trial, hence the need for ‘specific expertise’ when reviewing trials in this population. Pregnancy might pose additional risks to women, although the same would be true of a variety of conditions for which special expertise is not, apparently, required. It is tempting to suggest that, although many other circumstances which might make people vulnerable could have been included in §19, they are too varied to constitute a ‘population’, whereas defining populations such as minors, incapacitated adults and pregnant women as in Article 10 is more straightforward.

The interpretation above does not promulgate the notion that pregnant women *per se* are vulnerable in the sense of lacking decisional capacity; it supports and reinforces the autonomy of pregnant women to volunteer to participate in clinical trials as any competent adult could do, but only trials which have been approved after ‘specific expertise’ has been obtained, and the decision made, presumably, that foetal interests are not likely to be significantly adversely impacted by the trial. That said, this construction does not take account of the fact that embryos/foetuses are not specifically mentioned in §10 or §19, nor in Article 10, although it may be argued they are included by default once pregnant women

⁴³⁵ Scott, R. (2004). The English Fetus and the Right to Life. *Eur.J.Health Law*, **11**, 347-364

⁴³⁶ Regulation (EU) No 536/2014 of the European Parliament and of the Council, Chapter 1, Article 2, para 20.

⁴³⁷ Directive 2001/20/EC of the European Parliament and of the Council, Article 4 (minors), Article 5 (incapacitated adult).

are included as a population, and they are mentioned specifically in respect of assessment of potential benefits in Article 33 and §34.

The conceptual disadvantage of this construction is that, in contrast to the situation which would obtain for any other competent adult, potentially, the trials which are approved for pregnant women have already made an assessment of the potential risks to another entity - the foetus - and as a result restricted the studies in which pregnant women may participate. Again, this is indicative of a 'two-patient' model. The implications of this will be considered next.

6.3.4 RECs and Maternal-Foetal Models

If the foregoing is a correct interpretation, it leads to some intriguing implications regarding the maternal-foetal models. Clearly, the Regulation does not recognise the 'one-patient' model, in which the foetus is effectively disregarded. The absence of any change of the consent requirement (the consent of the pregnant woman alone is sufficient) is perhaps more supportive of the maternal-foetal dyad model than the 'two-patient' one, in that the decision-making remains exclusively with the pregnant woman, rather than any third party who might be identified to represent the foetus' interests, given that the foetus, clearly, cannot consent, and that pregnant women may be considered as having conflicts of interests when ascribing moral worth to the foetus (see Chapter 4.2).

However, if, as suggested above, one of the considerations of the REC is that foetal interests should not be adversely affected by the trial, this indicates a recognition of the two-patient model; the foetus is 'not nothing' and has interests separate from those of the pregnant woman, which may be affected by the trial.⁴³⁸ Article 33(b) addresses clinical trials which have no direct benefit for the pregnant woman or her embryo, foetus or child after birth, and stipulates at (b)(iii) that such trials may be conducted only if they pose "a minimal risk to, and imposes a minimal burden on, the pregnant ... woman concerned, her embryo, foetus or child after birth". Thus, it would appear that the RECs may be obliged to decline to approve a clinical trial which could generate information beneficial to pregnant women, because of the potential risk to the foetus. It also appears that, in contrast to trials involving non-pregnant competent adults, the voluntary burden pregnant women are permitted to carry may be limited by the REC. If this is the case, in effect the Regulation is recognising the 'two-patient' model, and requires potential benefits to one

⁴³⁸ Per Judge, LJ in *St George's Healthcare NHS Trust v S* [1998] 3 W.L.R. 936. at 45.

population to be subordinated to the risks of another, despite the foetus' lack of legal personality and the recognised autonomy of pregnant women. If this analysis is correct, then, arguably, the autonomy of pregnant women to participate in clinical trials is compromised because they are pregnant - but is that really a fair conclusion?

For reasons of commercial confidentiality, RECs rarely publish their decisions or the reasons for them, but it takes relatively little imagination to conceive of clinical research which could provide information which would be medically useful, but only by using methods which would be ethically unacceptable. Knowledge, although important, may be less important to a civilised society than the way in which it is obtained, and in entrusting such decisions to the RECs, we all are deemed to accept that our individual autonomy may be compromised for the sake of relational autonomy - our relationship with the rest of society. For this reason, any individual's freedom to take part in clinical trials is subordinated to the need to ensure that trials are considered to be ethically acceptable.

Under the CTD, the condition upon which the legal representative of an incapacitated adult or a minor may give permission for their inclusion in a trial was that it represented the subject's presumed will. This condition is absent in the Regulation,⁴³⁹ suggesting the view may have been taken that the legal representative, however well-intentioned, might not accurately represent the subject's presumed will, despite, in the case of minors, that representative usually being one or both parents. There are considerable difficulties in determining the presumed will of another, even where evidence of past views and wishes is available. In the absence of clear evidence that the individual has ever been able to turn his or her mind to the kinds of matters under consideration, these difficulties are profound and this would clearly be the case with a foetus. Nevertheless, additional safeguards to protect special groups are in place and these will have been considered before the person who is legally empowered to make the decision is asked to give consent, be that a minor's representative, an incapacitated person's representative, or the pregnant woman. So, if the earlier construction regarding the classification of the foetus as the vulnerable entity is correct, or at least that the risk to the foetus is an important factor, it suggests that, without explaining the premise upon which the decision has been reached, the European legislators have concluded (a) that the foetus deserves similar consideration in this respect as those with legal personality who are unable to consent for themselves, (b) that a common

⁴³⁹ Regulation (EU) No 536/2014 of the European Parliament and of the Council, Chapter 1, Article 2, para 20.

standard of ethics review will be applied to all these categories, and (c) the REC may limit the pregnant woman's choice more than any other competent adult to participate in a clinical trial. In doing so, this reduces the sovereignty of pregnant women to make decisions which impact their foetuses, and applies a prospective judgment regarding the balance of interests between a pregnant woman and her foetus.

The approach taken in Regulation 536 seems akin to the policy decision underlying the Congenital Disabilities (Civil Liability) Act (1976), which allowed children born injured to recover damages for injuries suffered *in utero* without attempting to resolve the apparent contradiction of the harmful behaviour taking place before the children had legal personality, and that no duty of care can be owed to a foetus; this is discussed further in Chapter 7. Regulation 536 similarly avoids resolving that issue by stipulating that if the potential risk to the foetus, or the burden upon the pregnant woman, is considered to be more than minimal (Article 33(b)(iii), it may constitute a basis upon which to refuse approval for a non-beneficial clinical trial to proceed. Under the 'dyad' model described in Chapter 4.4, the autonomy of the pregnant woman is unfettered; she decides the burden she will carry, and the extent of risk to which she is willing to expose her foetus. The European Commission, through Regulation 536, is effectively recognising a 'two-patient' model, and empowering the RECs to make the types of decisions which, under the 'dyad' model, the pregnant woman would make. The foetus seems to be considered as a trial participant in its own right, whose interests need to be protected; this will be examined shortly. Every section of Article 33 (Clinical trials on pregnant or breastfeeding women) which makes specific reference to pregnant women also makes specific reference to the foetus, perhaps suggesting that the two are considered as equivalent.

This aspect of Regulation 536 appears to offer a more consistent level of protection for the foetus than might be the case were the decisions to be left in the hands of individual RECs, Investigators and pregnant women, and from that perspective is also to be welcomed. Clinical trials in this population will certainly be seen as 'sensitive'; children will inevitably be born with injuries following but not necessarily related to such trials, which probably will elicit calls for such trials to cease. This would have the paradoxical, undesirable effect of increasing the risk of future iatrogenic injuries to both pregnant women and foetuses. The more that can be done to reduce weaknesses in the approval system for such trials, of which inconsistency would be one, the greater the prospect that calls for such trials to cease can be resisted.

If the foregoing analysis is correct, the criteria defined within Regulation must reduce the autonomy of pregnant women who volunteer to participate in such trials, and they may be seen as paternalistic. Pregnant women will be free to participate in trials which the RECs have considered meet the criteria defined in the Regulation, but they will never become aware of trials the RECs considered as unacceptable, so they will be oblivious to their autonomy having been compromised. The requirement for ‘specific expertise’ indicates that such trials raise complexities which the RECs would not usually face, so if the experienced members of RECs are deemed to require assistance, how much more difficult might it be to explain such complexities to the target population in such a way as to ensure consistency whilst maintaining ethically-acceptable levels of risk to which the foetus can be exposed? None of this is attractive, but more acceptable alternatives seem difficult to define, in a sense similar to the current position regarding pregnant women who drink to excess. (see Chapter 3.5). Perhaps like other situations involving the foetus, the ‘least detrimental option’ may be the best one, in this case the compromised autonomy of pregnant women.

6.3.5 Studies with no therapeutic benefit to the study population

The second issue raised by the parts of the Regulation specific to pregnant women relates to the study designs which, implicitly, are being contemplated. Article 33(b) permits the conduct of studies offering no therapeutic benefit, which represents a significant change in stance. As explained in Chapter 1, as part of the FDA-mandated exclusion of women of child-bearing potential from early-phase, i.e., Phases I and II, clinical trials in 1977, on the grounds that such trials held no prospect of benefit for the participants,⁴⁴⁰ a specific and narrow exemption was made for clinical trials in women with life-threatening conditions, i.e., a population in which a therapeutic benefit was sought for the most critical conditions. As explained in Chapter 1.3, no requirement or incentive existed in the UK to encourage the conduct of such trials. This new provision indicates that Phase I trials to assess the pharmacokinetics of investigational drugs are now considered legitimate in this population in a wider range of circumstances, albeit with the safeguard provided within Article 33(b)(iii), discussed above. A clinical trial of this type revealed the inadequacy of the

⁴⁴⁰ Department of Health and Human Services, US Food and Drug Administration (1977). General Considerations for the Evaluation of Drugs. Publication No. HEW (FDA). 88-3040 Washington D.C. Government Printing Office, 1977.

advice relating to anthrax prophylaxis;⁴⁴¹ the pregnant women enrolled to this study were healthy - they did not have anthrax. The new position is also consistent with the 1996 version of the Declaration of Helsinki, described earlier in this Chapter. The Regulation thus appears to have constructed a way to enable non-therapeutic studies to be undertaken in accordance with the ethical standards defined in the Declaration of Helsinki which will minimise the risk of harm to the foetus, albeit at the expense, to a degree, of the pregnant woman's autonomy.

6.4 Consent and Related Matters

In legal and ethical terms, the consent of an individual to participation in research is fundamental and there are few exceptions to this 'golden rule'. The requirement derives from the principle of autonomy, one of the pillars of medical ethics (autonomy, beneficence, non-maleficence and equality) described by Beauchamp and Childress.⁴⁴² The intent of the consent process is to ensure the patient or subject understands the purpose, benefits, risks, and other options regarding the treatment or the clinical trial. The assumption underpinning the doctrine of consent is that the process protects the rights, welfare and autonomy of individuals to make free and informed choices; it respects the patients' rights of self-determination, although O'Neill adopts a different perspective, suggesting that the function of consent is to limit deception or coercion.⁴⁴³ Despite ostensible resemblances in the issues raised, consent in the research setting has developed quite distinctly from consent for conventional treatment. In the UK, the latter is largely a product of common law, with some later statutory modifications. Consent to research has been shaped by professional codes, statutes and administrative regulations, with the courts playing, until now, a less formative role.

Issues relating to consent may arise, broadly, in two contexts. The first is the absence of consent. In conventional medicine, failure to obtain consent could give rise to civil claims

⁴⁴¹ Andrew MA, Easterling TR, Carr DB, *et al.* (2007). Amoxicillin pharmacokinetics in pregnant women: modeling and simulations of dosage strategies. *Clin. Pharmacol. Ther.*, **81**: 547-56; American College of Obstetricians and Gynecologists. Committee Opinion 268, February 2002. Management of asymptomatic pregnant or lactating women exposed to anthrax. *Obs.Gyn.* **99**, 366-368; Inglesby, T.V., *et al.* and for the Working Group on Civilian Biodefense (2002). Anthrax as a biological weapon, updated recommendations for management. *JAmMedAssoc.* **287**, 2236-2252. See Chapter 1.

⁴⁴² Beauchamp, T.L., Childress, J.F. *Principles of Biomedical Ethics*, 7th edn. 2012. OUP. Part II: Moral Principles.

⁴⁴³ O'Neill, O. (2003). Some limits of informed consent. *J.Med.Ethics*, **29**, 4-7.

for damages, for example, on the basis of assault and battery, or trespass to the person,⁴⁴⁴ and although untested in a UK court, there seems no reason to suggest this would not be the same in a research setting. Consent must be obtained from subjects prior to the conduct of any protocol-defined procedures not constituting normal medical care or investigation, including the collection of additional information. In the UK, failure to adhere to the principles of GCP, including these requirements for consent, constitutes a criminal offence under MHU 2004,⁴⁴⁵ the penalties for which include a fine and imprisonment.

The second context relates to the adequacy of the consent process, and in particular the information provided to the patient. Valid consent is predicated upon the adequacy of the information provided, with insufficient or inaccurate information providing the grounds for an action in negligence should anything untoward occur. For many years the standard for adequacy was that defined in *Bolam v Friern Hospital Management Committee*,⁴⁴⁶ based on the Scottish case of *Hunter v Hanley*,⁴⁴⁷ and was that which a reasonable doctor, as adjudged by a responsible body of medical opinion, would provide, i.e., the information the medical profession considered appropriate for a patient to know. One of the issues physicians were duty bound to consider, according to Lord Scarman, was whether the patient's best interests were served by withholding certain information - the notion of therapeutic privilege.⁴⁴⁸ Over succeeding years, *Bolam* was followed in many cases, although not without challenges, perhaps the most compelling of which were those in *Sidaway v Board of Governors of the Bethlem Royal Hospital*⁴⁴⁹ and *Pearce v United Bristol Healthcare NHS Trust*.⁴⁵⁰

In his dissenting judgment in *Sidaway*, Lord Scarman argued that the Bolam test should not be applied to the matter of consent; his opinion was that a physician should have a duty to inform the patient of the inherent and material risk of the treatment proposed to enable

⁴⁴⁴ Grubb, A., Laing, J., McHale, J. (Eds) *Principles of Medical Law*, 3rd Edn., Oxford: OUP, 2010, p1205. Cases confirming this in both the treatment and research contexts are: *Airedale NHS Trust v Bland* [1993] AC 789, [1993] 1 All ER 821; *Malette v Shulman* (Canadian) [1991] 2 Med.L.Rev. 162; *Re T (Adult: Refusal of Treatment)* [1993] Fam. 95; *Chatterton v Gerson* [1981] Q.B. 432; *Simms v Simms* [2003] Fam. 83.

⁴⁴⁵ The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), Part 8, Section 52.

⁴⁴⁶ *Bolam v Friern Hospital Management Committee* [1957], 2 All E.R. 118.

⁴⁴⁷ *Hunter v Hanley* [1955], SC 200.

⁴⁴⁸ Lord Scarman. (1987). Consent, communication and responsibility. *Arbitration*, **53**, 161-165. Lecture delivered to Forum on Medical Communication of the Royal Society of Medicine on 6 June 1985, when he would have been considering his judgment in *Sidaway*.

⁴⁴⁹ *Sidaway v Board of Governors of the Bethlem Royal Hospital* [1985] AC 871.

⁴⁵⁰ *Pearce v United Bristol Healthcare NHS Trust*, [1999] P.I.Q.R. P53.

an objective, reasonable, prudent patient to decide whether to proceed.⁴⁵¹ In *Pearce*, Lord Woolf MR, whilst applying *Bolam*, endorsed the ‘prudent patient’ standard described by Lord Scarman, although he concluded that the plaintiff in that case would have proceeded with the operation even had she been aware of the risk which subsequently materialised.⁴⁵²

The year before *Pearce*, in *Bolitho v City & Hackney Health Authority*⁴⁵³ the once-unthinkable question had been raised of whether that responsible body of opinion relied upon under *Bolam* might, in some cases, be neither reasonable nor responsible, and concluded that could - rarely - occur. In *Birch v University College London Hospital NHS Foundation Trust*,⁴⁵⁴ the court held that the duty to inform a patient of the risk of a particular procedure was sometimes discharged only if the patient was also made aware of an alternative procedure with fewer or no associated risks. The standard was moving to one of provision of information which a reasonable, prudent patient would expect, largely on the premise of patient autonomy.⁴⁵⁵ In *Montgomery v Lanarkshire Health Board*⁴⁵⁶ this movement progressed further, the Supreme Court holding that physicians were required to discuss all relevant options for treatment and associated risks with their patients, including those arising from the option of no treatment. The concept of therapeutic privilege remained, Lord Kerr warning that its use was “

not intended to subvert that principle (of the patient being provided with all the information he or she considered necessary to make the decision to proceed) by enabling the doctor to prevent the patient from making an informed choice which the doctor considers to be contrary to her best interests.”⁴⁵⁷

The test of materiality was whether, in the circumstances of the particular case, a reasonable person in the patient's position would be likely to attach significance to the risk, or the doctor is or should reasonably be aware that the particular patient would be likely to attach significance to it. The court also recognised that a patient could exercise a right not to receive such information. By reaching their judgment, the court brought the law on

⁴⁵¹ *Sidaway v Board of Governors of the Bethlem Royal Hospital* [1985] AC 871 at 887.

⁴⁵² *Pearce v United Bristol Healthcare NHS Trust*, [1999] P.I.Q.R. P53 at p58.

⁴⁵³ *Bolitho v City & Hackney Health Authority* [1997] 3 WLR 1151.

⁴⁵⁴ *Birch v University College London Hospital NHS Foundation Trust* [2008] EWHC 2237 (QB).

⁴⁵⁵ For a general discussion on how the law has developed since *Bolam*, see Brazier, M., Miola, J. (2000). Bye-Bye Bolam: a medical litigation revolution? *Med.L.Rev.*, 8, 85-114.

⁴⁵⁶ *Montgomery v Lanarkshire Health Board* [2015] UKSC 11.

⁴⁵⁷ *Montgomery v Lanarkshire Health Board* [2015] UKSC 11, at 91, *per* Lord Kerr at 91.

consent in a conventional medical setting in line with the professional standard defined by the General Medical Council.⁴⁵⁸

In a conventional medical setting, while the patient's understanding should be facilitated, there is no legal duty on physicians to try to persuade patients to accept treatment,⁴⁵⁹ and some have argued that the physician's duty should be limited to providing information rather than advice.⁴⁶⁰ Others consider that "...such an approach reduces the professional to a technician and undermines his or her role responsibility as beneficent healer".⁴⁶¹ However, the key to this apparent impasse surely lies in the judgment in *Montgomery*:

"Most decisions about medical care are not simple yes/no answers. There are choices to be made, arguments for and against each of the options to be considered, and sufficient information must be given so that this can be done".⁴⁶²

The physician's greatest service to the patient is to provide sufficient information for the patient's needs such that the doctor is not acting negligently and giving due protection to the patient's right of autonomy⁴⁶³ - the essence of consent.

6.4.1 Consent in Clinical Trials

The vast majority of clinical trials entail administering the investigational drug (or placebo or comparator agent) to each subject, and monitoring the sequelae. If the subject has capacity, the subject gives consent prior to the conduct of any trial-specific procedures. If the subject lacks capacity, then the MHU Regulations 2004 stipulate the classes of person who may give permission for the trial to proceed (legal representative or, in the case of a minor, a parent), and the basis upon which they do so (that the decision represents the presumed will of the subject).⁴⁶⁴ In either case, in the event of injury, established pathways exist by which compensation may be recovered.

Reliable evidence that a consent process has been correctly followed and consent properly obtained is stipulated within the MHU Regulations 2004, which define consent as a

⁴⁵⁸ General Medical Council(2013). Good Medical Practice, available at http://www.gmc-uk.org/guidance/good_medical_practice.asp, accessed 28th September, 2015

⁴⁵⁹ See, for example, *Attwell v McPartlin* [2004] EWHC 829.

⁴⁶⁰ Kennedy, I. The patient on the Clapham omnibus. In: *Treat me Right*. Oxford: OUP, 1998, pp182-183.

⁴⁶¹ MacLean, A. (2006). Autonomy, Consent and Persuasion. *Eur.J.Health Law*, **13**, 321-338.

⁴⁶² *Montgomery v Lanarkshire Health Board* [2015] UKSC 11, at 109, *per* Baroness Hale of Richmond DPSC

⁴⁶³ Herring. *J. Medical Law and Ethics*, 4th Edn., Oxford: OUP, 2012, p 170.

⁴⁶⁴ The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 1031/2004), Schedule 1, Part 4, §13 (minors), Schedule 1, Part 5, §12 (incapacitated adults).

‘decision which must be written’ (Article 2(j)), except in ‘exceptional cases as provided for in national legislation’ (Article 3.2(d)). This absolute requirement for documented (normally by dated signature) subject consent prior to enrolling in a clinical trial seems likely to provide a deterrent to subjects being included into clinical trials unknowingly, i.e., to reduce the prospect of the first issue described above arising - the absence of consent. However, clinical trials may be more susceptible than conventional medicine to the second issue - the adequacy of the consent process.

Most commentators consider that the subject’s rights regarding provision of information are greater in the research setting. In the UK, the move towards a ‘prudent subject’ standard had begun before *Chester and Birch*,⁴⁶⁵ but once again, the USA took the lead. In 1991, the Department of Health and Human Services issued the Common Rule, one part of which specified the elements of information which had to be provided to a subject (or legal representative) participating in research.⁴⁶⁶ These included a description of the objective(s) of the research, foreseeable risks and benefits to participants and others, provision for compensation in the event of injury, and reasonable alternatives, where relevant. In 1995, the ICH version of GCP⁴⁶⁷ (later captured as ICH Guideline E6, subsequently codified in the CTD and the GCP Directive) expanded this list to encompass a further twelve elements to be included in consent forms used for clinical trials. Consequently, RECs will and do expect consent forms to comply with these requirements. Should a research case come before the courts in the UK, it would seem likely that the assessment of ‘sufficiency’ would be based upon the requirements stipulated in the MHU Regulations 2004 and also in the light of the judgment in *Montgomery*, i.e., the information must be sufficient to enable the particular subject to choose which risks to undertake in a manner reflecting the subject’s autonomy and ability to determine his or her own life course. It would seem unreasonable to set a lower standard of information provision to those volunteering for research intended to benefit others than to those receiving conventional medical treatment which will benefit themselves.

⁴⁶⁵ Doyal, L., Tobias, J.S. (1996). Informed consent in medical research. *Br.Med.J.*, **316**, 392-393.

⁴⁶⁶ U.S. Department of Health and Human Services. 45 CFR 46. Fed. Reg. 1991;**56**:28012.

⁴⁶⁷ International Conference on Harmonisation Guidance on Good Clinical Practice (Topic E6) (CPMP/ICH/135/95).

A number of studies have examined the difficulties experienced by trial participants in relation to the concepts, terminology and design of clinical trials.⁴⁶⁸ For many years, consent documents have been subjected to review and re-assessment by commentators and researchers, many concluding that they contain significant shortcomings, resulting in poor participant understanding of the research processes, and a lack of knowledge regarding the expectations and demands of trials.⁴⁶⁹ The areas of poor understanding which feature most commonly include potential risks and the probabilities of particular risks actually occurring, the concept of randomisation resulting in therapeutic misconception (a mistaken belief that subjects will receive whichever treatment was best suited to them), benefits to participants and provision for compensation.⁴⁷⁰ These documents are often long, and employ complex, *quasi*-legal language.⁴⁷¹ Proof of comprehension by trial subjects is not required and rarely obtained.⁴⁷² Considering the functions the consent documents are expected to fulfil, these analyses are perhaps not surprising, as the documents face the competing, and at times incompatible, goals of completeness and comprehensibility.⁴⁷³ If a consent form includes all risks relating to the illness and treatment(s), the length of the document may grow to the point of being incomprehensible to most subjects.⁴⁷⁴

The UK RECs do not appear to have released information regarding their experiences of reviewing forms developed by study sponsors, but their USA counterparts have done so. While IRBs generally seek to decrease the length and complexity, institutions and industry

⁴⁶⁸ See, for example, Featherstone, K., Donovan, J.L. (2002) “Why don’t they just tell me straight, why allocate it?” The struggle to make sense of participating in a randomised controlled trial. *Soc.Sci.Med.*, **55**, 709–719; Donovan, J., Mills, N., Smith, M. *et al.* (2002) Quality improvement report: Improving design and conduct of randomised trials by embedding them in qualitative research: ProtecT (prostate testing for cancer and treatment) study. *Br.Med.J.*, **325**, 766–70; Mills, N., Donovan, J.L., Smith, M., *et al.* (2003) Patients’ perceptions of equipoise are crucial to trial participation: a qualitative study of men in the ProtecT study. *Cont. Clin. Trials*, **24**, 272–82.

⁴⁶⁹ See, for example, Prescott R.J., Counsell, C.E., Gillespie, W.J. *et al.* (1999). Factors that limit the quality, number and progress of randomised controlled trials. *Health Tech.Assess.*, **3**, 139; Flory, J., Emmanuel, E. (2004). Interventions to improve research participants’ understanding in informed consent for research: a systematic review. *J.Am.Med.Ass.*, **292**, 1593-1601.

⁴⁷⁰ Gillies, K., Huang, W., Skea, Z Cotton, S. (2011). Analysis of patient information leaflets (PILs) used in clinical trials using the Informed Consent Evaluation instrument (ICEi). *Trials*, **12**, A121; Montalvo, W., Larson, E. (2014). Participant Comprehension of Research for Which They Volunteer: A Systematic Review. *J. Nursing Scholarship*, **46**, 423-431; Dal-Re, R., Morell, F., Tejedor, J.C., Gracia, D. (2014). Therapeutic misconception in clinical trials: fighting against it and living with it. *Rev.Clin.Espanola*, **214**, 470-474.

⁴⁷¹ Reinert, C., Kremmler, L., Burock, S., *et al.* (2014). Quantitative and qualitative analysis of study-related patient information sheets in randomised neuro-oncology phase III-trials. *Eur.J.Cancer*, **50**, 150-158.

⁴⁷² Rowbotham, M.C., Astin, J., Greene, K., Cummings, S.R. (2013). Interactive informed consent: randomized comparison with paper consents. *PLOS ONE*, **8**, Article Number: e58603

⁴⁷³ May, T., Craig, J.M., Spellecy, R. (2007). Viewpoint: IRBs, hospital ethics committees, and the need for “translational informed consent.” *Acad.Med.*, **82**, 670-674.

⁴⁷⁴ Spellecy, R., Leuthner, S., Farrell, M. (2013). Risk, respect for persons, and informed consent in comparative effectiveness research. *Am.J.Bioethics*, **13**, 46-48.

sponsors often seek to position these as ‘legal’ documents, a practice Savulescu has described as ‘pernicious’,⁴⁷⁵ with the result that the length and complexity has increased substantially over time.⁴⁷⁶ The perception of sponsors and institutions seems to be that once a subject has been informed of all possible risks associated with the study procedures, the investigational drug and the comparator(s), by then agreeing to participate in the study the subject is implicitly accepting these risks;⁴⁷⁷ there may be a degree of truth in this, as will be discussed in Chapter 7.5. However, as mentioned earlier in this chapter, providing progressively more information may constitute ‘disclosure’ rather than improved understanding.⁴⁷⁸

No requirement exists for any assessment of the effectiveness of the consent process. Most processes in the pharmaceutical industry are subject to routine quality control procedures,⁴⁷⁹ and whilst inspection of the consent process would inevitably be retrospective, the findings could be applied prospectively to improve the consent process for future subjects. At present, we have no way to ascertain whether subjects truly understand the clinical trial process, and its consequences, for which they have volunteered, and as Chapter 7 will demonstrate, this lack of knowledge may have significant consequences in the event of a child being born with an injury.

6.4.2 Consent in Clinical Trials in Pregnant Women

For trials involving pregnant women, the wording of the information provided and the consent form should also explain the relevance for the foetus of the woman’s consent, and provision for compensation in the event of iatrogenic injury, is likely to be particularly important. Clinical research is an inherently uncertain exercise; future risks and benefits are largely unknown and sufficient evidence rarely exists to assign an objective probability

⁴⁷⁵ Savulescu, J. (2014). . One success in research ethics. Practical ethics in the news. <http://blog.practicaethicsox.ac.uk/2014/11/one-success-in-research-ethics/> accessed 28th September, 2015.

⁴⁷⁶ Berger, O., Gronberg, B.H., Sand, K. (2009). The length of consent documents in oncological trials has doubled in twenty years. *Ann.Oncology*, **20**, 379-385.

⁴⁷⁷ Klitzman, R.L. (2013). How IRBs view and make decisions about consent forms. *J.Empirical Res. Human Res.Ethics*, **8**, 8-19.

⁴⁷⁸ O'Neill, O. (2004), Accountability, trust and informed consent in medical practice and research, *Clin. Med.*, **4**, 269-276; Dixon-Woods, M., Ashcroft, R.E., Jackson, C.J. (2007). Beyond "misunderstanding": written information and decisions about taking part in a genetic epidemiology study. *Soc.Sci.Med.*, **65**, 2212-2222; Freer, Y., McIntosh, N, Teunisse, S. *et al.* (2009). More information, less understanding: a randomized study on consent issues in neonatal research. *Pediatrics*, **123**, 1301-1305.

⁴⁷⁹ World Health Organisation, 16th December 2006. Quality assurance of pharmaceuticals A compendium of guidelines and related materials Volume 2, 2nd updated edition Good Manufacturing Practices and inspection. Available at http://apps.who.int/prequal/info_applicants/Guidelines/OA_Pharmaceuticals-Vol2.pdf, accessed 19th September, 2015.

to a particular risk - especially when an investigational drug is being administered to a specific group, such as pregnant women, for the first time. On what basis is a pregnant woman able to consent to taking investigational drugs to assess their properties, particularly when the foetus is not an intended beneficiary?

Medical research commonly involves risk which is undertaken for the benefit of others and clinical trials in pregnant women not intended to benefit the foetus will be categorised as non-therapeutic for the foetus. Under the MHU Regulations 2004, non-therapeutic clinical trials are acceptable in incompetent adults and minors as a carefully-controlled, risk-minimised method to accrue information which will help others in the future, provided the same information cannot be acquired from different populations *and* the trial will produce some benefit for the populations represented by the incompetent adult or minor.⁴⁸⁰ Proxy consent is acceptable in these circumstances. So, if the foetus was to be considered morally, rather than legally, as *incapax* or an extreme minor, given these same conditions, with the pregnant woman giving proxy permission, that would not be different to the current positions regarding the *incapax* and minors, assuming the appropriate prior deliberations of the REC. The information gained in these trials will be used to better manage maternal illnesses, some of which have the potential to harm the foetus. Defining an alternative study population from which the data would be as applicable seems impossible, as pregnancy is a unique condition.

In giving her consent, the pregnant woman is consenting for *herself*; the foetus has no legal personality, and is not independent of the pregnant woman: she cannot participate in a clinical trial without involving the foetus, and so this is part of her consideration prior to enrolling. Accordingly, in this setting, the pregnant woman is not giving permission for the foetus to be the **subject** in a clinical trial, although, arguably, it has become a **participant**.⁴⁸¹ The primary objective will be to collect data as it relates to the pregnant woman. However, inherent in her consent is her acceptance that her foetus will be a participant in the trial. This is quite different from the position in a neonatal trial, in which permission would be provided by the parent(s) and the neonate would be the trial subject. The pregnant woman may withdraw her consent at any time, just as the parents of a neonate may do.

⁴⁸⁰ Statutory Instrument 1031, 2004; The Medicines for Human Use (Clinical Trials) Regulations, Part 4, ss.9-11

⁴⁸¹ See Chapter 6.3.1 for discussion of this point.

Some commentators have argued that if doing so does not generate a high personal cost, the pregnant woman has a duty to prevent harm to the foetus.⁴⁸² In opposition, proponents of maternal autonomy argue that no one but the pregnant woman can make such intimate decisions.⁴⁸³ If we adhere to the notion of consent, which is entirely voluntary in nature, then the duty argument must fail; doing something because others perceive it as a duty surely vitiates the voluntary essence of consent.

As described in Chapter 6.2.1, the MHRA appears to have the authority to allow studies to proceed in the absence of preclinical information defined in the ICH Guidelines, and so potentially-relevant information may not have been generated, but most trial subjects seem unlikely to be aware of that. In consequence, whilst the known and reasonably foreseeable risks can be explained, the relative lack of knowledge regarding the investigational drug creates an unavoidable uncertainty, which should be reflected in the information provided to potential subjects, and this, as the next chapter will show, may impact the provision for compensation in the event of injury.

6.4.3 Motivation for Pregnant Women to Participate in Trials

Perhaps as a result of the exclusion of pregnant women from clinical trials for so long, research into trial participation during pregnancy to date has largely focused on the general attitude to trials and on reasons for participation and non-participation, and there has been a lack of qualitative research in this area.⁴⁸⁴ Some studies have explored the difficulties experienced by trial participants regarding the concepts, terminology and design of clinical trials,⁴⁸⁵ and there are published reports describing the particular problems experienced by

⁴⁸² Schucklenk, U., Kleinsmidt, A. (2007). Rethinking mandatory HIV testing during pregnancy in areas with high HIV prevalence rates: ethical and policy issues. *Am.J.Public Health*, **97**, 1179–1183.

⁴⁸³ Johnsen, D.E. (1986). The creation of "fetal rights": conflicts with women's constitutional rights to liberty, privacy, and equal protection. *Yale Law J.*, **99**, 599-625; Perry, C. (2011). Unacceptable risk in pregnancy: whose choice and responsibility? *Am.J.Bioethics*, **11**, 64-65; Laufer-Ukeles, P. (2011). Reproductive choices and informed consent: fetal interests, women's identity, and relational autonomy. *Am.J.Law Med.*, **37**, 567-623.

⁴⁸⁴ Kenyon, S., Dixon-Woods, M., Jackson, C.J., *et al.* (2006). Participating in a trial in a critical situation: a qualitative study in pregnancy. *Qual.Saf.Health Care*, **15**, 98-101.

⁴⁸⁵ See, for example, Featherstone, K., Donovan, J.L. (2002) "Why don't they just tell me straight, why allocate it?" The struggle to make sense of participating in a randomised controlled trial. *Soc.Sci.Med.*, **55**,709–19; Donovan, J., Mills, N, Smith, M. *et al.* (2002) Quality improvement report: Improving design and conduct of randomised trials by embedding them in qualitative research: ProtecT (prostate testing for cancer and treatment) study. *Br.Med.J.*, **325**, 766–70; Mills, N., Donovan, J.L., Smith, M., *et al.* (2003) Patients' perceptions of equipoise are crucial to trial participation: a qualitative study of men in the ProtecT study. *Cont.Clin.Trials*, **24**, 272–282.

people approached to take part in trials during stressful critical situations, such in pre-term labour and neonatal settings.⁴⁸⁶

One small labour-related study in the UK⁴⁸⁷ found that subjects depended upon their ‘socio-emotional’ interactions with the research staff when responding to recruitment invitations; they attributed their decisions to participate in the trial more to this interaction than to written trial information or their own thoughts regarding the trial interventions or processes. A few studies report that women in active labour have impaired recall of the informed consent process when assessed *post-partum*, some authors suggesting this indicates diminished decisional capacity during labour and delivery.⁴⁸⁸ Others dispute this,⁴⁸⁹ and two recent publications support the validity of consent sought during labour.⁴⁹⁰ However, other than in trials involving drugs under assessment for the management of labour, this sub-population is not likely to be included in the evaluation of investigational drugs; the physiological stresses of labour together with the attendant medical risks preclude this group as a stable cohort in which to conduct clinical trials, and the relevance of their results to the general population of pregnant women seems questionable.

Most potential subjects indicated their willingness to participate in a randomised placebo-controlled trial of an injectable medicine given throughout pregnancy in another small study in the USA, their reasons being benefit to foetal health (68%), benefit to personal health (27%), and altruism (5%). The first of these has been found in other studies too,⁴⁹¹ but all have been relatively small studies sited in the USA. The healthcare system in the USA is radically different from those of the UK and many EU countries, therefore the motivations for patients to become trial subjects may be somewhat different. The possibility of therapeutic misconception looms large in these reports; indeed, the first of

⁴⁸⁶ Snowdon, C., Garcia, J., Elbourne, D. (1997) Making sense of randomization: responses of parents of critically ill babies to random allocation of treatment in a clinical trial. *Soc.Sci.Med.*, **45**, 1337–1355.

⁴⁸⁷ Kenyon, S., Dixon-Woods, M., Jackson, C.J., *et al.* (2006). Participating in a trial in a critical situation: a qualitative study in pregnancy. *Qual.Saf.Health Care*, **15**, 98-101.

⁴⁸⁸ Swan, H.D., Borshoff, D.C. (1994). Informed consent - recall of risk information following epidural analgesia in labour. *Anaes. Int. Care*, **22**, 139-141; Frohlich, S., Tan, T., Walsh, A. *et al.* (2011). Epidural analgesia for labour: Maternal knowledge, preferences and informed consent. *Irish Med.J.* **104**, 300–302.

⁴⁸⁹ Pattee, C., Ballantyne, M., Milne, B. (1997). Epidural analgesia for labour and delivery: Informed consent issues. *Can.J.Anaes.*, **44**, 918–923; Broadus, B.M., Chandrasekhar, S. (2011). Informed consent in obstetric anaesthesia. *Anesth.Analg.*, **112**, 912-915.

⁴⁹⁰ George, R. T., Butcher, M., Yentis, S. M. (2014). Pregnant women's views on informed consent for research in labour. *Int.J.Obs.Anaes.*, **23**, 233-237; Reid, R., Susic, D., Pathirana, S., *et al.* (2011). The ethics of obtaining consent in labour for research. *Aus.NZ.J.Obs.Gyn.*, **51**, 485-492.

⁴⁹¹ Frew, P.M., Zhang, S., Saint-Victor, D.S. *et al.* (2013). Influenza vaccination acceptance among diverse pregnant women and its impact on infant immunization. *Hum.Vaccin.Immunother.*, **9**, 2591-2602; Marsh, H.A., Malik, F., Shapiro, E. *et al.* (2013). Message framing strategies to increase influenza immunization uptake among pregnant African American women. *Matern.Child Health J.*, **18**, 1639-1647.

these studies reported a greater rate of participation amongst low-income populations. Although the dataset is small, it seems hard not to suspect that, in the USA, the prospect of access to otherwise unaffordable treatment may play a role in the decisions of some pregnant women to participate in clinical trials. If this is so, then, at least in the USA, this population may be at risk of exploitation. If financial considerations underlay their decision-making process, that demonstrates these women retained decisional capacity, but this does not remove the risk of exploitation.

Information from Europe is even more sparse. The one published study found seven aspects which influenced the pregnant women's decision to participate: external influence (the Investigator), research and healthcare (altruism), perception own situation (therapeutic misconception), study design (science), intervention (therapeutic misperception), information and counselling (the Investigator), and uncertainty.⁴⁹² Once again, the relationship with the Investigator and the prospect of therapeutic misconception come to the fore.

The influence of the relationship with the Investigator and the misunderstandings which result in therapeutic misconception, combined with the lack of assessment of the consent process, leaves this population particularly liable to exploitation, as these women will in most if not all cases, most likely be considering not only themselves and their immediate families, but also the foetuses they are carrying. This could result in their enrolling into clinical trials which otherwise they would not have done, leading to the possibility that these pregnant women are being exploited.

6.4.4 Exploitation of Pregnant Women

Exploitation has been described in many ways. Two carefully defined models, one by Kant⁴⁹³ and the other by Wertheimer,⁴⁹⁴ have been considered in the clinical trials setting, and both seem applicable to clinical trials in pregnant women. Kant views exploitation as an affront to the principle of autonomy; therefore, exploitation of this type must involve the consent process. Wertheimer conceives of exploitation as an affront to the principle of justice, so mooted this type of exploitation does not necessarily involve the consent

⁴⁹² Rengerink, K.O., Logtenberg, S., Hooft, L, *et al*(2015). Pregnant womens' concerns when invited to a randomized trial: a qualitative case control study. *BMC Preg.Childbirth*, **15**, 207-217.

⁴⁹³ Kant, I. *The Metaphysical Elements of Justice*, trans. John Ladd.Indianapolis, IN: Bobbs-Merrill. 1965.

⁴⁹⁴ Wertheimer, A. *Exploitation*. Princeton: Princeton University Press. 1999.

process. Wendler⁴⁹⁵ concludes that it is a Wertheimer-type of exploitation to permit a misconception to exist among trial participants that the study-related interventions provided by the Investigator are based on clinical judgement, rather than mandated by protocol. On the other hand, failing to ensure participants understand randomisation or blinding before they can give a valid consent is essentially Kantian.

In clinical trials, there are, broadly, two ways in which a pregnant subject might be exploited. The first is the exploitative potential of subjects desperate for benefit, who may elect to participate in trials, at least in part, because they are unable to afford the treatment the trial offers. Since Appelbaum's landmark publications,⁴⁹⁶ numerous analyses have shown that therapeutic misconception remains a significant reason for patients agreeing to become subjects in clinical research. As Wild explains, situations in which the pregnant woman feels moral pressure to do what is 'best' for her foetus (or subsequent child) might constitute exploitation,⁴⁹⁷ and the theme of potential benefit clearly emerges from the examples cited earlier. It is, of course, conceivable that some women will overlook or downplay the risks to themselves in a clinical trial which held potential benefit for the foetus. Clinical trials intended to benefit the foetus directly are beyond the scope of this work, and will not be considered further. However, indirect benefit to the foetus resulting from improved management of a condition in the pregnant woman would surely constitute the type of exploitation described by Wild if therapeutic misconception was present. That said, some extensive reviews have demonstrated that, overall, subjects generally benefit simply by participating in randomised clinical trials.⁴⁹⁸ So, although therapeutic misconception may be present, patients may not actually suffer, medically, as a consequence. This form of exploitation seems to encompass both Kant's and Wertheimer's descriptions, and clearly is not unique to pregnant women, but given the concern most women have for the foetuses they carry, they may be more susceptible to it.

⁴⁹⁵ Wendler, D. (2009). Must research participants understand randomization? *Am J.Bioethics*, **9**, 3-8.

⁴⁹⁶ Appelbaum, P.S., Roth, L.H., Lidz, C. (1982) The therapeutic misconception: informed consent in psychiatric research. *Int.J.Law Psych.*, **5**, 319-329.

Appelbaum, P., Roth, L.H., Lidz, C.W., Benson, P., Winslade, W. (1987) False hopes and best data: consent to research and the therapeutic misconception. *Hast.Cent.Rep.*, **17**, 20-24

⁴⁹⁷ Wild, V. (2007). How are pregnant women vulnerable research participants? : *Int.J.Fem.App.Bioethics*, **5**, 82-104.

⁴⁹⁸ See, for example, Djulbegovic, B., Kumar, A., Glasziou, P. *et al.* (2013). Trial unpredictability yields predictable therapy gains. *Nature*, **500** (7463), 395-396; Vist, G. E., Bryant, D. *et al.* 2008. Outcomes of patients who participate in randomized controlled trials compared to similar patients receiving similar interventions who do not participate. *Cochrane Database of Systematic Reviews* 3: MR000009; Lantos, J.D., (1999) The "inclusion benefit" in clinical trials. *J. Pediatr.*, **130**, 130-131.

The second type of exploitation occurs when a particular research population bears most of the burden of research while another population reaps most of the benefits. Given the unique setting of pregnancy, it seems unlikely that other populations could benefit from the types of studies the Agencies have requested. Moreover, the perception of risk regarding such studies which developed during the years the embargo was in effect continues today, with pregnant women still being significantly under-represented in clinical trials.⁴⁹⁹ As a result, trials in this population seem unlikely to be undertaken to generate data which will be relevant to other populations; even if such a population could be defined, it would be difficult to imagine a population more complex than pregnant women in whom to conduct such trials, a consideration which reduces the prospect of this form of exploitation.⁵⁰⁰ It therefore seems likely that the pregnant population will bear the burden of generating data relevant to the pregnant population.

In the debates which led the FDA to rescind its prohibition of clinical trials in pregnant women, a number of commentators argued that there was no reason to believe that pregnant women could not make autonomous decisions or that pregnant women were particularly prone to being exploited.⁵⁰¹ Even if this is correct, it follows that pregnant women are no less likely to be exploited, especially if therapeutic misconception is present. However, there is a consideration unique to pregnant women - the foetus.

6.4.5 Foetal Exploitation

Some would exclude pregnant women from clinical trials on the premise that if the treatment is for the benefit of the woman, her capacity to consent for the foetus is compromised by the inherent conflict of putting the foetus in a hazardous situation without

⁴⁹⁹ Gonzalez, D; Boggess, K A.; Cohen-Wolkowicz, M. (2015). Lessons learned in pediatric clinical research to evaluate safe and effective use of drugs in pregnancy. *Obs.Gyn.*, **125**, 953-958; Frew, P.M.; Saint-Victor, D.S.; Isaacs, M.B. (2015). Recruitment and retention of pregnant women into clinical research trials: an overview of challenges, facilitators, and best practices. *Clin.Inf.Dis.*, **59**, S400-S407.

⁵⁰⁰ Adapted from Heyd, D. Experimentation Trial: why should one take part in medical research? In: Emanuel, E.J., Crouch, R.A., Arras, J.D., Moreno, J.D. Grady, C., (Eds). *Ethics and Regulatory Aspects of Clinical Research – Readings and Commentary*. Baltimore: Johns Hopkins University Press, 2003. Chapter 23, p161-166.

⁵⁰¹ Anderson, C. (1994). Panel backs pregnant women in trials. *Science* **263**, (5151), 1216; Macklin, R. (1994). Reversing the presumption: The IOM report on women in health research. *J.Am.Med.Women's Ass.*, **49**, 13–16; *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Vol. 2. Workshop and Commissioned Papers. Mastroianni, A.C., Faden, R., Federman, D (Eds). Washington D.C.: National Academy Press, 1994.

countervailing benefit.⁵⁰² The alternative would be the insertion of a third-party to ‘consent’ on behalf of the foetus, as mentioned earlier in this chapter, but given the requirement for equipoise, there may be no benefit to the pregnant woman either. This argument is grounded on the premise that the foetus is a ‘person’, albeit *in utero* at the time of exposure to the drug, and that the combination of foetal ‘personhood’ and the pregnant woman’s conflict of interest entitle the foetus to protection, perhaps even representation. In conventional medicine, physicians regularly administer medication to pregnant women which have unknown effects on the foetus. Doubtless in some cases the pregnant woman is forewarned of a specific risk, and her capacity and right to consent to treatment for her own benefit is accepted within the medical and legal communities, even when that treatment may endanger her foetus, without the additional requirement of approval by a third party whose role is to consider foetal interests.⁵⁰³ Given the more stringent, formal consent requirements in clinical trial setting, the appointment of a foetal representative seems excessive. Yet is this not, in effect, the outcome of the requirement in Regulation 536 for ‘specific expertise’ as part of the process for considering applications to conduct clinical trials in pregnant women, as well as in the incapacitated and minors?

Foetal ‘exploitation’, accepting for the purpose of this analysis that an entity which lacks legal personality can be exploited, could arise in two ways. If one considers the foetus as a trial participant (see Chapter 6.3.1), then the second form of exploitation described above unavoidably arises. Should an investigational drug be teratogenic, then the foetus bears most of the burden of research while another population - future pregnant women and their foetuses - reaps most of the benefits.

Almost paradoxically, the setting in which there is no prospect of therapeutic benefit and for that reason was highlighted in most previous guidelines as being unacceptable - Phase I trials - is in this respect the most morally acceptable: the consent process will disclose to these subjects the absence of potential benefit for themselves and the foetus, and their decisions to participate seem more likely to be based on altruism, making the prospect of therapeutic misconception almost negligible.

⁵⁰² See, e.g., New Liability-Limit Law Designed to Boost Research, *AIDS Policy and Law*, 6, 2 (1991) (discussing enactment of a bill to limit the liability of pharmaceutical manufacturers testing an AIDS vaccine intended to prevent pregnant women from transferring HIV to their fetuses.

⁵⁰³ *St George’s Healthcare N.H.S. Trust v S.* [1998]; *R. Collins and Others., ex p S* [1999] Fam 26, at 45.

However, another possible method of exploitation exists. Under Article 33(d) of Regulation 536, a patient enrolling in a Phase II or III trial is entitled to compensation for expenses and loss of earnings directly related to the participation in the clinical trial. The provision of payment to volunteers in Phase I studies is customary in the UK. An analysis of a recent advertisement⁵⁰⁴ indicates the rate of payment to be approximately £12.50 per hour, which corresponds to around £26,100 per annum, close to the UK average salary of £26,500.⁵⁰⁵ Thus, based on average earnings, such payments do not seem disproportionate, but could payments of this magnitude entice pregnant women into enrolling for multiple consecutive trials as a means to earn an income, potentially increasing the risk to which the foetus is exposed? The USA has witnessed the growth of ‘professional’ trial volunteers who proceed from one trial to the next as a means of earning a living.⁵⁰⁶ If a pregnant trial subject gives birth to a child with a congenital abnormality, attributing that to a particular drug will be more difficult if the pregnant woman has taken multiple investigational drugs, which will affect the prospect of recovery of damages. In the wake of the TeGenero incident,⁵⁰⁷ a process was introduced in the UK to prevent volunteers from participating in clinical trials too frequently.⁵⁰⁸ This should provide another safeguard for the foetus, albeit by restricting pregnant women’s activities to the same extent as other potential trial participants, both by restricting the number of investigational drugs to which the foetus can be exposed within a trial setting (preventative) and by increasing the likelihood of being able to ascribe an abnormality to a specific intervention, thereby supporting recovery of damages (a corrective aspect).

The combination of the consent issues (Chapter 6.4.1), the misguided motivations for pregnant women to participate in clinical trials (Chapter 6.4.2) and the potential means by which both the pregnant woman (Chapter 6.4.3) and foetus (above) might be exploited

⁵⁰⁴ https://www.quintilesclinicaltrials.co.uk/upcoming-trials/healthy-males-aged-18-55/?utm_source=Google&utm_medium=CPC&utm_campaign=Brand&utm_content=Baxter&gclid=CPGCI7OthcMCFelLtAodPBMAw accessed 20th September, 2015.

⁵⁰⁵ <http://www.mirror.co.uk/news/uk-news/uk-average-salary-26500-figures-3002995> accessed 20th September, 2015.

⁵⁰⁶ Tishler, C.L., Bartholomae, S. (2003). Repeat participation among normal healthy research volunteers - professional guinea pigs in clinical trials? *Perspect.Biol.Med.*, **46**, 508-520; Abadie, R. *The Professional Guinea Pig: Big Pharma and the Risky World of Human Subjects*. Durham, North Carolina: Duke University Press, 2010; Dresser, R. (2014). Subversive subjects: rule-breaking and deception in clinical trials. *J.Law Med.Ethics*, **41**, 829-840; C. Elliott, “Guinea-Pigging,” *New Yorker*, January 7, 2008, 36-41.

⁵⁰⁷ Suntharalingam, G., Meghan R. Perry, M.R., Ward, S. *et al.* (2006). Cytokine storm in a Phase 1 trial of the Anti-CD28 monoclonal antibody TGN1412. *N.Engl.J.Med.*, **355**, 1018-1028.

⁵⁰⁸ Health Research Authority National Health Service. The Over-volunteering Prevention System (TOPS), available at <http://www.hra.nhs.uk/about-the-hra/our-committees/the-over-volunteering-prevention-system/>, accessed 19th September, 2015.

combine to produce a situation in which pregnant women may become involved in clinical trials without fully understanding the consequences of doing so. Assuming the trial has been appropriately approved and is properly conducted, this lack of understanding does not connote a greater immediate risk to the foetus - but it may form the basis of a future risk relating to compensation in the event of injury, which will be addressed in Chapter 7.

6.5 Conclusions

Taken together, the combination of approvals, permissions and consent required creates a process which should ensure that the risks to participants in clinical trials have been minimised, and to a large extent the process appears likely to achieve that, at least for the vast majority of subjects who will normally be enrolled, i.e., competent adults. However, the level of protection for the foetus appears to be deficient in a number of respects, and the implications of the way in which the foetus appears to be considered under the new Regulation 536 raises some questions which, at present, probably cannot be answered satisfactorily.

The introduction of the specific expertise requirement under Regulation 536 is surely to be welcomed. As Lord Mustill phrased it, “the foetus is a unique organism”,⁵⁰⁹ and the law has for decades wrestled with the ‘not one but not two’ model of pregnancy. Most pregnant women would wish to be assured regarding any potential risk to their foetus resulting from trial participation. Whilst the Regulation seems unclear regarding the precise purpose or provider of the ‘specific expertise’, the fact that the trial will receive additional focus must increase the prospect of risks being identified and possibly mitigated. This therefore represents an increased level of protection for the foetus compared to the current position. The introduction of the ‘register’ restricting the number of trials in which an individual may participate similarly increases the level of protection for the foetus. That said, the seeming absence of any technical impediment to the REC approving a clinical trial in pregnant women in the absence of reproductive toxicology data remains a concern, and will remain so until RECs are required to make public the basis upon which clinical trials are approved.

Another concern relates to the apparent authority of the MHRA to adjudge the risk-benefit ratio in the absence of ICH-defined preclinical information, as exemplified by Götzsche’s experience. When he first requested the information, he was told (by the Investigator, the

⁵⁰⁹ *Attorney-General's Reference (No. 3 of 1994)*, [1998] A.C. 245 at 256.

CRO and then the sponsor) that the documents which contained it were confidential, despite a decision by the European ombudsman in 2010 that trial protocols do not contain commercially confidential information.⁵¹⁰ This combination of circumstances suggests that the MHRA may approve clinical trials in pregnant women in the absence of these data, that the trial participants do not need to be made aware of this fact, and that, if they ask, they may be refused the information, even if it exists. This seems an unsatisfactory position, and the obvious solutions would appear to be (a) that the MHRA should not approve clinical trials in this population in the absence of such data without documented justification, and (b) requests by potential trial participants for such information as part of the consent process should be honoured, bearing in mind that consent is a continuous process. Moreover, the responsibilities of the regulatory authorities to draw attention to potentially teratogenic comparators might usefully be clarified. Few trial subjects, probably, would contemplate asking such questions, but as Chapter 7 will illustrate, iatrogenic teratogenic injury attributable to the comparator has significant implications regarding the process for recovery of damages.

Similarly, few trial subjects, probably, would be aware that the constraints of GCP mean that the physician acting as an Investigator changes responsibility to that of ensuring compliance with the approved protocol whilst minimising risk of harm to the trial subject. In many cases, physicians enrol their own patients into clinical trials. A number of ethical guidelines for clinical research suggest that the voluntariness of consent by patients may be compromised when their own treating physician obtains consent,⁵¹¹ and several studies have shown that treating physicians can have a considerable influence on the decision-making of their patients with regard to research.⁵¹² The knowledge physicians gain by virtue of their relationship with patients is substantial which should contribute significantly to the safety of patients who become trial subjects, and so should not be disregarded - but

⁵¹⁰ Gøtzsche, P.C., Jørgensen, A.W. (2011). Opening up data at the European Medicines Agency. *Br.Med.J.*, **342**, d2686.

⁵¹¹ Appelbaum, P.S., Lidz, C.W., Klitzman, R. (2009). Voluntariness of consent to research: a preliminary empirical investigation. *IRB Ethics Human Res.*, **31**, 10-14.

⁵¹² See, for example, Gammelgaard, A., Mortensen, O.S., Rossel, P. (2004). Patients' perceptions of Informed consent in acute myocardial infarction research: a questionnaire based survey of the consent process in the DANAMI-2 trial. *Heart*, **90**, 1124-1128; Kleiderman, E., Avard, D., Black, L. *et al.* (2012). Recruiting terminally ill patients into non-therapeutic oncology studies: views of health professionals. *BMC Med.Ethics*, **13** 33-44; Eggly, S., Albrecht, T.L., Harper, F.W. *et al.* (2008). Oncologists' recommendations of clinical trial participation to patients. *Patient Educ.Couns.* **70**, 143-148; Kass, N.E., Sugarman, J., Faden, R. *et al.* (1996). Trust, the fragile foundation of contemporary biomedical research. *Hast.Cent.Rep.* **26**, 25-29.

the trial subjects perhaps need a clearer explanation of the limitations within which the ‘doctor’ must now operate as part of the consent process.

Finally, the status of the foetus needs to be clarified. From being not mentioned at all under the CTD, Regulation 536 seems to confer upon the foetus the status of a trial participant incapable of providing consent (or assent), but whose ‘interests’ are such that a trial may legitimately be declined by the REC, thereby compromising the pregnant woman’s autonomy. However if the pregnant woman’s consent is considered as equivalent to proxy consent for minors or the *incapax*, other trial participants incapable of providing consent, then the pregnant woman’s consent should not constitute a barrier to recovery of damages in the event of injury *in utero*. The implications of this will be addressed in the next chapter.

Chapter 7 Routes to Compensation in the Event of Trial-Emergent Injury

7.1 Introduction

Previous chapters have described the legal and moral standing of the foetus, and the aspects of the trial approval processes which offer a level of protection for the foetus in clinical trials recruiting pregnant women. Within the UK, as with many other countries, we have imposed legal constraints, founded on moral and, in some cases, practical considerations, to prevent the termination of pregnancy other than in defined circumstances. We have created laws to impose criminal or civil liability on those other than the pregnant woman who inflict harm on the foetus resulting in *postnatal* death or injury. One of the purposes of the clinical trial approval process is that of minimising risk of harm to participants, and the argument was advanced in Chapter 6.3.1 that in clinical trials involving pregnant woman, even where the foetus is not the primary trial subject, it is nevertheless a trial participant.

As outlined previously, the protection for the foetus in clinical trials may be viewed as comprising two elements: a preventative component (risk reduction and prevention of injury), and a corrective component (provision for compensation should injury occur) i.e., protection of the interests of the child the foetus will become, should injury arise. Clinical research is an inherently uncertain exercise, and despite the pre-trial approval processes, trial participants will, occasionally, suffer injury. Should a child be born injured after a pregnant woman had participated in a trial, she would naturally seek compensation for the child, as well as any additional costs that arise in raising it. The mechanisms by which damages may be recovered in such circumstances will be examined in this chapter.

Clinical trials, generally, have a remarkably good safety record,⁵¹³ although there have been tragic exceptions, such as the death in the USA of a volunteer in a 1999 gene therapy trial,⁵¹⁴ and of a volunteer in an asthma study in 2002,⁵¹⁵ as well as the TeGenero trial in the UK in 2006, which will be addressed later in this chapter. Based on possibly misinterpreted information, the popular press has reported that both healthy volunteers and

⁵¹³ Stein, C.M. (2003). Managing risk in healthy subjects participating in clinical research. *Clin.Pharmacol. Ther.*, **74**, 511-512.

⁵¹⁴ Raper, S.E., Chirmule, N., Lee, F.S., *et al.* (2003). Fatal systemic inflammatory response syndrome in an ornithine transcarbamylase deficient patient following adenoviral gene transfer. *Mol.Genet.Metab.*, **80**, 148-158.

⁵¹⁵ Savulescu, J., Spriggs, M. (2002). The hexamethonium asthma study and the death of a normal volunteer in research. *J.Med.Ethics*, **28**, 3-4.

patients enrolled in clinical trials experienced serious, unexpected suspected adverse reactions; one report cited injuries (none classed as treatment-related) to 7,187 subjects over five years. With 90,000-95,000 subjects now participating in clinical trials in the UK annually, this suggests annually 1-2% of trial participants may experience such reactions.⁵¹⁶ Of course, adverse reactions may result from many causes, including the investigational drug, a comparator agent, a procedure, which may be protocol-specified or part of normal clinical care, or the underlying condition.

Trials recruit subjects over variable periods of time. A small (perhaps 6 subjects) single-dose Phase I study may recruit and treat all the subjects within a two week period, whilst a Phase III study may enrol hundreds of pregnant subjects over a 2-3 year period, and involve treatment for twelve months or more. In the latter example, it is likely that a large number of pregnant women will have been treated for variable periods of time, and in the former the study will most likely be complete before any effects on the foetus are suspected. This will particularly be the case where problems become apparent at birth or some time afterwards. Thus, the possibility of taking preventative action by suspending enrolment or stopping a trial should something untoward be detected will, in some cases, not exist at all, and in other cases it will be of limited impact.

As explained in Chapter 6, the possibility that such events may occur and the provisions for compensation should be addressed within the consent process. Should they occur, a child born injured potentially may seek compensation from a range of sources, depending upon the circumstances of the injury. These could include, in theory, those who approved a trial if the approval was found to be inappropriate, i.e., the REC and the MHRA, the Investigator, the Investigator's employer (should the Investigator's conduct be in some way deficient), and the sponsor of the trial if the drug is 'faulty'. The legal bases upon which these potential respondents might be approached varies. This chapter will explore each of these, focussing on their relevance to the foetus exposed to an investigational drug when a pregnant woman participated in a clinical trial.

Two matters may impact attempts to recover damages regardless of the route taken and so will be considered as preliminary issues: the limitation period for personal injury claims,

⁵¹⁶ Gagot, G. Trial and error: Thousands left seriously ill or disabled by clinical tests of new drugs. 11th June, 2015. Available at <http://www.mirror.co.uk/news/uk-news/trial-error-thousands-left-seriously-5867052> accessed 30th September, 2015.

and the retention of records. Thereafter, the general position regarding insurance coverage for clinical trial subjects will be summarised before considering potential respondents.

7.2 Limitation Period

In England and Wales, section 11(4) of the Limitation Act 1980 provides that in personal injury cases the limitation period is three years from the date upon which the cause of action accrued, or from the date (if later) that the person is aware of the injury. Section 38 defines personal injuries broadly, including both physical and psychological injuries, even if the latter do not constitute recognised psychiatric injuries, which has the particular advantage to children of encompassing developmental, behavioural and cognitive injuries. The 3-year period need not commence from the date the injury was inflicted, e.g., by the administration of an investigational drug to a pregnant woman; it can be argued to commence from the time at which the claimant had ‘requisite knowledge, defined in Section 14 as the date the claimant first had knowledge

- (a) that the injury in question was significant; and
- (b) that the injury was attributable in whole or part to the act or omission which is alleged to constitute negligence, nuisance or breach of duty; and
- (c) of the identity of the Defendant.

Under section 28 of the Act, for injured children the time limit begins from the date of their 18th birthday. A claimant may overcome the statutory bar by proving that s/he did not acquire knowledge of essential elements of his cause of action, usually ‘significant injury’ and ‘attribution’, until a later date. Furthermore, under section 33, the court retains a discretion to permit the claim to proceed where it is equitable to do so. This extended limitation period constitutes a significant advantage for children injured *in utero*; with the possible exception of diethylstilboestrol,⁵¹⁷ all drugs suspected of expressing teratogenic effects have done so within this period. Of course, cases may be brought before the child has legal capacity to institute proceedings, in which case the claim will need to be brought on child’s behalf, but it remains the child’s claim.

⁵¹⁷ Royal College of Obstetricians and Gynaecologists(2002) Fetal and maternal risks of diethylstilboestrol exposure in pregnancy. Statement No. 2. Available at <http://www.cancerscreening.nhs.uk/rcog-statement-no2.pdf> accessed 30th September, 2015.

An injury may be immediately apparent, as was the case for thalidomide, or it may take years to become manifest, as happened with diethylstilboestrol. The consent document, a copy of which the pregnant woman would have been given, will name the Investigator, the NHS Trust, and the trial sponsor so the identity of the defendant(s) is likely to be known, although with the passage of time such documents may have been lost. However, the principal challenge is likely to arise regarding knowledge that an act (or omission) may have caused injury and that there may have been negligence. The applicability of the limitation period depends upon the court's interpretation of the word 'knowledge'. English courts had traditionally rejected suspicions and beliefs as constituting knowledge, but this changed with Lord Donaldson's comment in *Halford v Brookes*⁵¹⁸ that 'reasonable belief will normally suffice' to mean 'knowledge'. Regarding the extent to which a belief is considered 'reasonable', Lord Donaldson in *Halford* and subsequently Purchas LJ in *Nash v Eli Lilly & Co*⁵¹⁹ adopted a common approach, defining 'reasonable belief' as a belief that makes the claimant contemplate preliminary steps in the pursuit of a claim. The later case of *Spargo v North Essex District Health Authority* appeared to raise the threshold for the test of reasonableness, requiring the claimant to have taken some action, e.g., consulting a solicitor, to demonstrate that belief.⁵²⁰

Thus, the limitation period *per se* seems unlikely to be a major problem in most cases where a child who allegedly suffered injury *in utero* in a clinical trial seeks damages, although the associated criteria may be difficult to satisfy if the injury has a long onset time, where the link between the injury and the trial may not be obvious.

7.3 Record Retention

As the examples of diethylstilboestrol⁵²¹ and Creutzfeldt-Jakob Disease⁵²² illustrate, iatrogenic injury may take years to become apparent. This alone will render the causal relationship between a drug and a condition difficult to establish. If the drug is licensed, as a condition of approval the manufacturer of the drug (which in almost every circumstance will also be the legal sponsor of any trial in which harm arose) is required to submit to the

⁵¹⁸ *Halford v Brookes* [1991] 3 All ER 559.

⁵¹⁹ *Nash v Eli Lilly & Co* [1993] 4 All ER 383, at 392c *per* Purchas LJ

⁵²⁰ *Spargo v North Essex District Health Authority* [1997] PIQR P235, at 242 *per* Brooke LJ. This is supported by S.14(3) of the Limitation Act 1980 which accepts the proclamation of 'knowledge' so long as the claimant takes reasonable steps to obtain or act on expert advice.

⁵²¹ Saunders, E.J., Saunders, J.A. (1990). Drug Therapy in Pregnancy: The lessons of Diethylstilbestrol, Thalidomide, and Bendectin. *Health Care for Women Intl.*, **11**, 423-432.

⁵²² Brown, P., Preece, M., Brandel, J.P. *et al.* (2000). Iatrogenic Creutzfeldt-Jakob disease at the millennium. *Neurology*, **55**, 1075-1081; the incubation period for this condition is up to 30 years.

regulatory authorities all preclinical and clinical information relating to the drug, and to keep that up to date until two years after the last patent for the drug expires. Furthermore, the manufacturer must retain registration-related documentation, i.e., data relating to the approval of the drug in any indication, for 10-15 years after the last withdrawal of the drug from any market.⁵²³ So, theoretically, all of the information the manufacturer accumulated during the development phase of the drug is recoverable. This was the situation in the Paxil[®] cases, in which the manufacturer allegedly failed to warn prescribers of the drug's risks after the company began receiving reports of birth defects; these reports were considered during the (much) later litigation.⁵²⁴ For pregnant women whose foetuses may have been harmed in pre-registration clinical trials, this is potentially helpful; even if a drug is withdrawn a year after its approval, and the clinical trial in which they participated was conducted immediately before approval, this creates a period of at least 11 years after the trial for harm to the child to become manifest during which complete records need to be retained.

However, should the drug not proceed to be licenced, the challenge may become significantly greater for a child who wishes to make a claim as the manufacturer is not mandated to retain all data relating to investigational drugs which do not proceed to registration. In Europe, manufacturers are not required to compile formal preclinical or clinical reports to support initial applications to conduct clinical trials, and so data may not have been released to European regulatory agencies, which could later be recovered should the need arise. This is not the case in the USA, so if a drug is withdrawn from development for any reason following an application to conduct a trial in the USA, such documentation will have been submitted to and is potentially recoverable from the FDA. Under the provisions in the European GCP Directive, the REC is required to retain specified essential documents for three years, and the sponsor and the Investigator for five years, after completion of a trial.⁵²⁵ Thus, data which might disclose preclinical evidence of an association between a congenital abnormality and an investigational drug may no longer exist if the harm does not become apparent for a significant period of time

⁵²³ Directive 2005/28/EC codified by Statutory Instrument 2006/1928

⁵²⁴ Teather, D. Glaxo faces drug fraud lawsuit, 3rd June., 2004, available at <http://www.theguardian.com/business/2004/jun/03/mentalhealth.medicineandhealth> accessed 30th September, 2015; see also Feeley, J. Glaxo withheld paxil birth-defect data, witness says (Update2), 16th September, 2009, available at <http://www.bloomberg.com/apps/news?pid=newsarchive&sid=aOBwEVFEEXdc> accessed 30th September, 2015.

⁵²⁵ Commission Directive 2005/28/EC, Articles 6 (REC) and 17 (Sponsor and Investigator).

following the trial, although still within the limitation period for personal injury litigation in the UK.

The mother may suspect the injury occurred as a result of the clinical trial but, initially, she will have neither proof nor a ready way to confirm her suspicion, especially if the injury became apparent years after the trial. She may not have retained her trial-related medical records or a copy of the data which was sent to the trial sponsor for analysis, if she was even offered these, and she will rarely have the medical knowledge to analyse potential associations between the drugs in the trial and the suspected congenital injury. She may, of course, seek access to her own and her child's hospital notes, which should contain information relating to her participation in the clinical trial, but these may not be as helpful as one might anticipate.

A key concept in all clinical trials is that the information collected can be verified by comparing it to the source data. ICH Guideline E6 §1.51, defines source data as "All information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial." ICH Guideline E6 §1.52, defines source documents as "Original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial)". Under Directive 91/507/EEC,⁵²⁶ the Investigator is obliged to retain patient files and other source data for the maximum period of time permitted by the hospital, institution or practice, although the treatment allocation code must be retained for at least 15 years after the completion or discontinuation of the trial.

⁵²⁶ Commission Directive 91/507/EEC of 19 July 1991 modifying the Annex to Council Directive 75/318/EEC on the approximation of the laws of Member States relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of medicinal products, specifically Part 4 B 2(b); available at <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:31991L0507&from=en> .

Under the NHS Records Retention Schedule,⁵²⁷ an adult trial subject's medical files must be retained for a minimum period of five years, and a child's files for at least 25 years. Thus, if trial participation records were kept in the pregnant woman's medical file, it is possible that these would have been destroyed (with the exception of the treatment allocation code) before injury to the child became apparent. Conversely, if the injury was apparent at birth or during childhood, assuming it was recorded in the child's medical file, that information should be accessible for at least as long as the limitation period for personal injury litigation.

The attrition rate of drugs in clinical development is ferocious. Approximately 1/3 of drugs which enter Phase I trials will not reach Phase II, of those which enter Phase II, 2/3 will not reach phase III, and of those which reach Phase III, 1/3 will not achieve registration; this corresponds to an overall attrition rate of 85-90%.⁵²⁸ Thus, even if studies in pregnant women are commenced during the Phase III development programme, the risk of the drug not proceeding to licensing, and thus imposing the obligation on the sponsor to retain the data beyond five years, is around 33%. Obviously, if these studies are conducted earlier in the development programme, this allows more time for any injury to become apparent, an advantage offset by the increased prospect of the drug being withdrawn from development.

The required retention periods may be appropriate for most trials involving adults without mental health conditions, whose psychological and physiological functions have reached relative stability. Whether they are appropriate for those whose functions are still developing, including minors and the foetus, and whose participation in trials was not widely in contemplation when these periods were specified, merits consideration. It might not seem unreasonable to create a legal requirement for the REC, sponsor, Investigator and the NHS to retain all documentation relating to such trials for 25 years, as would be the case for a child's file, such that most developmental issues should have been detected within the limitation period for personal injury litigation in the UK.

⁵²⁷ Available at https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/200139/Records_Management_-_NHS_Code_of_Practice_Part_2_second_edition.pdf, accessed 30th September, 2015.

⁵²⁸ Hay, M., Thomas, D.W., Craighead, J.L., *et al.* (2014). Clinical development success rates for investigational drugs. *Nature Biotech.*, **32**, 40–51.

7.4 Insurance Provisions

As described in Chapter 6.2.2, part of the purpose of the REC review is to establish whether sufficient insurance or other coverage exists to meet the potential costs of injuries to trial participants.

For studies conducted within NHS facilities, the NHS indemnifies its own staff, medical academic staff with honorary contracts, and those conducting clinical trials against litigation arising from negligent harm caused to patients or healthy volunteers who are subjects of clinical research.⁵²⁹ The NHS Indemnity does not apply to non-negligent harm, such as teratogenic injury possibly related to an investigational drug, although in exceptional circumstances NHS bodies may consider whether an *ex-gratia* payment could be offered.⁵³⁰

Sponsors of clinical trials usually indemnify the NHS against personal injury claims except where the injuries are attributable to negligence by NHS staff. The NHS body also carries legal liability for claims in negligence (or compensation under the sponsor's indemnity will be abated) where there has been significant non-adherence to the approved protocol, or negligence on the part of an NHS employee, e.g., by failing to deal adequately with an adverse drug reaction.⁵³¹

As the NHS Guidance Document notes, the form of indemnity may not be readily accepted by sponsoring companies outside the UK or which are not members of the Association of the British Pharmaceutical Industry (ABPI).⁵³² The NHS body will carry liability for any claims in negligence if the indemnity is not honoured by the trial sponsor and there is no supporting insurance.⁵³³ Annex B of the NHS Guidance Document stipulates that the NHS body and the sponsor will each give to the other such help as may reasonably be required for the efficient conduct and prompt handling of any claim by or on behalf of subjects (or their dependants), and requires the Sponsor to operate in good faith the Clinical Trial Compensation Guidelines published by the ABPI. This appears to signify a genuine intent to resolve such issues rapidly.

⁵²⁹ NHS Indemnity Arrangements for Clinical Negligence Claims in the NHS, available at <http://www.nhs.uk/claims/Documents/NHS%20Indemnity.pdf>, accessed 30th September, 2015

⁵³⁰ NHS Indemnity Arrangements for Clinical Negligence Claims in the NHS, Annex A, §16

⁵³¹ NHS Indemnity Arrangements for Clinical Negligence Claims in the NHS, Annex B, S.2, §6

⁵³² NHS Indemnity Arrangements for Clinical Negligence Claims in the NHS, Annex B, S.2, §7.

⁵³³ NHS Indemnity Arrangements for Clinical Negligence Claims in the NHS, Annex B, S.2, §10.

The NHS Indemnity is, therefore, extensive, and certainly offers a potential route to the protection of the future interests of a child injured *in utero* as a result of the pregnant woman's participation in a clinical trial, but only if the injury can be shown to be the result of negligence by NHS staff. In most of the recognised cases of teratogenic injury, the cause is related to other factors, and in a clinical trial setting, suspicion will inevitably fall upon the investigational drug, assuming trial conduct has complied with the protocol.

The ABPI's Clinical Trial Compensation Guidelines recommend the assurance ABPI members provide, mostly without legal commitment, through the Investigator to the REC. The Guidelines state that subjects need to establish only that they were injured as a result of participating in a trial; they do not need to prove that anyone was at fault,⁵³⁴ in effect offering no-fault compensation, although causation needs to be established. These Guidelines apply when the study is conducted according to the protocol, and the sponsor is notified of the injury and has control over any offer of compensation. The coverage provided by the Guideline is not legally binding upon the sponsor of the trial, and as mentioned above, not all trial sponsors are ABPI members. In many cases, sponsors do not self-insure and rely instead upon specialist insurance companies.⁵³⁵ However, there are some specific potential limitations of the ABPI scheme which are relevant to clinical trials in pregnant women, which will be discussed in the next section of this chapter.

As explained in Chapter 6.3, Regulation 536, which will replace the CTD, should go some way toward addressing potential concerns regarding the adequacy of insurance coverage, as it requires member states to “ensure that systems for compensation for damages suffered by a subject are in place which are appropriate to the nature and the extent of the risk”,⁵³⁶ and places the onus for provision of insurance on the member states.⁵³⁷ Member states will also be required to demonstrate proof of insurance cover or indemnification.⁵³⁸ One might reasonably assume that most member states of the EU are better-placed financially to

⁵³⁴ ABPI Insurance and compensation in the event of injury in Phase I clinical trials, 28th June, 2012, available at <http://www.abpi.org.uk/our-work/library/guidelines/Pages/clinical-trials-insurance.aspx>; ABPI Clinical trial compensation guidelines, 12th November, 2014, available at see <http://www.abpi.org.uk/our-work/library/guidelines/Pages/ct-compensation.aspx>, both accessed 30th September, 2015.

⁵³⁵ See, for example, JLT Specialty Global insurance broker; <http://www.jltgroup.com/risk-and-insurance/sectors/life-science-and-chemicals/clinical-trials-insurance/> accessed 30th September, 2015.

⁵³⁶ Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, §62.

⁵³⁷ Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, Chapter XII, Article 76.

⁵³⁸ Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC Annex 1, o, 68.

discharge these obligations than most pharmaceutical manufacturers; the costs of life-long treatment for a child injured *in utero* in a clinical trial could be substantial, and member states would be expected to have greater access to funds and support facilities than, possibly small, private companies. As suggested previously, the system may, in part, be funded by a system of user fees, and so the costs may be borne, at least in part, by trial sponsors. At §61, Regulation 536 stipulates that the conditions for liability in the case of a subject sustaining injury as a result of participating in a clinical trial, including issues of causality and the level of damages and sanctions, should remain governed by national law. Once again, it would appear that recourse to tort law is the most likely route to a remedy in the event of injury, a route which is likely to present particular challenges as the courts have not yet formulated an adequate theoretical basis for addressing the distinctive issues of research, and because research-related injuries often do not conform to the elements required in tort litigation.⁵³⁹ An alternative approach will be explored in Chapter 8.

Since the trial sponsor is the most obvious respondent, the ABPI Guidelines will be considered first, followed by the Investigator and then the bodies responsible for approving the trial, before considering some of the specific legislative instruments which were introduced in part to overcome the challenges recognised in the application of tort to medical injury cases.

7.5 The Sponsor as a Respondent - The ABPI Guidelines

The latest version of the ABPI's Clinical Trial Compensation Guidelines⁵⁴⁰ is applicable to all clinical trials commenced from 1st January 2015 onwards. §5.4 requires the trial sponsor to encourage the Investigator "to make clear to participating patients that the trial is being conducted subject to the ABPI Guidelines relating to compensation for injury arising in the course of clinical trials and have available copies of the Guidelines should they be requested". The Guidelines are eight pages long, and are laid out in a relatively clear format, with a Flesch-Kincaid level⁵⁴¹ of 9.4, so should be comprehensible to

⁵³⁹ E.H. Morreim, E.H. (2003). Medical research litigation and malpractice tort doctrines: courts on a learning curve", *Houston J. Health Law Policy* **4**, 1-86.

⁵⁴⁰ ABPI Clinical Trial Compensation Guidelines, available at http://www.abpi.org.uk/our-work/library/guidelines/Documents/compensation_guidelines_2014.pdf accessed 30th September, 2015.

⁵⁴¹ Flesch, R. (1948). A new readability yardstick. *J. Appl. Psych.*, **32**, 221-233; Kincaid, J.P., Fishburne, R.P., Rogers, R.L., Chissom, B.S. (1975). Derivation of New Readability Formulas (Automated Readability Index, Fog Count, and Flesch Reading Ease formula) for Navy Enlisted Personnel. Research Branch Report 8-75. Chief of Naval Technical Training: Naval Air Station Memphis. Although somewhat elderly now, these measures are still commonly-used to assess ease of reading of documents, in part because they are embedded

someone aged 14-15 years. They are available for the trial subject to see “should they be requested”, rather than being required to be offered to the subject together with the study-specific information and consent documents. One recent study in 2014⁵⁴² found that the median length of consent documents given to all potential participants was 20 pages (range 8-28 pages), and that they were “complex to read” (although the Flesch-Kincaid score averaged 9.8, so on this scale they were only slightly more complex than the ABPI Guidelines). This observation regarding complexity has been made by others,⁵⁴³ although there is some evidence that these documents are becoming easier to read.⁵⁴⁴ Nevertheless, the absence of a specific instruction to offer trial subjects a copy of the Guidelines seems disappointing, considering the plethora of information being provided to trial subjects. Given the seeming importance attached to these Guidelines, arguably, their provision should be part of the consent process, although this would add to the volume of written information being provided. Since a similar Flesch-Kincaid score for consent documents was judged to be complex in the 2014 study, consideration should also be given to the simplification of the Guidelines, to try to improve understanding by trial participants.

7.5.1 Phase I Studies

The background paragraph of the section addressing Phase I clinical trials contains a requirement that member companies sponsoring Phase I studies ensure that the arrangements they put in place for these studies create a “legally binding obligation, through the terms of the consent form and subject information, to pay compensation to the volunteer in the event of injury due to participation in the study”. As the wording ‘due to participation’ makes clear, a successful claim will be predicated upon the establishment of causation. This section of the Guidelines does not mention trials in pregnant women (nor minors, nor the incapacitated) from which one might infer that these groups will be considered in the same manner as all others participating in Phase I studies, or that the conduct of Phase I studies in these populations was not in the contemplation of those who developed the Guidelines.

in Microsoft Word programmes. The reading grade levels are US-related; similar information does not appear to have been generated for the UK.

⁵⁴² Malik, L., Kuo, James, J., Yip, D. *et al.* (2014). How well informed is the informed consent for cancer clinical trials? *Clinical Trials*, **11**, 686-688.

⁵⁴³ Reinert, C., Kremmler, L., Burock, S. *et al.* (2014). Quantitative and qualitative analysis of study-related patient information sheets in randomised neuro-oncology phase III-trials. *Eur.J.Cancer*, **50**, 150-158.

⁵⁴⁴ Sand, K.; Eik-Nes, N. L.; Loge, J. H. (2012). Readability of informed consent documents (1987-2007) for clinical trials: a linguistic analysis. *J.Emp.Res. Human Res.Ethics*, **7**, 67-78.

Instinctively, the term ‘volunteer’ does not sit easily with minors and the *incapax*; whilst their proxies may believe they are reflecting the subjects’ presumed will, the ‘voluntary’ intent is clearly absent. However, the same is not true for pregnant women, for two reasons: pregnant women are undoubtedly trial subjects capable of expressing their own will, and it is not possible to infer any kind of will or presume it for a foetus. As discussed in Chapter 6.3.1, even if Regulation 536 is adopting a ‘two-patient’ model, the special expertise inherent in the prior approval of the trial by the REC means that pregnant women should be able to consent to participate in trials in exactly the same way as other competent adults. Thus, a pregnant woman can ‘volunteer’ for a Phase I trial, and in doing so knowingly commits her foetus to the risks of exposure to an investigational product or its effects, i.e., consistent with the ‘dyad’ model in which the pregnant woman and the foetus are considered holistically. Given the unique considerations for pregnant women discussed previously, clarification of the application of the Guidelines to Phase I studies in this population would be useful. Replicating §1.3 of the Phase II - IV Guidelines described in the next section within the Phase I section would have the advantage of providing the same degree of clarity for all pregnant participants.

7.5.2 Phase II and III Studies

The section addressing Phase II, III and IV clinical trials contains a recommendation that a member company sponsoring a study should provide a written assurance to the Investigator (and through the Investigator to the REC) that the Guidelines will be applied in the event of injury caused to a participant and attributable to participation in the trial. This again emphasises the need to establish causation, but without this assurance forming a legal commitment. The lack of legal commitment is a long-standing position which has been the subject of similarly long-standing criticism.⁵⁴⁵

This section of the Guidelines does make explicit mention of pregnant subjects, §1.3 stating: “Compensation should be paid to a child injured *in utero* through the participation of the subject’s mother in a clinical trial as if the child were a patient-volunteer with the full benefit of these Guidelines.”

The phraseology in this paragraph is reminiscent of the *nasciturus* principle, the guidelines being construed such as to favour the foetus. The categorisation of the child born injured

⁵⁴⁵ Guest, S. (1997). Compensation for subjects of medical research: the moral rights of patients and the power of research ethics committees. *J.Med.Ethics*, **23**, 181-185.

as a patient-volunteer (and accordingly as a research subject) is interesting; it suggests this situation will be interpreted in the same way as, for example, an injury sustained by a neonate for whom the parent(s) had given consent to participate in a clinical trial. This approach is consistent with the ‘crystallisation’ construction first advanced in *Montreal Tramways*,⁵⁴⁶ and discussed in Chapter 3.3. However, as the discussion later will demonstrate, this provision may not be as comprehensive as the wording of this paragraph might suggest.

§1.6 stipulates that the fact that the patient has freely consented to participate in the trial should not exclude the patient from consideration for compensation under the Guidelines. Once again, however, the phraseology is important; “consideration for compensation” means precisely that, as the wording of §4.2.2, addressed below, illustrates.

§1.7 asserts that the trial subject is not required to “prove that the (sponsor) company has been negligent in relation to research or development of the medicinal product under trial or that the product is defective”. Here, too, the comprehensive tone of this paragraph is somewhat qualified in §4.

Under §5.2, the sponsor’s responsibilities extend to injury arising (at whatever time) from all administrations, clinical interventions or procedures occurring during the course of the trial, i.e., the Guideline is not restricted to iatrogenic injury and does not apply the usual limitation period for personal injury.⁵⁴⁷ Accordingly, the later recognition of a possible association between a now-approved medicine and a teratogenic injury may result in these compensation provisions being engaged.

As explained in Chapter 4.4.3, establishing causation for congenital injury will always be challenging, due to the underlying natural incidence of birth defects. According to a World Health Organisation report published in 2014, there are approximately 3.2 million birth defect related disabilities every year affecting an estimated 1 in 33 infants globally.⁵⁴⁸ The most recent published data for Europe in 2010 shows congenital anomalies occur in 1 in 42 infants,⁵⁴⁹ and incomplete data for the UK for the same year indicates an incidence of 1 in

⁵⁴⁶ *Montreal Tramways v Léveillé* [1933] 4 DLR 339.

⁵⁴⁷ Limitation Act 1980, ss. 11, 14 and 33

⁵⁴⁸ World Health Organisation Congenital Anomalies Factsheet No. 370, April, 2015. Available at <http://www.who.int/mediacentre/factsheets/fs370/en/> accessed 30th September, 2015.

⁵⁴⁹ Dolk, H., Loane, M., Garne, E. (2010). The prevalence of congenital anomalies in Europe. *Adv.Exp.Med. Biol.*, **686**, 349-364.

45 live births.⁵⁵⁰ Thus, even in a relatively small Phase II study of 100 pregnant women, one would expect 2-3 congenital abnormalities. In a Phase I study of 10-20 subjects, a single congenital abnormality would not immediately appear to be unexpected. In both situations, of course, the nature of the abnormalities is important; the uniqueness of those produced by thalidomide was instrumental in identifying the drug as the causative agent. In the absence of distinctive characteristics, the balance of probabilities suggests that such occurrences are unlikely to be related to investigational drug treatment - yet it is entirely possible that a particular case would not have arisen but for exposure to the investigational drug.

Claims relating to the first few occurrences of any iatrogenic injury are always likely to fail under a 'balance of probabilities' argument. In a current case in the UK,⁵⁵¹ a trial sponsor and ABPI member has declined to compensate an injured subject on the basis that the sponsor "is unable to establish on the balance of probabilities that [the subject's] development of [the injury] was caused by his participation in the trial". This subject is the first to have developed the particular injury following administration of the investigational drug, but a temporal relationship does not establish causation: the development of the injury could be coincidental. The Guidelines contain provision for arbitration (§4(iii)), but each case is considered independently, so it seems difficult to envisage a process by which a possibly erroneous ascription of causation could be avoided.

The Guidelines also contain other limitations which, although applicable to all trials, are of particular interest when considering trials in pregnant women, and are addressed below.

7.5.3 Comparator Agents

A number of approved drugs which might be used as comparators in clinical trials of investigational drugs in pregnant women are associated with hazard to the foetus.⁵⁵²

⁵⁵⁰ British Isles Network of Congenital Anomaly Registers. Congenital Anomaly Statistics 2010. England and Wales, July 2012. Available at http://www.binocar.org/content/Annual%20report%202010%20FINAL%2031_07_12%20v2.pdf accessed 30th September, 2015.

⁵⁵¹ MacFarlane, J. Ex-priest who volunteered for blood drug trial sues pharmaceutical firm for more than £1million after suffering 'catastrophic' brain damage, 18th January, 2015. Available at <http://www.dailymail.co.uk/news/article-2915009/Ex-priest-volunteered-blood-drug-trial-sues-pharmaceutical-firm-1-million-suffering-catastrophic-brain-damage.html> accessed 30th September, 2015.

⁵⁵² Kulaga, S., Zagarzadeh, A., Berard, A. (2009). Prescriptions filled during pregnancy for drugs with the potential of fetal harm. *Br.J.Obs.Gyn.*, **116**, 1788-1795.

§3.2 states that “No compensation should be paid for injury caused by other licensed medicinal products administered to the patient for the purpose of comparison with the product under trial.” Thus, if a pregnant woman has been randomised to the comparator and delivers a child with a congenital abnormality, although she has been injured as a result of participation in the trial, neither she nor her injured child will be able to seek compensation under the Guidelines; they will need to pursue claims through other mechanisms. In one sense, this does not seem unreasonable; why should one trial sponsor meet costs associated with another company’s drug? The answer may be that the trial sponsor specified the comparator, and so must live with the consequences, consistent with the wording in §5.2. In refusing to meet these costs, the sponsor is passing the burdens associated with recovery of damages on to the subject who has volunteered to assist with the sponsor’s research, aware that she may gain no personal benefit by doing so. §3.2 also brings a new meaning to the term randomised: subjects are randomised not only to a particular treatment but, as a consequence, to a particular path to recovery of damages in the event of foetal harm. It would be interesting to establish the proportion of pregnant subjects who understand this when consenting to participate in a trial, particularly given the absence of a requirement to provide a copy of the ABPI Guidelines to trial subjects. Whilst the 15 year retention period for the treatment allocation code should be adequate for most purposes, should an injury become apparent at a later time, establishing the treatment to which the pregnant woman had been allocated may no longer be possible. Once again, a requirement to retain such information for a 25 year period may be appropriate.

§3.3 stipulates that “No compensation should be paid to patients receiving placebo in consideration of its failure to provide a therapeutic benefit”. Given the requirement for equipoise in all clinical trials, this seems entirely consistent; the approval of a placebo-controlled study is dependent on the premise that no treatment for the condition under study has been approved, or that the condition under study is relatively benign and so randomising subjects to placebo does not result in materially increased risk to the health of these subjects.

7.5.4 Limitation of Compensation

§3.4 of the Guidelines states that “No compensation should be paid (or it should be abated as the case may be) to the extent that the injury has arisen:

§3.4.1 through a significant departure from the agreed protocol;

§3.4.2 through the wrongful act or default of a third party, including a doctor's failure to deal adequately with an adverse reaction;

§3.4.3 through contributory negligence by the patient.”

Although the circumstances defined in §§3.4.1 and 3.4.2 are covered by the NHS Indemnity, these sections raise concerns. Trial subjects do not see the protocol, and so are unlikely to suspect an injury to the foetus may be the result of either of these circumstances unless they had greater than average insight into the conduct of clinical trials. Information relating to adverse reactions and their management is normally contained in the protocol and Investigators' Brochure,⁵⁵³(a compilation of the clinical and nonclinical data on the investigational drug relevant to its study in humans) another document trial subjects do not see. Given that the harm might not be apparent for many months (until birth) or years (as the child begins to show developmental abnormalities), the prospect of a trial subject's parents relating a developmental abnormality to a departure from the protocol or a wrongful act must be remote once again placing a child injured *in utero* at a disadvantage seeking to claim compensation under these Guidelines.

Providing the protocol and the Investigators' Brochure to the trial subjects will not resolve this issue; few participants will have the knowledge or experience to use the information they contain. Congenital abnormalities are reported to the regulatory authorities as serious adverse events, and causality assessed independently by the Investigator and the sponsor. For a child whose injuries are apparent at or before birth, assuming pre-study examinations gave no cause for concern, an independent assessment may establish whether there was a significant departure from the agreed protocol or a wrongful act, as a finding of fact rather than an assignment of causation. The sponsor may be keen to ensure that an association between the injury and the investigational drug is not established, and an Investigator may wish to ensure that the conduct of the trial is not criticised. The REC has the advantage of such independence; however, such investigations may be beyond the capacity of most RECs, which are composed of volunteers, and the investigative traits which may be necessary place such assessments more in the province of the MHRA. However, the possibility of using the arbitration function defined within the Guidelines to examine such cases should be considered, as this would provide an independent assessment, and those

⁵⁵³ Center for Drug Evaluation and Research. Guidance for Industry; E6 Good Clinical Practice, April, 1996, available at <http://www.fda.gov/downloads/Drugs/.../Guidances/ucm073122.pdf> accessed .30th September, 2015.

involved in such activities almost certainly will have developed the necessary investigative traits.

For injuries which become apparent long after birth, solutions are less obvious. A number of regional registers exist which capture congenital abnormalities at birth,⁵⁵⁴ but not later-onset developmental abnormalities, and they are not configured to follow up trial participants. The advantages of some form of prospective registry for pregnant trial participants will be considered in Chapter 8. However, the prospect that some form of tracking of developmental abnormalities might uncover a protocol departure which possibly occurred many years earlier seems remote, and, accordingly, the child's prospects of recovering compensation are low.

7.5.5 Contributory Negligence

The third category in §3.4 - contributory negligence - is perhaps the most controversial and legally complex. The underlying concept is that an individual's acts or omissions contributed to the harm or the extent of the harm sustained by that individual. In such cases, a defendant may argue that this should defeat a claim for compensation entirely or reduce the level of damages, depending on the extent of the contribution to the harm. In clinical trials involving pregnant women, it seems reasonable that this approach should apply to injuries sustained by the women themselves as much as they do to any other study participant. However, the application of these criteria to injuries sustained by the foetus *in utero* is a different matter. As discussed in Chapter 3.5, the pregnant woman has never been held to owe a legal duty of care to her foetus, and no child has successfully brought a claim against its mother in the UK for harm caused by her behaviour during the pregnancy.

With one exception (attempting to procure an abortion) the law in the UK does not seek to control pregnant women's behaviours which might adversely affect the foetus. Should a child be born injured as a result of the pregnant woman's acts or omissions, then, again with one exception (injuries sustained by the foetus in a road traffic accident when the pregnant woman is driving), she is immune from suit by the child under the Congenital Disabilities (Civil Liability) Act 1976 (CDCLA 1976), which will be examined later.

⁵⁵⁴ See, for example, British Isles Network of Congenital Anomaly Registers. Congenital Anomaly Statistics 2010. England and Wales, July 2012. Available at http://www.binocar.org/content/Annual%20report%202010%20FINAL%2031_07_12%20v2.pdf accessed 30th September, 2015, and European Surveillance of Congenital Anomalies website <http://www.eurocat-network.eu/>, accessed 30th September, 2015.

However, whilst the child cannot generally sue its mother for injuries arising from her negligence during the pregnancy, S.1.7 of the CDCLA 1976 does permit contributory negligence by the parent to be considered when assessing the child's claim for compensation against a defendant who owed a duty of care to the pregnant woman and whose wrongful act caused foetal injury 'to such extent as the court thinks just and equitable having regard to the parent's responsibility'.

The ABPI Guidelines make the same provision (§3.4.3), but it is unclear how this part of the Guidelines will be applied, i.e., whether it is intended to apply only to the pregnant woman to reduce a claim for compensation for injuries she has suffered herself, and that §1.3 (that the child should be treated as a patient-volunteer) should be read as applying to the child. If §1.3 should be read in this way, then the pregnant woman's behaviour is irrelevant to any claim by the child; the child cannot be said to have contributed in any meaningful way toward its own injury when it was *in utero*. This interpretation of the Guidelines requires that the foetus is to this extent viewed as an independent research subject from the pregnant woman, which would be consistent with the 'two-patient' construction in Regulation 536 discussed in Chapter 6.3. Conversely, if this provision of the Guidelines affects the compensation payable to the child as a result of the conduct of the woman, they are consistent with the CDCLA 1976, i.e. a 'dyad' model. However, if compensation for *in utero* injury payable to the child is influenced by the conduct of someone who is, in this sense, an independent trial participant, that seems inconsistent with the principle laid down in §1.3 that the child should be treated as a patient-volunteer. This apparent inconsistency between the ABPI Guidelines and the CDCLA 1976 seems unlikely to clarify matters, and so ensuring consistency between these two instruments would be desirable.

Precedent for contributory negligence on the part of the pregnant woman which could affect the compensation recovered by the child is sparse. A Canadian case⁵⁵⁵ concerning medical treatment rather than research concluded that the pregnant woman had contributed to the injuries with which her children were born, but that case was complicated by a failed termination. The woman underwent an 'abortion' early in pregnancy, but failed to attend a post-operative examination. Some three months later she discovered she was still pregnant and elected to continue the pregnancy, delivering twins, one of whom had a congenital

⁵⁵⁵ *Fredette v Wiebe* [1986] 5 WWR 222 (British Columbia Supreme Court).

heart defect. The physician was held to be negligent for not having reviewed a report which would have indicated the termination had failed, and the woman's failure to attend the post-operative examination was held to constitute contributory negligence. There appears to be only one reported clinical negligence case in the UK in which the court found contributory negligence by the patient.⁵⁵⁶ In that case, a woman was held to have contributed to the development of her own cervical cancer by having disregarded smear test appointments for six years. However, here the (non-pregnant) claimant was the victim as well as the person who was contributorily negligent. Given the paucity of cases, it appears that such issues are rarely raised and so the extent to which UK courts would be willing to ascribe contributory negligence to pregnant women giving birth to injured children within a conventional medical setting is unclear. Even if all of the requirements for negligence could be established, one might assume that the policy which generally prevents a child from suing its mother for *antenatal* injury would remain a significant consideration, and might add to the reluctance of courts to reduce damages by ascribing contributory negligence to pregnant women. It therefore seems unlikely the courts will support a radically different approach regarding clinical trials in which pregnant women are, seemingly knowingly, assuming a greater risk than their non-trial counterparts, to enable the generation of information which could help the wider population, and given the scrutiny which all clinical trials must undergo before enrolling participants. Consistent with the ABPI Guidelines, it seems likely that mere participation would not be considered as contributory negligence and it would require some very significant conduct by a pregnant woman before that would be regarded as affecting any compensation to the child.

Herring⁵⁵⁷ has described circumstances in which patients could, conceivably, be partly to blame for injuries which befall them. These include cases where the patient has (i) not revealed relevant facts, (ii) chosen the wrong treatment, (iii) failed to take the treatment provided, and (iv) an unhealthy life-style which worsens the consequences of the negligence. Other commentators have proposed that patients have responsibilities in addition to their rights,⁵⁵⁸ which should follow, in essence, the 'neighbour' principle set out by Lord Atkinson in *Donoghue v Stevenson*.⁵⁵⁹

⁵⁵⁶ *Pidgeon v Doncaster Health Authority* [2002] Lloyd's Rep Med 130.

⁵⁵⁷ Herring, J. (2009). Blaming the patient: contributory negligence in medical malpractice litigation. *Prof.Neg.*, **25**, 76-90.

⁵⁵⁸ See, for example, M Brazier, M. (2006). Do no harm - do patients have responsibilities too? *CLJ*, **65**, 397-422; Draper, H. Sorrell, T. (2002). Patients' responsibilities in medical ethics. *Bioethics*, **16**, 335-352;

However, few authors have considered pregnancy or the foetus, and all have restricted their deliberations to the conventional medical setting, rather than the clinical trial context, where the application of these considerations is perhaps somewhat tenuous. The foetus cannot be accused of any of the acts described by Herring. Of the four circumstances Herring outlines, within a trial setting, the second and third are likely to be under the control of the Investigator. The fourth circumstance, if relevant, should have been addressed in the selection criteria within the protocol, which, of course, the trial subject does not see, and so cannot answer to, although she may be able to infer some of the criteria from the questions she is asked, but such deduction is clearly different from being given the information.

The first circumstance, however, may be relevant. Pregnant women may conceal information for many reasons, including (see Chapter 6.4) a desire to participate in the belief that doing so would confer benefit to herself or her foetus, i.e., therapeutic misconception. The Investigator ought to be able to rely upon a competent pregnant woman's statements,⁵⁶⁰ doing so will not normally constitute negligence, so the NHS Indemnity will not be relevant. The concealed information may have excluded her from the study. Should the pregnant woman experience a serious adverse event, that will impose additional work on the Investigator and medical team in managing and reporting the event to the sponsor, and for the sponsor in reporting the event to regulatory agencies worldwide. This will inevitably incur costs which, should the child be born with a serious injury, could be substantial. The pregnant woman appears to bear no liability towards any party, excepting, perhaps, her injured child in the form of a possible reduction of damages due to her contributory negligence should she make a successful claim on behalf of the child, and the concealed information was discovered. Given the clear challenges of ascribing causality for any congenital abnormality, seeking to relate an abnormality to specific information withheld by the pregnant trial subject seems likely to be extremely difficult.

Kangasniemi, M., Halkoaho, A., Lansimies-Antikainen, H. *et al.* (2012). Duties of the patient: A tentative model based on metasynthesis. *Nursing Ethics*, **19**, 58-67; Coggon, J. (2012). Would responsible medical lawyers lose their patients? *Med.L.Rev.*, **20**, 130-149.

⁵⁵⁹ *Donoghue v Stevenson* [1932] A.C. 562.

⁵⁶⁰ *Venner v North East Essex Health Authority and another* [1987]. *The Times*, 21 February 1987, cited in Herring, J. (2009). Blaming the patient: contributory negligence in medical malpractice litigation. *P.N.*, **25**, 76-90.

However, in all of this there is also the matter of justice for the child; why should its claim against a trial sponsor be reduced because of the conduct of its mother? The child is clearly not at fault and it cannot recover damages from her. Conversely, there is the argument that a sponsor should not be held liable to a child if the injury, or its extent, is not wholly attributable to some aspect of the trial within the sponsor's control, including an inherent defect in the investigational drug. The acts or omissions which would constitute relevant contributory negligence are unclear in both the ABPI Guidelines and S.1.7 of the CDCLA 1976.

Both §3.4.3 of the Compensation Guidelines and S1.7 of the CDCLA 1976 could potentially be invoked in such a circumstance to reduce any compensation payable to the child. It is not obvious that these circumstances would necessarily be brought to the attention of a potential trial subject within the consent process. An abatement of compensation due to contributory negligence of the pregnant woman could amount to a potential injustice to the child, but that would be the same as in any other *antenatal* injury situation.

The lack of clarity regarding the behaviours which would constitute contributory negligence, the remarkably small number of reported occasions upon which this appears to have been invoked, and the resulting injustice to the child, together, suggest that retaining this provision is unwarranted, and it should be removed from both the ABPI Guidelines and the CDCLA 1976, with removal from the latter restricted to a clinical trial setting, for reasons which will be explained in Chapter 8.

7.5.6 Relative Risks, Benefits and Consent

§4.2 of the ABPI Guidelines defines additional restrictions regarding compensatory payments in the event of trial-related injury. It states:

“Compensation may be abated, or in certain circumstances excluded, in the light of the following factors (on which will depend the level of risk the patient can reasonably be expected to accept):

§4.2.1 the seriousness of the disease being treated, the degree of probability that adverse reactions will occur and any warnings given;

§4.2.2 the risks and benefits of established treatments relative to those known or suspected of the trial medicine.”

This section is based on the premise that, having been properly informed of the potential risks, by enrolling into the trial, the subject has accepted the level of risk and so cannot reasonably seek compensation for the occurrence of an adverse reaction of which she was told. Essentially, the ABPI is prospectively invoking a *volenti* defence⁵⁶¹ which seems to contradict the essence of §1.6 (the fact that the patient has freely consented to participate in the trial should not exclude her from consideration for compensation under the Guidelines) and §1.7 (that the trial subject is not required to prove that the (sponsor) company has been negligent or that the product is defective).

The interpretation of §4 should a foetus be injured *in utero* is unclear. Having given her consent, the pregnant woman has also ‘consented’ for the foetus (see Chapter 4). Even if the child is considered as a patient-volunteer under §1.3, it would appear that the pregnant woman’s consent may restrict the child’s possibility of recovery as much as it would affect the pregnant woman’s, if she were the injured person. If this is correct, and if the criteria under §4.2 are deemed to be met, then a child born with a congenital injury would appear not to have a basis for claim under these Guidelines. An alternative, canvassed earlier, might be that if §1.3 of the Guidelines is construed to favour the child,⁵⁶² the pregnant woman’s consent may not constitute a bar to recovery. The latter would be the preferable situation, for reasons of justice to the child.

§4 raises two further issues. The first is the appropriateness of another person giving consent and the possibility of the foetus being injured when the pregnant woman is not. This was explored in Chapter 4; the conclusion was that the maternal-foetal ‘dyad’ represented the best model, with the fully-informed pregnant woman taking decisions in the knowledge of the possible effects upon the foetus. However, both the ABPI Guidelines and Regulation 536 seem to categorise the foetus as ‘another subject’ - although the ‘other subject’ cannot consent. As discussed in Chapter 6.3, if the pregnant woman is considered as giving proxy consent for the foetus, i.e., a ‘two-patient’ model, as exists for paediatric and incapacitated subjects, then a child injured *in utero* should be able to claim

⁵⁶¹ The Latin phrase ‘*volenti non fit injuria*’ is commonly used to describe a defence from tortious liability whereby the plaintiff “freely and voluntarily, with full knowledge of the nature and extent of the risk he ran, impliedly agreed to incur it”: *Letang v Ottawa Electric Rly. Co.* [1926] A.C. 725 at 731 (citing *Osborne v London and North Western Rly. Co.*) (1888) 21 QBD. 220.

⁵⁶² This is discussed in Chapter 7.5.2.

compensation in exactly the same way as minors and the *incapax*. Perhaps the issues simply need to be disentangled. The pregnant woman - alone - may consent to participate in a clinical trial which the REC - having utilised the special expertise specified in Regulation 536 - has decided is acceptable for pregnant women. Should the resulting child be born injured, and that injury is held to be attributable to the clinical trial, then the child should receive appropriate compensation under §1.3, without limitations; this will be discussed in Chapter 8.

The second relates to the statement regarding the gravity of the condition being treated. More serious conditions generally require more aggressive treatment, which may carry with it an increased risk of an adverse event, including foetal harm. The adverse event might be considered to constitute a ‘less detrimental option’ than the untreated condition, at least as far as the woman is concerned, but could lead to an abatement of compensation. Should a pregnant woman enrol in a clinical trial with an investigational drug which offers the potential to treat her life-threatening condition, one would expect that the potential risks to her and her foetus would have been explained and accepted as part of the consent process. If the woman is also giving consent ‘for’ her foetus, then the resulting child would be considered to have assumed the same risks as the pregnant woman who gave her consent for the trial. Such a construction is certainly internally-consistent, if somewhat unedifying. One might think that a pregnant woman who enrolled in a clinical trial would expect assurance that in doing so she was not also taking a significant risk of disadvantaging her future child, and that would still be the case where the condition she was suffering from was a serious one. Women are legally entitled to balance the risks for themselves and their foetuses when considering medical treatment and if a drug was being given as part of routine medical treatment for a life threatening condition, a child born damaged may similarly find difficulty in recovering compensation. However in a clinical trial setting, the additional issue arises that the demands of equipoise mean there may be no countervailing benefit to the woman to offset the risk to the foetus, as considered earlier.⁵⁶³

Under §4.2.2, compensation may be abated, or in certain (undefined) circumstances excluded, depending on the risks and benefits of established treatments relative to those known or suspected of the trial medicine. As described in Chapter 6.2, it would appear that, in the UK, clinical trials may proceed in advance of ICH-specified preclinical testing.

⁵⁶³ See Chapter 4.4 for discussion of this point.

If clinical trials in pregnant women proceed in parallel to or in advance of reproductive toxicology testing, then - arguably - the investigative drug may have no known or suspected teratogenic effect, because the relevant research has not been conducted, in which case it may appear to be 'safer', or at least no riskier, than established treatment. Furthermore, established treatment may be simply supportive care; there may be no known treatment for a particular condition. As discussed in Chapter 4.4, if the condition itself is teratogenic or foetotoxic, then once again the investigational drug may appear to be a 'better' or 'less detrimental' option, as a result of which, should it express teratogenic effect, then recovery of compensation may prove challenging. The occurrence of teratogenesis is not yet predictable, and so an approach which may deny compensation to a child born injured on the premise that an alternative treatment might have done the same seems flawed; it is arguably consistent with a 'fault' approach and less consistent with a no-fault one.

A related issue arises when an investigational drug is administered to pregnant human subjects for the first time. Given the lack of predictive accuracy of preclinical models,⁵⁶⁴ it would seem inconceivable that the consent documents would not contain a warning that the effects of the drug on the foetus are unknown, and yet that information, intended to inform and support the pregnant trial subject is the same piece of information that seemingly results in her child, if born injured, being prevented from seeking compensation.⁵⁶⁵ The child born injured is prevented from asserting a legal claim for compensation as that would be contrary to the prior conduct of another, i.e., the pregnant woman, signing the consent document warning that there were unknown teratogenic risks. So, although consent to participate *per se* should not exclude a claimant from consideration for compensation under the Guidelines (§1.6), and the claimant does not need to establish negligence or that the product was defective (§1.7), it would appear that the pregnant woman signing a consent form which contains relevant warnings may potentially prevent her child's claim - and yet signing the consent form is a prerequisite for participation. If correct, this construction would also seem, potentially, to exclude claims from all subject groups. Since awards under these Guidelines are not made public, the accuracy of this construction cannot be ascertained.

⁵⁶⁴ Scialli, A.R. (1993). Animal studies and human risk. *Reprod.Toxicol.* **7**,533-534; Brent, R.L. (2004). Utilization of animal studies to determine the effects and human risks of environmental toxicants (drugs, chemicals, and physical agents). *Pediatrics*, **113**, 984-995.

⁵⁶⁵ See the argument proposed in Alghrani, A., Brazier, M. (2011). What is it? Whose it? Re-positioning the fetus in the context of research? *CLJ*, **70**, 51-82.

7.5.7 Relevance of the ABPI Guideline in this population

Whilst the absence of a requirement to furnish all trial subjects with the ABPI Compensation Guidelines (when the trial sponsor is an ABPI member) is disappointing, based on the analyses above, the Guidelines may not provide the level of protection which the trial subjects may believe is the case.

The Compensation Guidelines, like the data retention periods discussed earlier in this chapter, may be applicable to the vast majority of the people who now become trial participants annually. Were this not the case, the press and the courts would surely abound with cases, and they do not. The Guidelines were introduced in 1970, and so we have 45 years of experience, involving an unknown number of trial participants (due to incomplete record-keeping prior to the implementation of the CTD in 2004), upon which to make this conclusion. However, for the reasons explained in the Introduction to this thesis, the number of pregnant trial subjects on whom to base an assessment of these Guidelines is infinitesimally small, and given the low incidence of iatrogenic teratogenicity, the number of cases which would arise for consideration would - hopefully - be even smaller.

However, the ABPI Guidelines clearly contain a number of limitations and uncertainties which are scattered throughout their eight pages, and so may not be readily-assimilated by participants, which could mean, even if they request a copy of the Guidelines, they remain unaware of the impacts of these restrictions. Since pregnancy constitutes a unique condition which raises many distinct issues, a separate set of Guidelines specifically for use in clinical trials in pregnant women may be an appropriate means by which potential participants are properly informed regarding this route to compensation in the event of foetal injury. Of course, should the sponsor not be a member of the ABPI, these Guidelines would be inapplicable, and recourse may need to be made directly to the courts, most likely *via* the provisions within the CDCLA 1976.

7.6 The Investigator as a Respondent - the NHS Indemnity

The current position regarding NHS insurance is contained in the recently-released document by the Department of Health to all universities in the UK.⁵⁶⁶ In the event of negligent harm during a clinical trial, when the NHS body owes a duty of care to the

⁵⁶⁶ NHS Indemnity Arrangements for Clinical Negligence Claims in the NHS, available at <http://www.nhs.uk/claims/Documents/NHS%20Indemnity.pdf>, accessed 30th September, 2015.

healthy volunteer or patient harmed, the NHS Indemnity comes into effect, as described earlier in this chapter. Public bodies, including the Department of Health, the Medical Research Council and NHS trusts, are unable to pay compensation for non-negligent harm, although they may consider an *ex-gratia* payment in the case of a claim. In the event of foetal harm manifesting upon birth, the mother, representing her child, would need to raise an action in negligence against the Investigator should she elect to follow this route, again most likely *via* the provisions within CDCLA 1976. As indicated in the previous section, evidence of negligence in the form of departure from the protocol or disregard of information within the Investigators' Brochure, i.e., fault, would be particularly difficult to establish, in addition to the causation requirement.

7.7 The Trial Approvers as Respondents

7.7.1 The REC

Successive UK governments have seemed keen to distinguish between the ethical and legal issues associated with clinical trials. This distinction seems sensible. The purpose of the review by the REC is to assess whether a proposed study is ethical; the REC structure in most European countries, whilst admitting lawyers, is neither intended nor equipped to provide a comprehensive review of compliance with applicable legislation, and approval from the REC is predicated upon the condition that the trial will be conducted in a manner consistent with applicable law. The most recent version of Department of Health's Governance Arrangements for Research Ethics Committees,⁵⁶⁷ published in 2011, states at §5.4.2 that "RECs will accept credible assurances that others will do what is expected of them" and gives the following examples:

- (a) A REC need not reconsider the quality of the science, as this is the responsibility of the sponsor (the TeGenero incident, discussed later, arguably illustrates the flaw in this position);
- (b) A REC can expect to rely on established mechanisms for ensuring the proper conduct of the research at individual sites (the processes in NHS hospitals for establishing protocol non-compliance months or years previously are not established);

⁵⁶⁷ Department of Health Governance arrangements for research ethics committees, May 2011. Available at https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/213753/dh_133993.pdf, accessed 30th September, 2015.

- (c) Where others have a regulatory responsibility, a REC can expect to rely on them to fulfil it; the Medicines and Healthcare products Regulatory Agency has the primary legal responsibility for considering the safety of the research it regulates, and it may authorise trials in the absence of data defined in the relevant ICH Guidelines.

The responsibility for ensuring legislative compliance rests with the sponsor, and a list of Enforcing Authorities is given in Appendix D of the Governance Arrangements. Appendix D also contains the statement: “An appointing (health) authority.... indemnifies members of its RECs to relieve them of personal liability in respect of their opinions of the ethics of research”. The reason for this indemnification is not immediately obvious, nor is the basis upon which the REC, seemingly, cannot be held liable in negligence by subjects injured in clinical trials. The answer appears to be that a REC lacks a legal personality separate from that of its members; it is an unincorporated association brought together for a particular purpose but which does not have legal personality⁵⁶⁸ as would be the case for a limited company. As a result, an action regarding a REC’s conduct must be brought against the individual members or the Health Authority (hence the members’ indemnification), as the appointing body, and possibly, for some of the members, the employer. Neither the MHU Regulations 2004 nor Regulation 536 alters the existing legal position of the REC. Thus the prospect for successful action against the REC itself is doubtful, although RECs may be subject to judicial review.⁵⁶⁹ Were an action to be brought against an NHS REC it would need to be brought against the body establishing the REC and individual members would be joined in the action. Alternatively the NHS body establishing the REC may be held to owe a duty owed to research subjects; the REC is, in effect, a sub-committee of the Health Research Authority, and the Authority is legally responsible for the decisions of the REC.⁵⁷⁰

Thus, in the event of injury, the REC would appear to be unlikely to shoulder any legal liability, although the RECs’ apparently unquestioning acceptance of assurances from

⁵⁶⁸ See discussion in Brazier M. (1990) Liability of ethics committees and their members. P.N. 6, 186-190; Huxtable, R. (2013). The best of both worlds? Combining courts and clinical ethics committees. P.N., 29, 25-48.

⁵⁶⁹ *R v Ethical Committee of St Mary’s Hospital (Manchester) ex parte H.* [1988]. 1 FLR 512. The decisions of public bodies will be scrutinised if they are held to be *ultra vires* and may be challenged on the basis of legality, irrationality and procedural impropriety. <http://www.hra.nhs.uk/about-the-hra/our-committees/research-ethics-committees-recs/>

⁵⁷⁰ Brazier M. *Medicine, Patients and the Law.* 5th Edn., London: Penguin, 2011, pp463-468; see also <http://www.hra.nhs.uk/about-the-hra/our-committees/research-ethics-committees-recs/> accessed 7th May, 2016

other parties may be open to criticism. This is in contrast with the position in the USA, for example, where IRBs bear responsibility for ensuring legislative compliance.⁵⁷¹

7.7.2 The MHRA and Related Bodies

The MHRA also seems an unlikely respondent in the event of an action to recover damages for trial-related injury. The MHRA is neither a ‘producer’ nor ‘supplier’ under the Consumer Protection Act 1987, so no claim against the MHRA could be mounted on that basis; in any event, investigational medicinal products are not subject to this legislation. No cause of action for breach of statutory duty exists in relation to any breaches of the Medicines Act 1968, which provides the statutory basis for UK medicines regulation⁵⁷². Accordingly, if a trial subject brought an action for damages against the MHRA, it would most likely need to be framed as a common law action in negligence, on the basis that the MHRA did not properly consider the safety aspects of a trial in authorising it to proceed.

To date, there has not been a successful civil action for damages against the UK or any European regulatory body, although there have been attempts to establish liability. The most recent of these in the UK involved the development of Reyes Syndrome in a child given aspirin. The UK regulatory body at the time was the Committee on the Safety of Medicines (CSM). In *Smith v Secretary of State for Health*,⁵⁷³ Morland J found on the facts that no fault was established against the Secretary of State, the Department’s Secretariat or the CSM. He considered whether the CSM could owe a duty of care, and concluded that the relevant acts or omissions (in this case, an alleged failure to issue a warning in a timely manner) should be categorised in law as discretionary/policy decisions, taken in the exercise of statutory powers or duties, and so were not justiciable, although he did not rule out the possibility of the CSM ever owing a duty of care in tort to an individual member of the public affected by a failure to exercise or an improper exercise of its statutory powers and functions. This case appears not to have been cited subsequently,

⁵⁷¹ Icenogle, D.L. (2003). IRBs, conflict and liability; Will we see IRBs in court? Or is it when? *Clin, Med. Res.*, **1**, 63-68.

⁵⁷² Medicines Act 1968, S.133(2). See also *Smith (by her mother and next friend) v Secretary of State for Health* [2002] Lloyd’s Rep Med 305 at 37. Further, neither the National Health Service Act 2006 nor the now-repealed Ministry of Health Act 1919 have been held to give rise to such rights – see *R. v Central Birmingham Health Authority, ex p. Walker* [1987] 3 BMLR 32; *Danns v Department of Health* [1995] 25 BMLR 121.

⁵⁷³ *Smith v Secretary of State for Health* [2002] EWHC 200 (QB);

suggesting that any attempts to establish the MHRA's possible liability have not progressed to the courts.

7.8 Specific Legislative Instruments

The four instruments which might offer a route to compensation for foetal injury are the Congenital Disabilities (Civil Liability) Act 1976, the Vaccine Damage Payments Act 1979, the Consumer Protection Act, 1987, and the Sale and Supply of Goods Act 1994. The latter two are of less relevance to the setting of clinical trials of investigational drugs, and so will be addressed first before considering the two items of legislation introduced with the specific intent of providing routes to a remedy in the event of iatrogenic injury.

7.8.1 Sale and Supply of Goods Act 1994 (SSGA 1994)

The SSGA 1979 places upon sellers an obligation to ensure that merchandise meets the standard that a reasonable person would regard as satisfactory, taking account of any description of the goods, the price (if relevant) and other pertinent circumstances. The extent of this Act, defined in section 8 (3) is that it “has effect in relation to contracts of sale of goods, hire purchase agreements, contracts for the transfer of goods, contracts for the hire of goods and redemptions of trading stamps for goods (as the case may be)”, which clearly does not capture the situation which obtains in a clinical trial setting. Thus, whilst a reasonable person might not consider as satisfactory an investigational drug which is possibly teratogenic, this Act does not offer a child born injured a route to a remedy.

7.8.2 Consumer Protection Act, 1987 (CPA 1987)

The CPA 1987 is applicable to approved medicines. Pursuant to European Community Directive 85/374/EEC (the Product Liability Directive), Part 1 of the Act introduces a regime of strict liability for damage arising from defective products. Section 2 imposes civil liability in tort for damage caused wholly or partly by a defect in a product upon the producer and importers of the product into the European Union for commercial sale. Thus, the requirement to establish causation remains. As a condition of approval the manufacturer of the drug will have been required to submit to the regulatory authorities all preclinical and clinical information relating to the drug, to maintain the documentation described earlier in this chapter, and so recovery of relevant information in support of a claim should be possible. Section 4(1)(e) of the CPA 1987 provides a statutory defence, commonly referred to as the ‘Development Risks Defence’, which states that: “the state of

scientific and technical knowledge at the relevant time was not such that a producer of products of the same description as the product in question might be expected to have discovered the defect if it had existed in his products while they were under his control”.

Although not strictly analogous, Burton J.’s judgment in *A v National Blood Authority*,⁵⁷⁴ set something of a landmark: he considered that the ‘development risks’ defence did not apply where the existence of a generic defect was known or where it should have been known from accessible information, and the knowledge held by the medical profession was irrelevant; potential patients had a right to be warned too. This case was heard shortly after *Pearce*,⁵⁷⁵ and it is tempting to suggest that the concept of the ‘prudent patient’ was in Burton J.’s contemplation in coming to his ruling.

As the CPA 1987 is applicable to approved drugs, this ruling is irrelevant to investigational drugs, but the Act could be engaged regarding a comparator agent in a clinical trial, and to this limited extent it may therefore have some utility, although the difficulties in establishing causation would remain. The ‘development risks defence’ could provide a response to a thalidomide-type claim, or at least ensure such complicated litigation resulted that redress could be long deferred.⁵⁷⁶ As noted by Howells and Weatherill:

“Given the presence of the development risks defence it is likely that thalidomide would not be labelled defective because the state of scientific knowledge would not have revealed the defect.”⁵⁷⁷

Miller and Goldberg concur, contending that it is “strongly arguable” that for thalidomide one would have had to identify “some standard or general acceptance within the advanced sectors of the relevant scientific community that there was a need for ... testing on pregnant animals.” Given the absence of such a standard at the time, they conclude that the manufacturers of thalidomide may well have succeeded with a development risks defence had the Directive been in force.⁵⁷⁸

⁵⁷⁴ *A v National Blood Authority* [2001] 3 All E.R. 289.

⁵⁷⁵ *Pearce v United Bristol Healthcare NHS Trust*, [1999] P.I.Q.R. P53.

⁵⁷⁶ As Stevens comments, the “battle for the Thalidomide victims of Great Britain lasted longer than the Trojan War”. Stevens, T.D. *Dark Remedy: The Impact of Thalidomide and Its Revival as a Vital Medicine*. Cambridge: Basic Books, 2001, at p79.

⁵⁷⁷ Howells, G., Weatherill, S. *Consumer Protection Law*, 2nd Edn. Aldershot: Ashgate Publishing, 2005, at p249.

⁵⁷⁸ Miller, C.J., Goldberg, R.S. *Product Liability*, 2nd edn. Oxford, OUP, 2004 at p520.

Upon becoming aware of reports that a licenced drug may be associated with a teratogenic risk, the manufacturer is obliged to warn prescribers and patients of that risk. Had the risk been known prior to the approval of the drug, either the drug would not have been approved, or that information would have been contained in the package insert which accompanies all medicines, and it would also have been documented in the information provided to prescribers. The approval of the drug and the absence of relevant warnings indicate that the existence of the defect was not known and, arguably, “not discoverable in the light of the scientific and technical knowledge, available at the time.”⁵⁷⁹

Since the thalidomide tragedy was one of the main drivers behind both the CDCLA 1976 and the CPA 1987, these conclusions perhaps illustrate most poignantly how ineffective the legislative protection is for the foetus.

For trial subjects allocated to the investigational drug, the CPA 1987 does not provide an avenue to a remedy. Even if that drug goes on to become an approved medicine, and a claim can be brought within the limitation period, the development risks defence - that the defect could not have been known based on available information at the time of the injury - would potentially apply. For an approved drug being used as a comparator in a clinical trial, the CPA 1987 could be engaged, but causation would need to be established, and if the teratogenic injury was the first reported, the claim may be defeated by a combination of the development risks defence described above and the balance of probabilities argument addressed later in this chapter.

7.8.3 Congenital Disabilities (Civil Liability) Act 1976 (CDCLA 1976)

The perceived hiatus in the common and civil law approaches for the recovery of compensation for congenital injury in England and Wales in the wake of thalidomide led the Law Commission⁵⁸⁰ to recommend a legislative approach to permit the recovery of damages by a child born injured. Two years later, the CDCLA 1976 came into force in England and Wales; all claims for *antenatal* injury at common law are now brought under this Act. The Scottish Law Commission considered that Scots law already accorded a common law right of action to live-born children injured *in utero*.⁵⁸¹

⁵⁷⁹ *A v National Blood Authority (No.1)* [2001] 3 All E.R. 289

⁵⁸⁰ Law Commission Report *Injuries to Unborn Children 1974* (No. 60, Cmnd. 5709)

⁵⁸¹ Hansard HL Deb, 27 May 1976, Vol 371, cols 356–87; Scottish Law Commission, *Report on Liability for Antenatal Injury*, Scot Law Com No 30, Cmnd 5371 (HMSO Edinburgh, 1973), §§ 8–21.

The legislative approach seems attractive for many reasons, not least that it avoids the need for the courts to manipulate the traditional elements of tort law to resolve the apparent contradiction of a duty of care being owed to a foetus which lacks legal personality, and whose existence may be unknown at the time the injury is suffered, e.g., during the first trimester when the foetus is at its most biologically vulnerable as organogenesis begins.⁵⁸² The existence of the foetus will be known for clinical trials intentionally conducted in a pregnant population, and the fact that the Act explicit states that a duty may exist to compensate a child born injured as a result of acts or omissions before its birth provides a clear starting point for litigation. That said, the relevance of the provisions of the CDCLA 1976 to the clinical trial setting has not been clarified in the courts.

The Act imposes liability for *antenatal* injury when a child is born alive and suffering from a disability caused by a wrongful act affecting either parent in his or her ability to have a healthy child (section 1(2)(a)), or affecting the mother in her pregnancy, or the mother or the child in the course of birth (section 1(2)(b)). The defendant is liable to the child if he/she would also be liable in tort to the parent (section 1(3)). Liability to the child is derivative, usually from the mother,⁵⁸³ for example a physician negligently administering a teratogenic drug to a pregnant woman. Thus, the CDCLA 1976 might appear to be applicable to clinical trials involving pregnant women, as the Investigator certainly can be liable in tort to the trial subject - the pregnant woman (applying the 'dyad' model). Assuming the Investigator has complied fully with the approved protocol, and has not in any sense fallen short of the expected standards of a clinical Investigator in minimising the risk of harm, to the extent it was within his power to do so, to the pregnant woman and her foetus, as discussed in Chapter 5.4, then it is difficult to see how a congenital abnormality could be the result of a wrongful act by the Investigator.

However, an additional demand is imposed on a child seeking recovery for injury *in utero* regarding causation. The CDCLA at section 1(2)(b) provides that (emphasis added) "An occurrence to which this section applies is one which... (b) affected the mother during her pregnancy, or affected her or the child in the course of its birth, so that the child is born with disabilities *which would not otherwise have been present.*" Thus, in addition to

⁵⁸² Green, M.A. *Bendectin and Birth Defects: The Challenges of Mass Toxic Tort Substances Litigation*. Philadelphia: University of Pennsylvania Press, 1995.

⁵⁸³ The scope of the Act is sufficiently wide to embrace a claim derivative on a wrong done to the father too, e.g., damage to his sperm as a result of negligent exposure to toxic substances that resulted in foetal abnormality.

establishing causation, the child needs also to prove that but for the ‘occurrence’ he could have been born uninjured. The defendant could maintain that, despite proof that the pregnant woman had not been provided with adequate information regarding the risks, the claimant child still has to establish that, had adequate information been provided, the injury would not have happened, i.e., the woman would not have taken part in the trial because of the additional information, consistent with the judgement in *Pearce*,⁵⁸⁴ explained in Chapter 6.4, and as a result the child would have been born uninjured. This is in addition to the need to establish that the injury was, on the balance of probabilities, due to the trial drug, rather than being an unrelated congenital abnormality.

Section 1(5) of the Act stipulates that a person tortiously liable to the parent is not answerable to the child for anything he did or omitted to do when responsible in a professional capacity for treating or advising the parent, if he took reasonable care having due regard to then received professional opinion applicable to the particular class of case. This section contains three distinct elements: professional capacity, treatment and advice, which will be addressed in turn.

The reference to received professional opinion is reminiscent of the *Bolam*⁵⁸⁵ standard which was unchallenged when the CDCLA 1976 was enacted. In *Sidaway*,⁵⁸⁶ Sir John Donaldson MR commented that “‘Due regard’ involves an exercise of judgement *inter alia* as to whether ‘received professional opinion’ is engaged in the same exercise as the law”, and suggested the alternative wording (additional word emphasised) “The duty is fulfilled if the doctor acts in accordance with a practice *rightly* accepted as proper by a body of skilled and experienced medical men.” As discussed in Chapter 6.4.1, it seems likely that the standard defined in *Montgomery* would now be considered appropriate. The question of whether the ethics and regulatory review processes which preceded approval of the trial would constitute received professional opinion, thereby insulating the Investigator and the sponsor from liability, has similarly not been tested. If those reviews do constitute received professional opinion, issues might then arise in respect of the liability of the MHRA and/or the REC, but as discussed previously, this seems unlikely to be a successful route for legal action.

⁵⁸⁴ *Pearce v United Bristol Healthcare NHS Trust*, [1999] P.I.Q.R. P53.

⁵⁸⁵ *Bolam v Friern Hospital Management Committee* [1957], 2 All E.R. 118.

⁵⁸⁶ *Amy Doris Sidaway v The Board of Governors of the Bethlem Royal Hospital and the Maudsley Hospital and Coutts & Co. and Mrs. Valda Helen Falconer in their capacities as Executors of Mr. Murray A. Falconer deceased*, 1984] Official Transcript.

Given the uncertainties regarding the Investigator-Subject relationship explained in Chapter 5, and the restrictions regarding the information the Investigator has within a clinical trial, the treatment element of section 1.5 is difficult to sustain. In a Phase I study, the subject is not being treated at all. In a Phase II or III study, the subject may be receiving placebo or a comparator, and the Investigator may not know this. Given the ethical requirement for equipoise, even if the subject is allocated to the investigational drug, the conduct of the trial means that the efficacy of the agent is unproven, and it may be ineffective. Taken together, the Investigator can hardly be said to be *treating* the subject.

Similarly, as adherence to the approved protocol is a requirement under the MHU Regulations 2004, the Investigator is deprived of clinical freedom. A number of commentators have argued that the constraints on clinical freedom imposed by adhering to a protocol deprive the Investigator of the opportunity to advise.⁵⁸⁷ Thus, if the Investigator is not treating the patient, and is deprived of the opportunity to advise the patient, arguably, section 1.5 is not applicable to the clinical trial setting.

Nevertheless, if the trial participant has signed the consent document(s) approved by the REC, and the Investigator has been available to answer the pregnant woman's questions, the Investigator arguably has acted in a professional capacity when advising the participant insofar as that is possible within the constraints of a clinical trial described previously, and so would appear to have complied with the defence defined in the Act in section 1(5).

Finally, section 1.7 of the CDCLA 1976 creates provision to reduce damages to the extent the court considers just and equitable should the parent, in this setting the mother, share the responsibility for the child being born disabled. Given that participation in a clinical trial is entirely voluntary and therefore avoidable, one might construe that the mother is entirely responsible for the child's disability (factual causation of the but-for test). However, unless the mother was negligent in some way, e.g., not following the trial protocol, or withholding relevant information, as described above, her participation does not seem likely to be deemed to be the cause of the injury. The legal causation will come from the list given in the Introduction to this chapter (an adverse reaction to the investigational drug,

⁵⁸⁷ Morreim, E.H. (2005). The clinical Investigator as fiduciary: discarding a misguided idea. *J.Law Med. Ethics*, **33**, 586-598; Mello, M.M.; Joffe, S. (2007). Compact versus contract—Industry sponsors' obligations to their research subjects. *N.Engl.J.Med*, **356**, 2737-2743; Meyer, M. N. (2006). The plaintiff as person: Cause lawyering, human subject research, and the secret agent problem. *Harvard L.Rev.*, **119**, 1510-1531.

an adverse reaction to a comparator agent, an adverse response to a procedure, and an adverse consequence due to the underlying condition), but, as indicated above, the child will need to establish that the specific injuries would not have arisen but for one of these causes.

Unless negligence in some aspect of the conduct of the trial can be established, then the CDCLA 1976 does not constitute a promising route by which a child injured *in utero* by an investigational or an approved drug given to a pregnant woman in a clinical trial setting might seek a remedy. In such a circumstance, recourse would, where possible, be made to the ABPI scheme in the first instance to avoid the expense of and time for litigation. However, as explained in Chapter 7.5, the conditions within the Guidelines generate a number of uncertainties. Although it seems to be intended that compensation can be paid without proof of fault, a number of limitations within the Guidelines mean that the outcome may be the same under either route. The CDCLA 1976 was drafted when thalidomide, a marketed product, was, understandably, to the fore, and the conduct of clinical trials in pregnant women was not in contemplation. Both of these situations have now changed: acutely teratogenic drugs have not been seen since thalidomide, thalidomide has now found a therapeutic niche, and clinical trials are about to be conducted using thalidomide in pregnant women. The question of whether the CDCLA 1976 is relevant to clinical trials will be discussed further in Chapter 8.

7.8.4 The Vaccine Damage Payments Act 1979 (VDPA 1979)

There is no doubt that vaccination has played a significant role in reducing the incidence of a number of formerly commonplace infectious diseases, with a resultant reduction in morbidity.⁵⁸⁸ The rationale behind vaccination programmes is that of ‘herd immunity’: if a sufficiently large proportion of people in a community is immunised, then it is more difficult for that disease to be passed to unimmunised people.⁵⁸⁹ In the case of some vaccinations, therefore, this constitutes a medical procedure conducted primarily for the good of society as a whole, rather than for the clinical benefit of the recipient. The most obvious example of this is rubella vaccine for boys; the disease would probably be almost harmless to the child himself, but his vaccination contributes to the protection of the foetus which can be seriously harmed by maternal rubella during the first trimester of pregnancy

⁵⁸⁸ Pywell, S. (2002). A critical review of the recent and impending changes to the law of statutory compensation for vaccine damage. *J.P.I. Law*, **4**, 246-256.

⁵⁸⁹ Mello, M.M. (2008). Rationalizing vaccine injury compensation. *Bioethics*, **22**, 32-42.

(another example of foetal protection, in which we do something to the living to protect the not-yet-born).⁵⁹⁰ However, vaccination has long been known to carry a range of risks, and there have been numerous reports of ‘vaccine disasters’.⁵⁹¹

The VDPA 1979, like the CDCLA 1976, was one of the results of the Pearson commission, the major inquiry into civil damages in the UK in the 1970s. It is applicable to disabilities resulting from vaccinations against particular diseases specified by the Secretary of State, including those resulting from maternal vaccination against one of the diseases in the relevant list during pregnancy. In the mid-1970s the UK Government had started to make *ex gratia* payments for vaccine injury. The Commission recommended that the Government should accept liability to pay full ‘compensation’ for vaccine injury on the basis that this is the very occasional price that society pays for the benefit of defeating disease through national vaccination programmes, and the Government had recommended numerous such programmes.⁵⁹² The 1979 Act placed this recommendation on a statutory basis. Since the Act was originally passed, the list of diseases has been updated on a number of occasions, the extent of disability required has been reduced, the time within which to make a claim has been extended, and the size of payments increased. It does not specifically restrict disability to that resulting from an approved, licenced vaccine, and given the general benefit to society which has resulted from vaccination, one might infer that the Act could be engaged in respect of congenital injuries related to investigational vaccines targeting the specified diseases. The Act does not create a no-fault liability scheme, or, arguably, a compensation scheme; the classic view of tortious compensation is that its purpose is to put the victim back into the pre-tortious position, and this is clearly impossible in cases of the irreversible personal injuries which characterise vaccine damage.

Immunisation against whooping cough was much in the public eye in the mid-1970s.⁵⁹³ Vaccination rates were falling, due to concerns regarding the risk of vaccine-related neurological damage.⁵⁹⁴ Reassurances from the Joint Committee on Vaccination and Immunisation were not helped by the lack of reliable data on the incidence of vaccine-

⁵⁹⁰ Tindley, R. (2008). A critical analysis of the vaccine damage payments scheme. *Eur.Bus.Law Rev.*, **19**, 321-363.

⁵⁹¹ See, for example, <http://www.whale.to/m/smallpox/disasters.html>, accessed 4th April, 2016,

⁵⁹² Royal Commission on Civil Liability and Compensation for Personal Injury, Cmnd 7054-1 (1978), para 1408.

⁵⁹³ Anonymous. (1981). Pertussis Vaccine. *Br.Med.J.*, 282, 1563-1564.

⁵⁹⁴ Swansea Research Unit of the Royal College of General Practitioners. (1981). Effect of a low pertussis vaccination uptake on a large community. *Br.Med.J.*, 282, 23-26.

related damage.⁵⁹⁵ The Government-commissioned National Childhood Encephalopathy Study (NCES) was launched in 1976 to assess the risks of such injury. The initial report, published in 1981, found a significant association between pertussis vaccination and severe neurological injury and death.⁵⁹⁶ The Pearson Commission had recommended the introduction of strict liability in tort for vaccine damaged people. However, in 1983, the Government made clear that the recommendation would not be implemented, considering that the 1979 Act already provided vaccine damaged children with a measure of preference without prejudicing their right to institute legal proceedings on the grounds that negligence had occurred.⁵⁹⁷

Thus, there are two potential routes to financial recompense for the victims of vaccine damage: they can claim under the Vaccine Damage Payment Scheme created by the VPDA 1979 and/or bring claims before the civil courts. The latter route has never led to a successful claim in England or Wales, principally because of the outcome in *Loveday v Renton*.⁵⁹⁸ In an unusually proactive judicial intervention, Stuart-Smith LJ ordered discovery of some of the individual medical records examined in NCES and subsequently adjusted the data tables to eliminate the effect of certain cases which appeared to have caused errors. His Lordship concluded that the published results were erroneous, that the study did not reveal any meaningful additional risk attributable to pertussis vaccine, and that the claimant had failed to establish, on the balance of probabilities, that pertussis vaccine could cause brain damage in young children. The aim of the case was to determine the general issue of causation, not to ascertain whether pertussis vaccine had caused injuries to the claimant herself, and the financial provisions within the VDPA 1979 had been intended as a temporary measure pending the outcome of this test case. The study's authors subsequently published a follow-up study which addressed the judge's criticisms of the original study, and again concluded that on rare occasions, the vaccine could cause severe neurological injury.⁵⁹⁹

⁵⁹⁵ Department of Health and Social Security. Review of the evidence on whooping cough vaccination by the Joint Committee on Vaccination and Immunisation. London: HMSO, 1977.

⁵⁹⁶ Miller, D.L., Ross, E.M., Alderslade, R., *et al.* (1981). Pertussis immunization and serious acute neurological illness in children. *Br.Med.J.*, **282**, 1595-1599.

⁵⁹⁷ Hansard, H.C. Vol. 49, col. 417, November 28, 1983. The speaker was Tony Newton M.P., then Under-Secretary of State for Social Security in the Department of Health and Social Security.

⁵⁹⁸ *Loveday v Renton*, [1990] 1 Med.L.R., **1**, 117.

⁵⁹⁹ Madge, N; Diamond, J; Miller, D; *et al.* (1993). The National Childhood Encephalopathy study: a 10-year follow-up. A report on the medical, social, behavioural and educational outcomes after serious, acute, neurological illness in early childhood. *Dev.Med.Child Neurol.*, **68**, 1-118.

The Loveday case was the third case of alleged vaccine damage to reach court in Britain. The first claimant lost his case in the Court of Session in Edinburgh in 1985 because the court was not satisfied that his condition had been caused by the vaccine,⁶⁰⁰ although the Vaccine Damage Tribunal had previously accepted that a temporal relationship was sufficient grounds to establish a causal link between the vaccine and the brain damage but this was rejected in the Court of Session. The first English test case collapsed in 1986 when the legal aid certificate was discharged because the claimant's mother (in Lord Justice Stuart Smith's words) "was not telling the truth" about the date of onset of symptoms.⁶⁰¹

This therefore leaves the Vaccine Damage Payment Scheme as the more likely route for injured people to seek recompense. Up to June 2005, 918 of 5312 (17 per cent) of claims were successful. Approximately 850 awards were made between 1979 and 1989; the apparent progressive reduction in the number of awards may reflect the backlog of cases when the 1979 Act was introduced⁶⁰² and the continuing increase in the safety of vaccines, although a recent Parliamentary debate drew attention to injuries resulting from newer vaccines.⁶⁰³ Of the 4394 refusals, 4017 (91 per cent) were rejected on the grounds that causation was not established. Some 12 million children are vaccinated annually, meaning that in the 25 years since the VDPA 1979 was enacted approximately 300 million children had been vaccinated, of whom only 918 (0.0003 per cent) suffered harm satisfying the criteria described in the VDPA 1979.⁶⁰⁴ Yet the concerns in the 1970s which led to the VPDA 1979 seem still to be present, i.e., that in a small number of people vaccines cause significant injury, and we lack an effective mechanism to 'compensate' them.

The VDPA 1979 has, therefore, three potential shortcomings in the protection it provides for pregnant women participating in clinical trials: it does not cover disability resulting from drugs other than vaccines, it is restricted to specific diseases, and it requires the occurrence of specified level of disability. However, it has the advantages of an automatic entitlement without the need to establish negligence, and pre-defined fixed levels of

⁶⁰⁰ *Bonthrone v Millan* [1985] *Lancet* ii, 1137.

⁶⁰¹ *Department of Health and Social Security v Kinnear* [1984] 134 N.L.J. 886; *Times*, July 7, 1984; [1989] *Fam. Law* 146. See also Anonymous. (1986). The law tries to decide whether whooping cough vaccine causes brain damage: Professor Gordon Stewart gives evidence. *Br.Med.J.*, **292**, 1264-1266.

⁶⁰² Pywell, S. (2002). A critical review of the recent and impending changes to the law of statutory compensation for vaccine damage. *J.P.I. Law*, **4**, 246-256.

⁶⁰³ See <http://www.theyworkforyou.com/whall/?id=2015-03-24a.441.1>, accessed

⁶⁰⁴ Tindley, R. (2008). A critical analysis of the vaccine damage payments scheme. *Eur.Bus.Law Rev.*, **19**, 321-363.

payments. The major issue, however, is that of establishing causation, will now be addressed more extensively.

7.9 The Burden of Causation

To demonstrate factual causation in tort law, the claimant must establish that the loss suffered was caused by the defendant (assuming the defendant owed the claimant a duty of care), and in most cases a simple application of the 'but for' test will resolve the question of causation, i.e., 'but for' the defendant's actions, would the claimant have suffered the loss?⁶⁰⁵ This requirement is present in the CDCLA 1976 as well as the VPDA 1979. If the defendant's breach of duty is a factually relevant cause, the court must proceed to assess whether liability should follow, based upon the balance of probabilities. The principle of corrective justice requires that a defendant should only be liable only for harm that he/she has wrongfully caused.

Causation may be problematic where more than one possible cause exists. Over the years, a number of exceptions to the 'but for' test have been created. One example is the Fairchild principle, which allows claimants to succeed on causation grounds without having to prove a causal connection between the defendant's faulty behaviour and the pleaded harm, and was a policy-based response to the difficulties encountered by mesothelioma victims who had been negligently exposed to asbestos by multiple consecutive employers.⁶⁰⁶ This exception does not appear to be applicable to the setting of clinical trials in pregnant women, but the precedent of a policy-based exception will be discussed later.

Liability for injuries caused by medicinal products is notoriously difficult to prove. All bioactive substances can produce undesirable, just as desirable, effects. Thus the claimant faces the challenges of distinguishing a drug-related effect from the consequences of the condition for which the drug was prescribed or from the underlying incidence of the 'injury' in the population at large, entailing the consideration of hundreds of thousands of documents.⁶⁰⁷ The lack or uncertainty of scientific evidence regarding the cause of injuries

⁶⁰⁵ See, for example, *Barnett v Chelsea & Kensington Hospital Management Committee* [1969] 1 QB 428.

⁶⁰⁶ *Fairchild v Glenhaven Funeral Services Ltd* [2002] UKHL 22. See also Stapleton, J. (2002) Lords a'leaping evidentiary gaps. *Torts Law J.*, 10, 276-305.

⁶⁰⁷ Mildred, M. (2007). Pitfalls in product liability. *J.P.I.L.*, 2, 141-149.

is amongst the most difficult problems faced by courts in determining causation.⁶⁰⁸ These may arise from limitations in scientific knowledge about a particular biological process (general causation) or from the difficulty in providing a scientific explanation for the sequence of biological processes in an individual case (individual causation).⁶⁰⁹ Proof of the former is necessary but not sufficient in product liability and personal injury litigation, because even if the claimant falls within the class of individuals who might or could have sustained the relevant injury as a result of the postulated cause, it remains to be established whether the particular claimant in fact did so.

Scientific evidence frequently presents a problem for the courts: the subject-matter is often complex; the experts who present the evidence can be selected on the basis that they are already known to hold particular opinions; judges and juries are frequently unsure about how to assess the evidence.⁶¹⁰ Epidemiology is the study of disease patterns in populations which seeks to identify and understand causes of disease. By using this data to predict how and when diseases are likely to arise, it aims to prevent the disease and its consequences through public health regulation or the development of medication. Epidemiological studies may disclose an apparent association between a substance and a disease, and often are submitted as evidence in product liability and toxic tort litigation.⁶¹¹ At present, the UK courts are highly sceptical of epidemiological evidence,⁶¹² and judges have been known to re-analyse the data presented.⁶¹³

However, a distinction must be drawn between evidence of association from epidemiological data and proof of causation. In epidemiological research in the UK, the most common set of causal inference criteria used to assess whether a statistical association is indicative of a causal relationship between an exposure and a disease is the Bradford-Hill Criteria.⁶¹⁴ These criteria are:

⁶⁰⁸ Goldberg, R. (2009). Causation, idiopathic conditions and the limits of epidemiology. *Edin.Law Rev.*, **13**, 282-286.

⁶⁰⁹ Khoury, L. *Uncertain Causation in Medical Liability*. Oxford: Hart Publishing, 2006, pp 48-54.

⁶¹⁰ Danaher, J. (2011). Blind expertise and the problem of scientific evidence. *Int.J.Evid.Proof*, **15**, 207-231.

⁶¹¹ Gastwirth, J.L. (2003). The need for careful evaluation of epidemiological evidence in product liability cases: a reexamination of *Wells v Ortho* and *Key Pharmaceuticals*. *L.P. & R.*, **2**, 151-189.

⁶¹² McIvor, C. (2013). Debunking some judicial myths about epidemiology and its relevance to UK tort law. *Med.Law Rev.*, **21**, 553-587

⁶¹³ See, for example, *Loveday v Renton*, [1990] 1 *Med.L.R.*, **1**, 117.; *Sienkiewicz v Grief (UK) Ltd*; *Knowsley MBC v Willmore* [2011] UKSC 10.

⁶¹⁴ Hill, A.B. (1965). The Environment and Disease: Association or Causation? *Proc.Roy.Soc.Med.*, **58**, 295-300; Dolk, H., Loane, M., Garne, E. (2010). The prevalence of congenital anomalies in Europe. *Adv.Exp.Med. Biol.*, **686**, 349-364; British Isles Network of Congenital Anomaly Registers. *Congenital*

1. Strength (effect size): A small association does not mean that there is not a causal effect, though the larger the association, the more likely that it is causal.
2. Consistency (reproducibility): Consistent findings observed by different persons in different places with different samples strengthens the likelihood of an effect.
3. Specificity: Causation is likely if there is a specific population at a specific site and disease with no other likely explanation. The more specific an association between a factor and an effect is, the greater the probability of a causal relationship.
4. Temporality: The effect has to occur after the cause; if there is an expected delay between the cause and expected effect, then the effect must occur after that delay.
5. Biological gradient: Greater exposure should generally lead to greater incidence of the effect. However, in some cases, the mere presence of the factor can trigger the effect. In other cases, an inverse proportion is observed: greater exposure leads to lower incidence.
6. Plausibility: A plausible mechanism between cause and effect is helpful (but Hill noted that knowledge of the mechanism is limited by current knowledge).
7. Coherence: Coherence between epidemiological and laboratory findings increases the likelihood of an effect. However, Hill noted that "... lack of such [laboratory] evidence cannot nullify the epidemiological effect on associations".
8. Experiment: "Occasionally it is possible to appeal to experimental evidence".
9. Analogy: The effect of similar factors may be considered.

As explained in Chapter 7.5.2, the first few cases of any adverse reaction to a particular drug may be extremely difficult to link to the drug. In the well-known iatrogenic injury cases, such as thalidomide, TeGenero and, more recently, Bial,⁶¹⁵ the injuries were obvious, temporally-clustered, and occurred in a high proportion of those who were given the suspect drug, thereby satisfying criteria 1-4, above. Should a drug express a teratogenic effect in preclinical toxicology studies, the manufacturer will attempt to

Anomaly Statistics 2010. England and Wales, July 2012. Available at http://www.binocar.org/content/Annual%20report%202010%20FINAL%2031_07_12%20v2.pdf accessed 30th September, 2015.

⁶¹⁵ See http://ansm.sante.fr/Dossiers/Essai-Clinique-Bial-Biotrial/Essai-clinique-BIA-102474-101-du-laboratoire-BIAL/%28offset%29/0%20-%20paragraph_87255. last accessed 5th May 2016.

establish the mechanism, to assess whether it exists in humans, the species which exhibit the effect, and the dose or plasma concentration at which it occurs, to enable a decision to be reached regarding the adequacy of the safety margin.⁶¹⁶ Such an approach may satisfy a general causation argument. However, if a teratogenic effect is not detected at doses several times those anticipated to be clinically-effective in humans, and the literature is devoid of such information, as would be expected in pharmaceutical research where the focus is on developing patentable and therefore mechanistically-unprecedented agents, then a biologically-plausible explanation for a particular injury may not yet be known and coherence between findings impossible to establish. Teratogenic injury may not be immediately obvious, and the delay between drug administration and detectable consequence may be many months or years. Most clinical studies examine only one or two doses, and so a biological gradient may be difficult to identify. Taken together, the utility of the Bradford-Hill criteria in the area of teratogenesis does not appear high.

The balance of probabilities test will rarely favour a claimant. As explained earlier,⁶¹⁷ the incidence of spontaneous congenital abnormalities is in the range of 1 in 33 to 1 in 45 live births. The term 'spontaneous' denotes only that a specific cause has not been identified, and so the true rate of genuinely 'spontaneous' abnormalities may be substantially lower. If a drug is responsible for a teratogenic injury in 1 out of 333,000 pregnancies (approximately the same rate as vaccine damage injuries satisfying the criteria for payment; see Chapter 7.8.4), then the first example may arise long after the drug is approved for use, as an isolated, unprecedented case; neither the Bradford-Hill criteria nor the balance of probabilities upon which a civil claim for damages would necessarily be based would favour the claimant, given the underlying incidence of congenital abnormalities.⁶¹⁸ That said, if the drug is approved and marketed, the prospect always exists of developing a series of cases which may support a claim for damages. Conversely, if that first case arises during a pre-registration clinical trial, it may not be recognised as related to the drug, unless, like thalidomide, the injury is immediately obvious and has extremely unusual characteristics. If the drug concerned is withdrawn from development,

⁶¹⁶ Gupta, U; Cook, JC; Tassinari, MS; *et al.* (2003). Comparison of developmental toxicology of aspirin,(acetylsalicylic acid) in rats using selected dosing paradigms. *Birth Defects Res. Part B-Develop. Reprod.Toxicol.*, **68**, 27-37; Kozer, E; Costei, AM; Boskovic, R; *et al.*(2003). Effects of aspirin consumption during pregnancy on pregnancy outcomes: Meta-analysis. *Birth Defects Res. Part B-Develop. Reprod.Toxicol.*, **68**, 70-84.

⁶¹⁷ This topic is discussed in Chapter 7.5.2.

⁶¹⁸ World Health Organisation Congenital Anomalies Factsheet No. 370, April, 2015. Available at <http://www.who.int/mediacentre/factsheets/fs370/en/> accessed 30th September, 2015;

and never reaches clinical use, no further cases will arise, and so the opportunity to establish a causal link in epidemiological terms or a case series will never exist. However, if the drug's development is continued, then a second case may arise only after some 660,000 pregnant women have been treated, which could be many years after the clinical trial in which the first foetal injury occurred. So, although the opportunity might then exist to establish a case series, the prospect of recompense for that first, injured child is at best remote, and certainly much-delayed.

The latter scenario, however, illustrates another difficulty for the courts: that of resolving cases based on the existing evidence. The continuing accumulation of scientific knowledge means that, over time, the balance of probabilities may change. By then, of course, the original 'victim' may have been deprived of recompense for many years.

7.10 Alternative Potential Routes to Compensation

The time seems appropriate for the legal issues regarding provision for compensation in clinical trials specifically involving pregnant women to be reviewed. Such trials are in their infancy and Regulation 536 has yet to come into effect, so it seems likely a case will not arise for 2-3 years. Consolidation into a single process would have the advantage of providing one clear route to be followed in the event of congenital injury following trial participation. The unique characteristics of this population, and its small size from a clinical trials perspective, mean it offers a vehicle within which to explore the development and application of a new item of legislation, which could lay a foundation for future revisions affecting other trial populations. Given the challenges of applying existing compensation processes to this setting described above, the assessment of alternative approaches is warranted. A range of alternatives has been explored in personal injury cases, although none in the particular setting of congenital injury following maternal participation in a clinical trial.

The obvious starting point would be that of negotiation - but with whom? The parent is the person most likely to initiate a negotiation, and that discussion may need to involve the NHS authority in whose premises the trial was conducted, the Investigator, who may have moved or retired, and the sponsor, who seems unlikely to wish to be drawn into such a discussion, other than to refute liability. Even with legal representation, this seems unlikely to be a discussion amongst equals. If the sponsor is an ABPI member, then the claimant may be referred to the ABPI arbitration procedure.

Arbitration has simpler procedural and evidentiary rules than litigation, and may lead to more rapid resolution. The ABPI Guidelines contain provision for such a process, but the decisions in cases brought under the Guidelines have not been made public, and arbitration decisions do not set precedents for future decisions to follow. Therefore, each individual case would need to be settled separately, the consistency of decisions would be open to question, and the claimant would still need to establish that the injury was the result of some attributable act or omission related to the trial. Arbitration, sometimes but not always binding, is widely used in medical malpractice disputes in the USA, and less commonly in Mexico and a small number of European countries,⁶¹⁹ but apart from the ABPI scheme, this approach appears not to have been employed in the UK. Given the highly specialized knowledge and fact-finding needed in all medical injury claims, and probably more so in this area, once again this seems unlikely to be a process in which the parties are equals.

Mediation is a method of resolving disputes which involve the assistance of or interaction by a third party who does not have the authority to impose an outcome,⁶²⁰ which distinguishes mediation from arbitration. Attempts have been made in the UK to introduce this approach. A recent automatic referral to mediation (ARM) scheme piloted in the UK in 2004-2005 experienced a high opt-out rate; only a small proportion of cases was mediated, of which medical malpractice cases formed a fraction.⁶²¹ A similar pattern had been seen in the Central London Voluntary mediation scheme which ran from 1999-2004, in which the take-up rate was 4%,⁶²² and the voluntary mediation initiative by the National Health Service Litigation Authority, where the take-up rate was 15% over three years.⁶²³ The ARM scheme was initially based on the Canadian Ontario Mandatory Mediation

⁶¹⁹ Tena-Tamayo, C., Sotelo, J. (2005) 'Malpractice in Mexico: arbitration not litigation', *Br.Med.J.*, 331, 448-451; Hofreuter, D. H. Mendoza, E.M. (1993) Study tour examines health care systems in Germany, Holland – a comparison of three health care systems, Part 1. Available at http://findarticles.com/p/articles/mi_m0843/is_n4_v19/ai_13240427/print, accessed 28th September, 2015; Konsument Europa (2005) Promoting alternative dispute resolution. Baltic Sea Seminar, Stockholm, 2005. Available at http://www.konsumenteuropa.se/Documents/Engelska/prom_alt_disp_resol_seminar_050527.pdf, accessed 28th September, 2015.

⁶²⁰ Wall, J. A., Stark, J. B., Standifer, R. L. (2001) 'Mediation: a current review and theory development', *J. Conflict Resolution*, 45, 370–91.

⁶²¹ Genn, D. H., Fenn, P., Mason, M. *et al.* (2007) *Twisting Arms: Court Referred and Court Linked Mediation Under Judicial Pressure*. Ministry of Justice Research Series 1/07.

⁶²² Genn, D. H., Fenn, P., Mason, M. *et al.* (2007) *Twisting Arms: Court Referred and Court Linked Mediation Under Judicial Pressure*. Ministry of Justice Research Series 1/07.

⁶²³ Donaldson, L. (2003). *Making amends: a consultation paper setting out proposals for reforming the approach to clinical negligence in the NHS*. Department of Health, available at http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4010641 accessed 30th September, 2015.

Programme.⁶²⁴ However, the mandatory nature of the scheme was criticised in *Halsey v Milton Keynes NHS Trust*,⁶²⁵ as being inconsistent with Article 6 of the Human Rights Act 1998. This form of dispute resolution does not appear to have found favour in the UK, even when the dispute relates to medical malpractice and involves only the claimant and the physician. It seems difficult to conceive of a non-binding process of mediation which could involve claimants, Investigators, NHS trusts and trial sponsors being acceptable to all, particularly given the level of medical evidence likely to be led in cases of congenital injury.

The extension of the CPA 1987 and the SSGA 1994 to drugs prior to their approval could also be considered. The impact of such a step on the pharmaceutical industry would be particularly severe, and, arguably, the risks in other areas are just as great as they are for pharmaceuticals. Given that carefully-controlled, legally-regulated clinical trials constitute a required element of assessing whether an investigational drug merits approval, imposing sanctions should the trials detect adverse reactions, which is one of the objectives of all clinical trials and which, on a risk-benefit argument may be acceptable, seems inherently contradictory.

One option which has been widely considered is a no-fault compensation system. The philosophy underlying no-fault compensation in the conventional medical setting is that injuries may not be attributable to the act(s) or omission(s) of an individual, but rather from system errors. Moreover, the complexity of medical practice often makes it difficult to determine fault when errors occur.⁶²⁶ A no-fault scheme therefore should allow investigation and compensation of claims without the need for the claimant to establish negligence.⁶²⁷ As this and the preceding chapter have shown, the trial approval and injury compensation processes involve many individuals, commonly acting as members of a group (the REC, the MHRA, the sponsor, the Investigator and his staff), and so

⁶²⁴ Ministry of the Attorney-General, Ontario, Canada. Public Information Notice - Ontario Mandatory Mediation Program. Available at

<http://www.attorneygeneral.jus.gov.on.ca/english/courts/manmed/notice.asp>, accessed 28th September, 2015.

⁶²⁵ *Halsey v Milton Keynes General NHS Trust* (2004) EWCA Civ 576, per Dyson LJ at para 9: "It seems to us that to oblige truly unwilling parties to refer their disputes to mediation would be to impose an unacceptable obstruction on their right of access to the court . . . and, therefore, a violation of Article 6 [of the Human Rights Act 1998]. Even if (contrary to our view) the court does have jurisdiction to order unwilling parties to refer their disputes to mediation, we find it difficult to conceive of circumstances in which it would be appropriate to exercise it."

⁶²⁶ O'Connell, J. (1975) No-fault insurance for injuries arising from medical treatment: a proposal for elective coverage. *Emory L.J.*, **24**, 21-42.

⁶²⁷ Wadlington, W. (1991) 'Medical Injury Compensation, a Time For Testing New Approaches', *J.Am.Med.Ass.*, **265**, 2861.

establishing the individual who is answerable in the event of a congenital injury following trial participation is more complex than would be the case in a conventional medical setting. The system error approach inherent in the no-fault approach seems well-suited to the clinical trial setting.

When first proposed in the 1960s, the concept of no-fault compensation was recommended as applicable for all patients with untoward and unexpected medical outcomes.⁶²⁸ In the 1970s, the concept of relative avoidability was advanced,⁶²⁹ and all five Nordic countries (Sweden, Denmark, Norway, Finland, and Iceland) have replaced negligence-based compensation systems at different times over the last 30 years⁶³⁰ with an avoidability-based standard. An outcome is considered avoidable if it could have been avoided using an alternative course of treatment or which would not have occurred in the hands of the best practitioner, and so such avoidability does not necessarily connote negligence. However, the avoidability approach does not provide for compensation in cases where the injury was unavoidable because it was unforeseeable, as may be the case for congenital injury due to an investigational drug, or indeed a comparator.

New Zealand has also adopted a ‘no-fault’ model, driven initially by a desire to ensure that disability insurance was available to all those who became unemployable due to an accident at work, and was based on a ‘community responsibility’ philosophy.⁶³¹ In France, a no-fault compensation scheme was created to limit the use of the criminal law in medical malpractice.⁶³² Some countries have chosen a specific medical area for such an approach rather than implementing a general scheme, one example of which is the Obstetrical Injury Compensation Scheme begun in 2009 in Japan,⁶³³ so there would be some precedent for introducing a restricted, targeted scheme in the UK. No-fault schemes have worked well in

⁶²⁸ Ehrensweig, A. (1964) Compulsory “hospital accident” insurance: a needed first step toward the displacement of liability for “medical malpractice”, *Univ.Chicago L.Rev.*, **31**, 279–91.

⁶²⁹ Havighurst, C.C., Tancredi, L.R. (1974) “Medical Adversity Insurance” – A no-fault approach to medical malpractice and quality assurance. *Insurance L.J.*, **613**, 69–70.

⁶³⁰ Iceland Ministry of Health and Social Security: *Laws and Regulations*, 2006; Norsk Pasientskadeerstatning: *About the Norwegian System of Compensation to Patients*, 2006; Patientfo’rsa’ kringfo’ reningen: *The Patient Injury Act*, 2006; Patientforsikringen: *The Danish Patient Insurance Act*, 2006; Potilasvakuutuskeskus, *The Finnish Patient Insurance Centre: Patient Injuries Act*, 2006

⁶³¹ Peart, N., Moore, A. (1997). Compensation for injuries suffered by participants in commercially sponsored clinical trials in New Zealand. *Med.L.Rev.*, **5**, 1-21. Miller, R.S. (1989). The future of New Zealand’s accident compensation scheme. *University of Hawaii L.Rev.*, **11**, 3-80.

⁶³² Loi n0. 2002-303 du 4 mars 2002 relative aux droits des malades et à la qualité du système de santé. Cited in Kazarian, M., Griffiths, D., Brazier, M. (2011) Criminal responsibility for medical malpractice in France. *P.N.*, **27**, 188-199;

⁶³³ Tomizuka, T., Matsuda, R. (2009). Introduction of No-Fault Obstetric Compensation. *Health Policy Monitor*. Available at <http://www.hpm.org/survey/jp/a14/4> accessed 26th September, 2015.

countries which have a comprehensive social security system and high national insurance contributions, such as the Nordic countries, France and Japan, arguably because the additional costs above normal state-provided care are relatively small and therefore manageable.⁶³⁴ However, under these systems, injured parties do not necessarily receive the equivalent compensation they would have received had they successfully pursued medical negligence litigation; their essence is more restorative than punitive. A key feature of the Scandinavian and New Zealand systems is the limitation of compensation based on the severity of the injury. Under the New Zealand ACC scheme, the duration of disability and hospital stay is used as a proxy to determine severity and for setting the limits on compensation. In the Scandinavian countries, the injuries need to be more severe than the patient ‘could reasonably be expected to bear’.⁶³⁵

In England, proposals to introduce a no-fault compensation scheme for medical injury have been abandoned principally on grounds of cost.⁶³⁶ In Scotland, the No-fault Compensation Review Group recommended that, in conjunction with improved social welfare provisions, the Scottish government implement a no-fault system similar to that which operates in Sweden.⁶³⁷ Unlike the Swedish scheme, the proposed Scottish scheme would not be based on avoidability, but ‘on a clear description of which injuries are not eligible for compensation under the no-fault scheme’. From this, it is unclear whether the scheme would provide for compensation in cases where the injury was unavoidable. The Scottish Government still has the matter under active consideration and remains committed to exploring a no-fault compensation scheme.⁶³⁸

A limited form of no-fault liability was introduced by the National Health Service (Concerns, Complaints and Redress Arrangements) (Wales) Regulations 2011. The intent of the system is that of ‘putting things right’ by resolving issues locally rather than by

⁶³⁴ Dingwall, R. (2003). No fault is no panacea. *Br.Med.J.*, 326, 997-998.

⁶³⁵ Accident Compensation Corporation, ACC Background Paper: Comparison of International Schemes that Compensate for Medical Injury (2003), available at http://www.acc.co.nz/wcm001/groups/external_claims_care/documents/internet/wcmz002318.pdf accessed 28th September, 2015.

⁶³⁶ Cave, E. (2011). Redress in the NHS. *P.N.*, 27, 138-157

⁶³⁷ The Scottish Government, No-fault Compensation Review Group Report (15 February 2011), recommendation 2, available at <http://www.scotland.gov.uk/Topics/Health/NHS-Scotland/No-faultCompensation>, accessed 30th September, 2015.

⁶³⁸ Consultation Report - Consultation on recommendations for no-fault compensation in Scotland for injuries resulting from clinical treatment, 4th April, 2014. Available at <http://www.gov.scot/Publications/2014/04/6437>, accessed 28th September, 2015.

recourse to the courts,⁶³⁹ introducing a single system for dealing with complaints and claims of modest value, referred to as ‘concerns’. Under Regulation 25, the responsible body must consider whether there is a ‘qualifying liability in tort’, defined in the Regulations as ‘a liability in tort owed in respect of, or consequent upon, personal injury or loss arising out of or in connection with breach of a duty of care owed to any person in connection with the diagnosis of illness, or in the care or treatment of any patient:(a) in consequence of any act or omission by a healthcare professional; and (b) which arises in connection with the provision of qualifying services’. Thus, the Welsh system requires the establishment of both causation and breach of duty, combining the major challenges inherent in the ABPI Guidelines and the CDCLA 1976, respectively. Should both be established, the responsible body may offer compensation up to a £25,000 limit. If the offer is accepted, the complainant waives the right to bring civil legal proceedings in respect of the injury. The scheme is administered by NHS Wales, an arrangement open to criticism for lack of impartiality. However, given the level of compensation for congenital injury, it seems unlikely that many cases of that type would fall within the scheme and, again, recourse would need to be made to other mechanisms. In addition, concerns need to be raised within twelve months of coming to the notice of the person raising it, which may be insufficient time to establish whether a true congenital abnormality exists. During the period when the concern is investigated, the limitation period applicable under the Limitation Act 1980 is suspended.

.The operation of the Welsh system has recently been reviewed,⁶⁴⁰ concluding that the system is, in many cases, not operating as intended, with reports of delays, lack of patient involvement, lack of detailed investigation of quantum and concerns regarding the independence of the process. Thus, one of the potential deficiencies of employing arbitration or mediation - that of the parties not being equals in terms of knowledge - seems to arise here, perhaps not surprisingly as in the first stage of the investigation, the NHS body is effectively acting as defendant, judge and jury. Given the potential compensatory costs for congenital injury, inconsistency regarding quantum must be considered as a significant issue. Suggestions have been advanced for improvements to the process,⁶⁴¹ and

⁶³⁹ Welsh Assembly Government. Putting things right consultation document. Wales: Welsh Assembly Government, 2010.

⁶⁴⁰ Rosser, M. (2014). The Welsh NHS Redress arrangements – Are they putting things right for patients? *Clin.Risk*, 20, 144-149.

⁶⁴¹ Evans K. A. (2014). Review of concerns (complaints) handling in NHS Wales, available at <http://www.wales.nhs.uk/sitesplus/863/opensdoc/245221> accessed May 2016.

their implementation may resolve many of the complaints which have been made, but the major hurdle to implementing the system in cases involving congenital injury remains that of the financial ceiling of awards.

These systems were developed for use in conventional medical settings, and their application to the research environment does not appear to have been reported. Attempts to introduce no-fault systems in the USA, which carries out more clinical research than any other country, have been unsuccessful.⁶⁴² Provisions in other European countries are variable. In Germany, the trial sponsor is required to hold an insurance policy which provides benefits when no-one else is liable for the injury.⁶⁴³ Similarly, in Belgium, the sponsor assumes, without fault, liability for injury to participants related directly or indirectly to experimentation.⁶⁴⁴ Spain also requires mandatory insurance on a no-fault basis.⁶⁴⁵ Partly triggered by the impending Regulation 536 requirement for a system of national insurance for trial participants (Chapter 6.3), Spain is reviewing its current no-fault system and contemplating the institution of a negligence-based system.⁶⁴⁶ If compensatory payments have been made in these countries in respect of congenital injury, they appear not to have been reported publically. In France, payment of compensation for injuries caused in clinical trials may be avoidable if the researcher or the sponsor proves there was no negligence.⁶⁴⁷ The no-fault systems in Germany, Belgium and Spain require the injuries to be the result of participation in the clinical trial and quantifiable in financial terms, both extremely difficult to establish with congenital injuries becoming apparent many years after the trial in which the harm may have arisen.

7.11 Conclusions

The currently-available processes do not provide a straightforward legal route to a remedy for a child born injured following his mother's participation in a pre-registration clinical

⁶⁴² For a recent review, see Pike, E.R. (2012). Recovering from research - a no-fault proposal to compensate injured research participants. *Am.J.Law Med.*, **38**, 7-62.

⁶⁴³ Arzneimittelgesetz, English updated version available at http://hh.juris.de/englisch_amg/index.html, accessed 30th September, 2015.

⁶⁴⁴ C. Trouet, M. Gobert and M. Podoor, Clinical Trials in Belgium. The Belgian Implementation of the European Clinical Trials Directives (Antwerp: Intersentia, 2007), at p. 40, available at www.ejustice.just.fgov.be, accessed 30th September, 2015.

⁶⁴⁵ Real Decreto 223/2004, de 6 de febrero, por el que se regulan los ensayos clínicos con medicamentos. BOE núm. 33, de 7 de febrero de 2004, pp. 5429-5443, available at www.boe.es/diario_boe/txt.php?id=BOE-A-2004-2316, accessed 30th September, 2015.

⁶⁴⁶ Ramiro Avilés, M.A. (2015). Paving the road to negligence: the compensation for research-related injuries in Spain. *Accountability in Research*, **22**, 106-119.

⁶⁴⁷ Code de la Santé Publique, French version, 28 October 2013, available at www.legifrance.gouv.fr, accessed 30th September, 2015.

trial during her pregnancy. In some cases, the ABPI Compensation Guidelines will be applicable, in others the NHS Indemnity will be relevant, in some recourse will need to be made to the CDCLA 1976, whilst in others the CPA 1987 may be the preferred route - and all of this against a background of possibly incomplete record retention. Whilst a purposive approach to interpretation may avoid the difficulties raised by the intricacies of the CDCLA 1976 and CPA 1987, and give effect to the original intent of the legislation, there is little black letter law on the meaning and application of the key concepts of either Act in a research setting. The injured child cannot sue the mother as she is immune under the CDCLA 1976 although her contributory negligence may reduce any available compensation under that Act and, possibly, under the ABPI Guidelines. The Investigator cannot be sued if he has acted properly, nor the REC, the MHRA or the sponsor, assuming the pregnant woman's consent was valid, and that she consented to run the risk which subsequently eventuated, on the basis of adequate information.⁶⁴⁸ Even if the information was inadequate, the injured child may need to establish that this materially influenced the (now) mother's decision to participate. A pregnant woman has a legal right to consent to or decline treatment that will affect the foetus, and her consent appears to provide a defence for other possible respondents in an *antenatal* injury claim under the CDCLA 1976 and possibly the ABPI Guidelines.

Injuries to clinical trial participants seem to arise on remarkably few occasions, probably reflecting the extent of the preclinical testing which precedes them and the safeguards built into their designs,⁶⁴⁹ but possibly also the result of the majority of cases which do arise being settled before going to trial. A search of Westlaw conducted in August 2015 identified only two cases of clinical trial injuries being considered by the courts, one of which was a surgical trial, and the other was *Wylie*⁶⁵⁰ (see Chapter 5.2). It is tempting to speculate that a combination of the experience of *Gøtzsche* (Chapter 6.2), with the effective functioning of the ABPI scheme is responsible for the dearth of cases which have come before the UK courts. However, this situation may change if children are born injured following clinical trials, as claims for compensation may be significant in terms of their value and the willingness of their families to pursue them. As discussed above, it seems likely that establishing causation will prove a significant hurdle in such trials, and

⁶⁴⁸ See the argument proposed in Alghrani, A., Brazier, M. (2011). What is it? Whose it? Re-positioning the fetus in the context of research? *CLJ*, **70**, 51-82, at p.65.

⁶⁴⁹ Wood A.J.J.; Darbyshire J. (2006). Injury to research volunteers — the clinical-research nightmare. *N.Engl. J.Med.*, **354**, 1869-1871.

⁶⁵⁰ *Wylie v Grosset*, [2011] S.L.T. 609.

yet, given the risks these subjects take on behalf of society, one might consider society owes them a greater debt.

One spectacular case of trial-related injury, which did not reach the courts but did enter the public domain, was the TeGenero trial in the UK in 2006, in which healthy volunteers were seriously injured.⁶⁵¹ In that trial, the harm was apparent within an hour of drug administration, and the characteristics of the harm were so unusual that an association with the investigational drug was immediately obvious. TeGenero's insurance policy had a £2M cap, which was wholly inadequate for the harm which eventuated. Within four months of the incident, TeGenero filed for insolvency making it impossible for the injured participants to recover compensation from the sponsor. The MHRA investigation concluded that the adverse incidents did not involve errors in the manufacture, formulation, dilution or administration of the investigational drug, and that an unpredicted biological action of the drug in humans was the most likely cause of the adverse reactions.⁶⁵² In other words, as all of the relevant processes were followed and requirements satisfied, this was 'no-one's fault', demonstrating the exposed position of trial subjects in the UK. A subsequent report suggested that the adverse events in this case were, in fact, predictable,⁶⁵³ based on accumulated historical experience with investigational drugs of similar mechanism, information that was already available in the public domain, and which could have been generated with TeGenero's drug prior to the conduct of the trial had the MHRA required it. This trial has been described as ethically flawed,⁶⁵⁴ and an illustration of significant shortcomings in the clinical trial approval system in this country.⁶⁵⁵

The commencement of the limitation period for personal injury cases at 18 years of age, with potential for extension should harm not become obvious until later, provides a significant degree of protection for children who have been indirect trial participants (see Chapter 6.3.1) before birth, allowing time for many, possibly most, developmental abnormalities to become apparent. For drugs which are later licenced, it permits time for

⁶⁵¹ Suntharalingam, G., Meghan R. Perry, M.R., Ward, S. *et al.* (2006). Cytokine storm in a Phase 1 trial of the Anti-CD28 monoclonal antibody TGN1412. *N.Engl.J.Med.*, **355**, 1018-1028.

⁶⁵² Medicines and Healthcare products Regulatory Agency. Report entitled "Investigations into adverse incidents during clinical trials of TGN1412", available at <http://webarchive.nationalarchives.gov.uk/20141205150130/http://www.mhra.gov.uk/home/groups/comms-po/documents/websiteresources/con2023821.pdf> accessed 30th September, 2015.

⁶⁵³ Horvath, C.J., Milton, M.N. (2009). The Te Genero incident and the Duff Report conclusions: a series of unfortunate events or an avoidable event? *Tox.Path.*, **37**, 372-383.

⁶⁵⁴ Shamoo, A., Woekner, E. (2007). Ethical Flaws in the TeGenero Trial. *Am.J.Bioethics*, **7**, 90-92.

⁶⁵⁵ Hedgecoe, A. (2014). A deviation from standard design? Clinical trials, research ethics committees, and the regulatory co-construction of organizational deviance. *Soc.Studies Sci.*, **44**, 59-81

parents who suspect their children may have been affected by drugs taken during pregnancy to compile relevant information. This is less likely to occur with investigational drugs which have not proceeded to approval, and the relatively short mandatory document retention periods for such drugs reduce the prospect that children injured in this way will be able to recover damages. Creating a legal requirement for drug manufacturers, trial sponsors, RECs and Investigators to retain all documentation relating to clinical trials in pregnant women for a fixed period of 25 years after the end of the trial (end of trial is a key date, which must be made known under the CTD to the REC, the Investigators and the regulatory body), with appropriate penalties, would assist in the assessment of claims by increasing the security of relevant information. This is not, of course, a fail-safe approach; conditions with significantly-delayed onset, and particularly those which are inter-generational, may become apparent at a later date. However, this period would ensure that data were retained at least as long as the limitation period for the majority of personal injury claims and matches the retention period for children's medical files, thereby introducing a degree of consistency.

The apparent immunity from prosecution enjoyed by the REC and the MHRA seems - mostly - justifiable, if only on practical grounds. If subjects injured in clinical trials can involve the RECs in litigation, then the largely voluntary, normally rapid (initial decisions made within 60 days) system we enjoy at present will probably cease to function as REC reviewers become involved in protracted personal injury cases. Furthermore, faced with such liability, it would be relatively easy for the RECs to adopt a more conservative approach, which could render the UK a relatively unattractive location for clinical trials. The argument is, perhaps, less clear for the MHRA, and in particular the basis upon which trials are approved in the absence of information required in the ICH Guidelines; a scientific assessment may confirm the correctness of such decisions, but in the interests of transparency and potential future claims, those reasons should be documented. The reasons had not been documented in the TeGenero incident.

Clinical trials in pregnant women raise challenges regarding liability where the woman gives consent 'on behalf of' her foetus. By consenting, the pregnant woman also appears to accept any risk indicated in the consent documents not only for herself, but also 'on behalf of' her foetus, thereby compromising any later claim for compensation. If the injured child has a valid claim, it may be abated if the pregnant woman is found to have been contributorily negligent. If these circumstances are properly explained as part of the

consent process, they would seem likely to act as a deterrent to pregnant women to participate in clinical trials.

Establishing causation is likely to be problematic, particularly for a pregnant subject who is also a patient. She may have experienced disease-related consequences not attributable to the clinical trial which could have impacted the foetus; she might have received treatment for a serious condition which could have injured the foetus; or she could have been randomised to a comparator which had been approved for many years, and suspected of being teratogenic, but even there establishing causation is far from easy.⁶⁵⁶ Once again, if this is explained properly during the consent process, it seems unlikely to encourage pregnant women to participate in clinical trials.

The ABPI Guidelines were intended to provide a route to compensation without the need to establish negligence but they contain a number of uncertainties and apparent limitations. These may, in fact, have been clarified as a result of settlements made under the Guidelines, the details of which have not been made public. The Guidelines were drafted when clinical trials in pregnant women were not in contemplation and so the issues identified may be understandable, but that situation has now changed. The Guidelines should be amended to reflect that, or a specific Guideline should be developed for the pregnant population, given the unique issues in that group of subjects. In either case, the issues identified in Chapter 7.5 should be clarified, and a key aspect of that would be to clarify the nature of the Investigator-Subject relationship (Chapter 5).

The CDCLA 1976 was conceived in part to avoid the protracted difficulties which followed the thalidomide disaster and facilitate the process by which children injured *in utero* could gain compensation. However, the Act seems unsuited to a clinical trial, especially a Phase I, environment. There are clear problems with the application of tort doctrine in the research setting, in particular, identifying those who owe a duty of care to the future child and the applicable standard of care it would be reasonable to expect, as well as defining a breach of that duty. Since the thalidomide tragedy was one of the main stimuli behind both the CDCLA 1976 and the CPA 1987, the conclusions of the textbook writers cited above (Chapter 7.8.2) - that the manufacturers of thalidomide would likely have been able to employ the development risks defence successfully - illustrate most poignantly how ineffective the legislative protection is for the foetus. The conduct of

⁶⁵⁶ *Multiple Claimants v Sanifo-Synthelabo Ltd & anr.* [2007] EWHC 1860 (QB).

clinical trials is quite different from the practice of medicine, the Physician-Patient and Investigator-Subject relationships differ in key respects and the CDCLA 1976 seems unlikely to be effective in that setting without considerable judicial interpretation.

The importance of the information generated in trials in the pregnant population is such that circumstances which might deter participation would be deeply regrettable; it would reduce the benefits and increase the risks for both pregnant women and foetuses. One such circumstance would be that of a child of a trial subject being born with a congenital abnormality and facing a protracted struggle to recover compensation. Yet, taken together, the uncertainties described above seem more likely than not to create such a circumstance. The core of the challenge is causation. Under the ABPI Guidelines, the child would need to establish that his injuries were related to some aspect of the trial in which his mother had been a subject. Under the CDCLA 1976, the child would need to establish his injuries were the result of a wrongful act. To make a claim against the NHS, the child would need to establish negligence by an NHS employee.

The only way to have avoided harm in most clinical trials would be for the pregnant woman not to have participated, and given the drive to increase participation of this population, a failure to provide adequate recognition of the risks to foetuses and compensation to children who are born injured may act as a deterrent to achieving that objective. The current approaches, either in conventional or research settings, are not designed to provide compensatory justice for congenital injuries which may not immediately be apparent. Negotiation, arbitration and mediation seem likely to be ineffective, and extensions of the CPA 1987 or the SSGA 1994 would be likely to have much more wide-reaching consequences. Some form of targeted no-fault compensation system, such as the one in Japan, offers promise, but there is no perfect reform that adequately addresses the concerns regarding the present processes; every reform can be advocated or opposed for reason of fairness and/or public policy.

A major challenge in the concept of no-fault liability is in defining a compensable event. Although different countries with no-fault systems have developed different criteria for defining compensable events, such criteria are still debatable with respect to their appropriateness and fairness.

The system of compensation for such injury merits further consideration, as the need for reform to ensure easier routes to recovery of compensation for children injured *in utero* is overdue. An option for doing so will be presented in Chapter 8.

Chapter 8 Final Conclusions

8.1 Introduction

The medical justification for the requests from the EMA and FDA for data relating to the handling of investigational drugs in pregnant women prior to the drug's approval is unassailable. As described in Chapter 1.4, the changes of biochemistry and physiology which accompany pregnancy are marked, and can alter the absorption, distribution, metabolism and excretion, i.e., pharmacokinetics, of drugs to the extent that the efficacy and safety of approved dose regimens are altered. The health risks associated with sub-optimal management of conditions in pregnant women may also impact foetal health, as explained in Chapter 6.4.5. However, pregnancy can also alter the pharmacokinetics of medication given to pregnant women which is intended to benefit the foetus. A recent paper reported that the pharmacokinetics of folic acid supplements, routinely given to pregnant women to reduce the risk of neural tube defects,⁶⁵⁷ are altered in pregnancy, such that a steady-state red blood cell concentration is not achieved,⁶⁵⁸ explaining earlier clinical observations.⁶⁵⁹ The medical need to generate this type of information for the benefit of pregnant women and foetuses is clear. The question is whether, given the unavoidable risks associated with the studies necessary to generate the information, the legal recognition and protection of the foetus is adequate. The answer to that question appears to be a qualified 'no', particularly regarding provision for recovery of compensation in the event of a trial-related, iatrogenic injury.

The root cause is that the current legislation was developed without clinical trials of investigational drugs involving pregnant women being contemplated. Even the reference to consent in the 1989 Polkinghorne Report conveys the tone of a physician speaking to a patient in a conventional medical setting, rather than being a part of a global clinical trial. The CDCLA 1976 may be effective in a conventional medicine setting, and the ABPI Compensation Guidelines may work well in more customary clinical trial designs, involving subjects whose physical, intellectual and cognitive development is complete or at

⁶⁵⁷ Daly, L.E., Kirke, P.N., Molloy, A. *et al.* (1995). Folate levels and neural tube defects. Implications for prevention. *J.Am.Med.Ass.*, **274**, 1698–1702; MRC Vitamin Study Research Group. (1991). Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. *Lancet*, **338**, 131–137.

⁶⁵⁸ Shere, M., Nguyen, P., Tam, C. *et al.* (2015). Pregnancy-induced changes in the long-term pharmacokinetics of 1.1mg vs. 5mg folic acid: a randomized clinical trial. *J.Clin.Pharmacol.*, **55**, 159-167.

⁶⁵⁹ Bar-Oz, B., Koren, G., Nguyen, P. *et al.* (2008) Folate fortification and supplementation—are we there yet? *Reprod Toxicol.* **25**, 408–412; McNulty, B., Pentieva, K., Marshall, B., *et al.* Women's compliance with current folic acid recommendations and achievement of optimal vitamin status for preventing neural tube defects. *Hum.Reprod.*, **26**, 1530–1536.

least (in the case of children) fairly advanced, and in whom trial-related injuries are generally apparent relatively quickly. Clinical trials in pregnant women are, at present, not conventional, and trial-related injuries may not become apparent for years. With the impending implementation of Regulation 536, and the requests from the Agencies for clinical trial information from pregnant women prior to the approval of new drugs, the time seems right for amendment of the CDCLA 1976, or the introduction of new legislation, to address the conduct of clinical trials in this population within the UK.

As discussed in Chapters 3 and 4, law and ethics have, in various ways, accorded the foetus a degree of recognition which limits what can be done to it without penalty. The enactment of legislation relating to abortion and common law judgments regarding injury sustained *in utero* demonstrate this. Morally, it is difficult to distinguish a foetus *in utero* from a neonate, particularly given the wide window of viability, unless one accepts the fact of live birth as a moral argument. Numerous commentators have advanced a range of ethical arguments that the foetus, and the child it is intended to become, should be in our contemplation when conducting medical treatment and research. Some, mostly American, writers have developed these arguments to the point of viewing the foetus as a separate entity from the pregnant woman carrying it. This position raises many questions concerning the pregnant woman's autonomy, which has been recognised by the courts both in the UK and the USA, and was discussed in Chapter 4.

Largely as a consequence of the thalidomide tragedy in the early 1960s and the responses of the public and regulators, clinical trials of investigative drugs in pregnant women were not contemplated until the 1990s. During that period, legislation was enacted which was intended to protect the future interests of children harmed by drugs *in utero* (CDCLA 1976), and to provide defined routes to compensation for anyone who suffered injury from approved drugs which proved defective (VDPA 1979; CPA 1987). In addition, processes, some subsequently codified, were introduced to regulate the approval and conduct of clinical trials of investigative drugs (ICH-GCP, codified in the MHU Regulations 2004 and GCP Directive 2006), and to provide a route to compensation for those injured in clinical trials (ABPI Guidelines, 1970-2015). However, as explained in Chapters 6 and 7, none of these measures was constructed with the foetus in mind, and as a result a number of shortcomings are apparent.

A number of specific inadequacies and possible solutions were identified in Chapters 6 and 7, each of which could be categorised as predominantly preventative or compensatory in nature. These were:

- The basis upon which the MHRA can approve trials to proceed in the absence of ICH-defined preclinical data, in this case reproductive toxicology, needs to be documented; although seemingly immune from civil actions, the MHRA nevertheless must be seen to be accountable to the Government and to the public. (Chapter 6.2.1) (Preventative)
- A process by which teratogenic moieties in molecular structures can be identified from pre-clinical studies and the information made available within the approval process needs to be developed; in this way, suspect moieties might be more readily prospectively-identified, and molecules containing these structures withdrawn from development as new medicines, or subjected to additional monitoring measures for approved medicines. (Chapter 6.2.1) (Preventative)
- The content and format of consent documents needs to be further improved, and consideration given to assessing proof of comprehension, particularly regarding the processes for recovery of compensation in the event of injury; these deficiencies compromise the consent process, and are particularly of concern for pregnant women who are, in effect, also giving consent ‘for’ their foetuses. (Chapter 6.4.1) (Preventative)
- Care should be taken to avoid the exploitation of pregnant women by establishing a register to track or limit the number of clinical trials pregnant women may enter, similar to the process for all Phase I volunteers; with the scope to reimburse lost earnings for trial participants introduced within Regulation 536, the risks to the foetus of pregnant women enrolling into multiple clinical trials will need to be managed. (Chapter 8.3.1) (Preventative)
- We need to recognise the particular risks to the foetus resulting from pregnant women participating in clinical trials and develop approaches to compensate children born injured without providing incentives which would constitute exploitation. (Chapter 6.4.5) (Compensatory)
- The legal nature of the Investigator-Subject relationship needs to be clarified and the implications explained to potential trial subjects; this seems a central issue regarding the applicability, or not, of the CDCLA 1976 to a clinical trial setting. (Chapters 5 and 7.8.1) (Compensatory)

- Record retention practices need to be changed to ensure records remain available at least as long as the limitation period for personal injury; the current requirements potentially leave the child born with a delayed-onset injury in the position of being unable to prove the case. (Chapter 7.3) (Compensatory)
- The CDCLA 1976 is not suited to the relationships which exist in a research setting, and relies upon the tortious requirement for negligence; the application of tort law to personal injury arising in a research setting is contentious, and the reality is that scientists cannot know the unknowable, resulting in the unavoidable prospect of harm to the foetus which is not attributable to negligence. (Chapter 7.8.1) (Compensatory)
- The ABPI Compensation Guidelines need to be revised to clarify a range of matters relating to pregnant women in trials, or a separate Guideline generated for this population; a number of considerations are unique to this population, and so a unique Guideline does not seem unreasonable. (Chapter 7.5) (Compensatory)

A recurring conceptual issue arises regarding the maternal-foetal relationship, and the extent to which the decisions the pregnant woman makes ‘for’ the foetus can have consequences in the event of teratogenic injury. The key instruments relating to compensation, i.e., the CDCLA 1976, Regulation 536 and the ABPI Compensation Guidelines, at different points all contain constructions consistent with the ‘two-patient’ and ‘dyad’ models. The intent in all of these may be one of creating safeguards which would otherwise not exist for a child born injured, and these safeguards are to be welcomed. The Guidelines, however, do not seem to be based on a coherent or consistent approach to concepts of the model of pregnancy and therefore may lead to confusion and inconsistency. That said, the Guidelines may simply be reflecting the underlying lack of consensus as described in Chapter 4, but nonetheless, this lack of consensus poses problems for those drafting and interpreting regulation.

As discussed in Chapter 6.4, pregnant women have a variety of reasons, possibly sometimes misguided (therapeutic misconception), for participating in clinical trials. Regardless of their reasons, their participation enables the generation of information which will guide the future treatment of millions of pregnant women, and in the process increase the safety of treatment for both pregnant women and their foetuses, and so is highly valuable. Given both the clear medical need for clinical trials in pregnant women and the requests for such information from the Agencies, any occurrence which would deter participation would be unfortunate: it would result in not only the continuation of the

present level of risk for existing treatments, but an unknowable level of risk relating to future treatments. An essential aspect of clinical research is the trust which participants, and potential participants, have in the Investigator, the ethics and regulatory processes (despite, generally, knowing relatively little about them) and the pharmaceutical company whose drug they are being invited to take.⁶⁶⁰ An event which damages confidence in any of these relationships is likely to be detrimental to trial participation. In the event of harm to the foetus or the birth of an injured child, the labyrinthine routes to compensation summarised in Chapter 7.10 seem likely to undermine that trust, as these are likely to result in significant delays to settlements. This seems likely to affect not only past trial participants, but - particularly with the rapid expansion of social media - also to deter future participants.

This concluding chapter will describe modifications to the current business processes which would potentially increase the safety of the foetus from a preventative aspect, and a range of relatively minor legislative revisions which would increase the prospects for recovery of compensation should injury arise. More importantly, two major changes to the legislative framework for recovery of compensation will be explored: the introduction of a broader no-fault compensation system that the one which currently exists within the ABPI guidelines, and the development of a 'no-causation' system intended to address the major issue regarding compensation for teratogenic iatrogenic injury - that of establishing causation. The development of the latter system is to an extent predicated upon the value brought by the participation of pregnant women in clinical trials of investigational drugs, and so that behaviour will be considered as a preliminary issue.

8.2 Is Trial Participation Supererogatory?

The reasons that people have, or give in response to questioning, for participating in clinical trials were examined previously.⁶⁶¹ Some will consider any trial participation as supererogatory. Participation would satisfy Mellema's condition⁶⁶² that a supererogatory act fulfills no duty or obligation (although it does not incorporate intention or beneficence on the part of the performer of the supererogatory act), as participation in clinical trials is

⁶⁶⁰ St.Clair, E.W. (2008). The calm after the cytokine storm: lessons from the TGN1412 trial. *J.Clin.Invest.*, **118**, 1344-1347.

⁶⁶¹ See discussion in Chapter 6.4.

⁶⁶² Mellema, G. *Beyond the call of duty: Supererogation, obligation and offence*. Albany, New York: SUNY University Press; 1991.

entirely voluntary. It would also fit Heyd's definition⁶⁶³ that the performance is good by virtue of its intended consequences, and that the action is done voluntarily for someone else's good. A pregnant woman volunteering to participate in a Phase I trial of an investigational drug would seem amply to satisfy these criteria. The 'special expertise' requirement within Regulation 536⁶⁶⁴ should ensure that such participation is not reckless, and so forms another layer of protection for the foetus.

The supererogation argument applies equally to all Phase I trial subject populations, in that these volunteers who 'go first' assume a risk on behalf of society, and from which they expect to receive no clinical benefit, assuming they have been properly informed within the consent process. Some, probably many, of these individuals will have relationships and possible dependents; they reach their decision regarding the risks of participating based on a holistic assessment of the information they have been provided, and consideration of the possible impacts on themselves and others. This seems no different to the situation which obtains when a pregnant woman contemplates participation in a clinical trial; the foetus becomes one such consideration. In the UK, the law does not seek to control the acts or behaviours of pregnant women to protect the foetus, whether these are legal or otherwise, with the exception of attempting to procure an abortion,⁶⁶⁵ so why would voluntary participation in a clinical trial which had followed the defined approval procedures be seen differently from a moral perspective?

The special expertise requirement in Regulation 536 described in Chapter 6.3 may go some way towards reassuring those who retain doubts regarding the morality of such trials. Others might consider this requirement imposes a greater limitation on a pregnant woman's freedom of choice. If the special expertise is intended to provide additional protection to the foetus, then that is similar to the additional protection afforded to minors (in addition to parental rights' considerations) and the *incapax* (in addition to family considerations), with the key difference that those who are asked to give consent for these groups are not the trial subjects, and is again consistent with a 'two-patient' model. If the construction suggested in Chapter 6.3.1 is valid, i.e., that the foetus is a trial participant, and that the pregnant woman in consenting to participate in a trial is, in effect, giving

⁶⁶³ Heyd, D. Experimentation Trial: why should one take part in medical research? In: Emanuel, E.J., Crouch, R.A., Arras, J.D., Moreno, J.D. Grady, C., eds. *Ethics and Regulatory Aspects of Clinical Research – Readings and Commentary*. Baltimore: Johns Hopkins University Press; 2003. Chapter 23, p161-166.

⁶⁶⁴ The requirement for special expertise is addressed in Chapter 6.3

⁶⁶⁵ Offences Against the Person Act 1861, §§58-59.

proxy consent for the foetus, then she may be limited in what she can consent to, as is the case for those giving proxy consent for minors and the *incapax*. On this basis, it would be consistent that the REC may decline to approve trials on the basis of potential risk to the foetus, just as would be the case for minors and the *incapax*. If the effect of the new Regulation is to create such a construction, then, just as the consent of the proxy does not preclude minors and the *incapax* seeking damages for injury, then the same would be true of the child injured *in utero*, although this may not be borne out by our present approaches.

The moral position is perhaps less clear for Phase II and III studies, in which the prospect exists of benefit to the pregnant woman. An improvement in the pregnant woman's health may result in foetal benefit. Thus, the possibility of indirect benefit to the foetus may be seen as an additional pressure on a pregnant woman to agree to participate in a clinical trial. Yet the management of depression,⁶⁶⁶ epilepsy⁶⁶⁷ and hypertension⁶⁶⁸ all demonstrate that medicines which often benefit the pregnant woman clinically can, in some cases, have adverse consequences for the foetus, and the child it will become. The same is likely to be true for investigational drugs, with the added issue that adverse consequences may be more difficult to identify and predict. However, analogous to the discussion above, potential trial participants will be expected to reach a balanced judgement regarding their participation based upon the information provided, and for a pregnant woman, the foetus is, arguably, another consideration of which she must take account when reaching her decision. If true clinical equipoise exists regarding benefit, then there is neither advantage nor disadvantage to participating in the trial.

The teratogenic risk associated with treatment is not affected by the phase of the trial, although, as a generality, Phase II and III trials will probably entail substantially longer dosing periods than Phase I trials, and thus result in greater foetal exposure to potential hazard. The incidence of teratogenic effects of almost all drugs is extremely low, and the tenor of the guidance from the Agencies is that their desire is to gather data on the pharmacokinetics of drugs in pregnant subjects and the implications of that for dosing and efficacy, rather than detection of teratogenic effect. From this, it follows that the primary

⁶⁶⁶ Suri, R., Lin, A.S., Cohen, L.S. *et al*(2014). Acute and Long-Term Behavioral Outcome of Infants and Children Exposed in Utero to Either Maternal Depression or Antidepressants: A Review of the Literature. *J. Clin.Psych.*, **75**, E1142-E1152.

⁶⁶⁷ Recent reviews include Eadie, M.J. (2014). Treating epilepsy in pregnant women. *Exp.Opin. Pharmacother.*, **15**, 841-850; Hill, D.S., Wlodarczyk, B.J., Palacios, A.M. (2010). *Exp.Rev.Neurother.*, **10**, 943-959.

⁶⁶⁸ Chung, N.A., Lip, G.Y.H., Beevers, M. *et al*, (2001). Angiotensin-II-receptor inhibitors in pregnancy. *Lancet*, **357**, 1620-1621.

purpose of such studies is not to assess teratogenic potential, and equipoise clearly exists in that regard, as these studies are neither designed nor statistically-powered to answer that question. Thus, the foetus could be placed at greater risk, regardless of the trial phase, by the pregnant woman's participation.

Harris⁶⁶⁹ has advanced a number of arguments that a duty exists to participate in medical research: we all benefit from the existence of the social practice of medical research, many of us would not be here had infant mortality not been brought under control, and most of us will continue to benefit from medical advances. Since we accept these benefits, he argues, we have an obligation in justice to contribute to the social practice which produces them. His contention is that it is unfair to accept the benefits of research without contributing something back by participating in research, and that we have a social duty to maintain those practices and institutions that sustain us, including those which contribute to medical knowledge. They are consistent with Singer's formulation of the principle (emphasis added): "If it is in our power to prevent something very bad happening, *without thereby sacrificing anything of comparable moral significance*, we ought to do it".⁶⁷⁰ Others, more recently, have taken a stronger position, that a *prima facie* obligation exists to participate in biomedical research because such research produces the public good of biomedical knowledge, to which everyone has access.⁶⁷¹

Rennie, whilst broadly following the same approach regarding the 'duty' view, raises two caveats.⁶⁷² The first is that should participation be positioned as a moral duty, then it compromises the freedom associated with consent; potential subjects may enter clinical trials to avoid being seen as blameworthy, although such a situation might alleviate the current injustice that the majority of research participants tend to come from socially-disadvantaged groups.⁶⁷³ The second is a series of conditions that the relative worth or value (not in financial terms) of the study must be sufficient to justify the inherent risk of participation.

Provided patient autonomy is respected, and trials are executed competently, these might appear to be reasonable moral arguments, but are they still valid when the trial subject is a

⁶⁶⁹ Harris, J. (2005). Scientific research is a moral duty. *J.Med.Ethics*, **31**: 242-248.

⁶⁷⁰ Singer P. *Practical Ethics*. New York: Cambridge University Press; 1979.

⁶⁷¹ Schaefer, G.O.; Emanuel, E.J.; Wertheimer, A. (2015). The obligation to participate in biomedical research. *J.Am.Med.Ass.* **302**, 67-72

⁶⁷² Rennie S. (2011). Viewing research participation as a moral obligation: in whose interests? *Hast.Cent.Rep.*, **41**, 40-47.

⁶⁷³ Ho, A. (2008). Correcting social ills through mandatory research participation. *Am.J.Bioethics*, **8**, 39-40.

pregnant woman? None of those positing a moral ‘duty’ to participate in research appear to have considered research involving pregnant women. Given the caveats raised by Rennie, perhaps positioning participation as a duty is setting the standard too high for populations unable to represent their own interests, such as the incapacitated, minors and, particularly, the foetus; how can an entity which has not been born shoulder a ‘duty’ to anyone? Nevertheless, it is surely open to all of us to choose to behave in a supererogatory manner, and given the arguments set out in Chapters 2 and 3, there appears to be neither legal nor moral impediment to pregnant women electing to do so. In other words, legally-competent pregnant women can choose to participate in trials on the same basis as anyone else, and in doing so effectively become proxy decision-makers for the foetus.

Presumably, no REC or regulatory body would approve a clinical trial which held a known risk of miscarriage or congenital abnormality. Having elected to continue the pregnancy, the pregnant woman has accorded a degree of moral significance to the foetus (see Chapter 4), and thus there is no intent to ‘sacrifice’ something of moral significance. Given the lack of knowledge regarding the potential for teratogenicity, the reality may be that we do not know whether we are, in fact, risking a ‘sacrifice’, and we may not know until long after the conclusion of the trial. Accordingly, the participation of pregnant women in clinical trials probably violates Singer’s formulation and may go beyond the scope of the ‘duty’ Harris, Rennie and others propose.

Based on the above, the participation of pregnant women in clinical trials, assuming the absence of therapeutic misconception, may be considered as supererogatory. Given the restrictions regarding participation in multiple trials, the protection for the foetus in that regard seems reasonable; the only route to greater protection for the individual foetus would be a return to the previous embargo.

Supererogatory behaviour surely merits praise. There is normally no incentive for an individual to contribute to a public good even if the benefit of doing so to the individual is greater than the cost of contribution,⁶⁷⁴ but what of our response to injury suffered by those who behave in this way? The risk of harm to the foetus is engaged by participation in a single trial. We may be unable to further reduce the prospect of injury, but as a society, do we provide sufficient protection of the future prospects of those who take such risks on our

⁶⁷⁴ Olson M. *The Logic of Collective Action*. Cambridge, MA: Harvard University Press; 1965, cited in Schaefer, G.O.; Emanuel, E.J.; Wertheimer, A. (2015). The obligation to participate in biomedical research. *J.Am.Med.Ass.* **302**, 67-72.

behalf? The discussions in the previous chapter led to the conclusion that the provision of protection of the future interests of foetal trial participants was inadequate, and so when considering options for future legislative change, the supererogatory behaviour of pregnant trial participants must come into that consideration.

8.3 Amending Current Business Processes, Legislation and Guidelines

Some of the shortcomings identified above relate to business processes, and could be addressed without requiring the creation of new legislation, but would require changes to current legislation, and to the ABPI Guidelines. Chapters 2 to 7 have described the current level of recognition and protection of the foetus outwith a clinical trial setting, the relationship between the investigator, the pregnant woman and the foetus, the clinical trial review and approval process, including potential shortcomings therein, and current mechanisms for recovery in the event that harm to the foetus does arise, again with the identification of apparent inadequacies. Based on these analyses, the next sections will address possible changes to current business processes and propose changes to legislation which, together, would significantly increase the level of protection for the foetus in a clinical trial setting, and the future interests of a child born injured as a result of a clinical trial.

8.3.1 MHRA-Related Changes

There appears to be no legal impediment to the MHRA requiring sponsors to complete all ICH-defined pre-clinical studies prior to embarking upon clinical studies, or documenting their reasons for not doing so; this is essentially a business process change. However, unless the same approach was taken by most other countries, such a requirement may place the UK at a disadvantage in terms of attracting commercial clinical research.

Similarly, there appears to be no legal impediment to the MHRA undertaking an analysis of pre-clinical reproductive toxicology reports and identifying suspect moieties, although no legislative requirement currently exists for such analyses be carried out either, so, again, this could be a business process change. The effort, and thus costs, required to do this would be substantial, and some of the expertise required may not exist within the MHRA. However, the MHRA is one of over 20 regulatory authorities within the European Union, and an analysis of this type would probably be better undertaken by the EMA, as suggested

in Chapter 6.2.1, which would have access to a wider range of expertise than any single national agency.

Following the TeGenero incident, the MHRA established a register for all Phase I trial participants,⁶⁷⁵ so there would appear to be no barrier to a similar register being established for pregnant trial participants; again, this is a business process change.

8.3.2 REC- and NHS-Related Changes

RECs already have the authority to require changes to the format and content of Information Sheets and Consent Documents, yet these documents continue to be reviewed critically in the academic press.⁶⁷⁶ Since the RECs are part of the NHS,⁶⁷⁷ there is no obvious obstacle to the NHS instructing all RECs to require some form of assessment of the comprehension of these documents. However, if this approach was applied retrospectively to studies already underway, the implications should the results indicate that significant numbers of subjects had not understood the process, and therefore may not have given valid consent, would be substantial, both in terms of the subjects' legal rights and the admissibility of the data by the regulatory authorities. Prospective application might significantly impair commercial clinical research in the UK, and so, as a minimum, this approach would need to be pan-European. The relevance of the judgment in *Montgomery*⁶⁷⁸ also needs to be considered in a clinical trial setting regarding the level of information provided to prospective trial subjects.

Regarding the retention of records, practically all of the clinical research conducted in the UK takes place within NHS premises, and although the individual facilities may be private, trial subjects' medical notes are accessed as part of trial conduct, and relevant observations entered into the medical notes. That means the fact of a subject's participation in the trial

⁶⁷⁵ Health Research Authority National Health Service. The Over-volunteering Prevention System (TOPS), available at <http://www.hra.nhs.uk/about-the-hra/our-committees/the-over-volunteering-prevention-system/>, accessed 19th September, 2015.

⁶⁷⁶ See, for example, Featherstone, K., Donovan, J.L. (2002) "Why don't they just tell me straight, why allocate it?" The struggle to make sense of participating in a randomised controlled trial. *Soc.Sci.Med.*, **55**, 709–719; Donovan, J., Mills, N., Smith, M. *et al.* (2002) Quality improvement report: Improving design and conduct of randomised trials by embedding them in qualitative research: ProtecT (prostate testing for cancer and treatment) study. *Br.Med.J.*, **325**, 766–70; Mills, N., Donovan, J.L., Smith, M., *et al.* (2003) Patients' perceptions of equipoise are crucial to trial participation: a qualitative study of men in the ProtecT study. *Cont. Clin. Trials*, **24**, 272–82; Prescott R.J., Counsell, C.E., Gillespie, W.J. *et al.* (1999). Factors that limit the quality, number and progress of randomised controlled trials. *Health Tech.Assess.*, **3**, 139; Flory, J., Emmanuel, E. (2004). Interventions to improve research participants' understanding in informed consent for research: a systematic review. *J.Am.Med.Ass.*, **292**, 1593-1601.

⁶⁷⁷ The legal position and governance of the RECs are addressed in Chapter 7.7.1.

⁶⁷⁸ *Montgomery v Lanarkshire Health Board* [2015] UKSC 11.

and other key information exists within the patient's medical file. Since children's files are retained for 25 years, there seems no reason that the NHS could not mandate that trial subjects' records would also be retained for that period following trial participation. With the gradual progression towards the use of electronic medical records within the NHS, the issue of storage of records for a longer period of time perhaps becomes less problematical than would be the case for paper records.

8.3.3 The Relationship: Doctor-Patient or Investigator-Subject?

The legal nature of the Investigator-Subject relationship, and the differences between an Investigator and a medical practitioner, need to be clarified; without this, the application of the CDCLA 1976, and particularly section 1.5, to a clinical trial setting is uncertain, but it is not clear how this might be effected. The Doctor-Patient relationship was defined - perhaps undefined - in the common law,⁶⁷⁹ and it may be that we need to await a relevant research case before we have a similar clarification of the Investigator-Subject relationship. There does not appear to be an item of legislation to which this definition could readily be attached. As this relationship would apply to all clinical trials, the CDCLA 1976 seems inappropriate. The Medical Act 1983 governs the regulation and credentials of the medical profession, and defines offences in respect of false claims of fitness to practice medicine; it makes no mention of research. The Medicines Act 1968 mentions clinical trials, but largely from an administrative perspective.

The tortious requirements of the CDCLA 1976 would not be easy to change for a clinical trial and yet retain as a single legislative instrument. The challenge of applying the CDCLA 1976 to a clinical trial setting seems substantial (Chapter 7.8.1); negligence needs to be established, and in addition the 'but-for' test needs to be satisfied. Although untested in court, this seems to be setting the barrier to recovery of compensation for harm inflicted *in utero* during a clinical trial rather high. Making changes to the other legislation cited in Chapter 7.8 would also be difficult, as those Acts were intended to cover a wide range of situations.

8.4 The Introduction of a No-Fault Scheme

The tortious requirements of the CDCLA 1976 would not be easy to change for a clinical trial and yet retain as a single legislative instrument. The challenge of applying the

⁶⁷⁹ By Lord Scarman, in *Sidaway v Board of Governors of the Bethlem Royal Hospital* [1985] AC 871 at 884.

CDCLA 1976 to a clinical trial setting seems substantial (Chapter 7.8.1); negligence needs to be established, and in addition the ‘but-for’ test needs to be satisfied. Although untested in court, this seems to be setting the barrier to recovery of compensation for harm inflicted *in utero* during a clinical trial rather high. Making changes to the other legislation cited in Chapter 7.8 would also be difficult, as those Acts were intended to cover a wide range of situations. The ABPI Compensation Guidelines also contain a tortious requirement in the event of injury sustained by trial subjects allocated to a comparator agent or to placebo.

As discussed in Chapter 7.10, perhaps the time has arrived for the legal issues regarding the conduct of clinical trials involving pregnant women to be brought together in a single item of legislation, including provision for compensation for injury. Although the MHU Regulations 2004 and the GCP Directive attempt this in many respects and Regulation 536 will do so too for trials in general, a range of issues remain unresolved for this population. Regulation 536 specifically does not address liability issues, deferring to national procedures.⁶⁸⁰

The introduction of legislation specifically applicable to pre-registration clinical trials in pregnant women stipulating that no-fault liability will apply to injuries sustained by the foetus during clinical trials which manifest as injury in the live-born child should be considered. This would avoid the tortious requirements within the CDCLA 1976, and which are likely to be particularly difficult to satisfy in a research setting. Injured research participants may have more difficulty than non-trial patients showing that a duty owed to them was breached, due to the different nature of the relationship, that the intervention many months or years earlier caused the injury, and that they did not, through the pregnant woman’s consent, ‘assume the risk’.⁶⁸¹ The application of a no-fault approach to the foetus would continue the policy approach introduced by the CDCLA 1976, and avoid the need to resolve the recurring issue of the duty of care owed to an entity which lacks legal status. However, as described in Chapter 7.9, the challenge of causation remains as a significant obstacle to the recovery of damages, and will be addressed in the next section.

⁶⁸⁰ European Union. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. Official Journal of the European Union. L158, Vol. 57, 27 May 2014, pp. 1-76, paras 61, 61 and Art.95

⁶⁸¹ This was addressed in Chapter 7.5.6

8.5 The Introduction of a 'No-Causation' Scheme

Two premises underly this proposal. The first is that of attempting to promote acknowledgement and reward of supererogatory behaviour which will generate the information to guide the future treatment of pregnant women, improve the legal recognition for the foetus, and the compensation of children in the event of teratogenic injury for which they bore no responsibility whatsoever, and notwithstanding any acts or omissions by the pregnant woman which may have contributed to such injury. The second is try try to find an approach to avoid the burden of establishing causation for those who have 'gone first' and been born injured, which is the major impediment to compensation.

8.5.1 The Relevance of Vaccine Damage to Clinical Trials in Pregnant Women

One of the aims of vaccination is to generate a form of protection for the rest of society; those who are vaccinated do not have the condition the vaccine is intended to prevent. The conduct of clinical trials in pregnant women will often have a similar aim, albeit indirectly, by generating information which will help ensure pregnant women receive drugs at appropriate dose regimens to attain the effect desired with minimal risk (see Chapter 1); often that information will be generated in Phase I trials, involving pregnant women who do not have the condition the drug is intended to treat. The results of such trials will hopefully provide better guidance on the prevention and management of a range of conditions from which can affect women whilst - but not necessarily because - they are pregnant. Better prevention and management in that setting should reduce the significant costs of pregnancy-related morbidity (see Chapter 1.1) and the extent of human suffering - much the same as is the case for vaccination programmes. They should also result in greater protection for the foetus, by defining dose regimens which can manage conditions in pregnant women without endangering the foetus, by keeping the concentrations of medicines circulating in the pregnant woman's system within therapeutic limits.

Vaccination is encouraged but not legally required by Government. The recent requests by the Agencies for pre-registration data relating to investigational drugs in pregnant women (see Chapter 1.6) effectively encourage, but again do not legally require, the conduct of such studies in that population. In the late 1990s, the Agencies issued similar requests for pre-registration data in the paediatric population; now, the provision of such information is

mandatory unless the Agencies grant a specific waiver to the requirement.⁶⁸² Accordingly, it is not impossible that the current request relating to pregnant women will, in time, evolve into a pre-approval requirement. That said, pregnant women cannot be compelled to participate in clinical trials, just as, with certain exceptions, mothers cannot be compelled to have their children vaccinated. Of course, during the pre-registration phase such studies will involve far fewer exposures than population-level vaccination programmes, but once drugs are approved, the number of foetal exposures will certainly increase.

If the rest of the drug (and vaccine) development process is conducted thoroughly, injuries should occur rarely, which certainly appears to be the case for vaccines, although under-reporting is frequently cited as a concern.⁶⁸³ As a consequence, however, the first few cases of drug- or vaccine-related injury may be dismissed as reflecting the underlying, natural rate of occurrence of the abnormality or the condition the drug or vaccine was intended to treat.⁶⁸⁴

Thus, a number of similarities exist between the situations relating to vaccine damage and teratogenic injury. One might also infer that the recommendations of the Pearson Committee which led to the creation of the CDCLA 1976 and the VPDA 1979 reflected the foreseeable challenges if tort was the only route by which to seek compensation for injuries in such settings. If we are to contemplate some system to provide ‘compensation’ for the latter in a clinical trial setting, the process used for alleged vaccine damage, which has now been in place for nearly 40 years, might seem to be a reasonable place to start. However, as the data relating to payments from the Vaccine Damage Tribunal testify (Chapter 7.8.4), the burden of establishing causation remains the most significant obstacle to the recovery of compensation.

There is, of course, one major difference between vaccination of children and the participation of pregnant women in clinical trials: equipoise. Children are vaccinated in the expectation that the vaccination will both reduce the probability of their developing the condition against which they were vaccinated, and in turn reduce the prospect of that

⁶⁸² See

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000293.jsp, accessed 5th May, 2016;

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm360507.pdf> accessed 5th May, 2016.

⁶⁸³ See, for example, <http://www.vaccine-side-effects.com/under-reporting-side-effects/>, accessed 5th May, 2016.

⁶⁸⁴ A recent example of such a case was described in Chapter 7.5.2.

condition being transferred to others. In contrast, the requirement for equipoise in the clinical trial setting means that pregnant women do not enjoy the same beneficial prospect, which makes their participation all the more praiseworthy.

8.5.2 A 'No-Causation' Scheme

“Since the 1960s, individual commentators and national commissions have agreed that the ethical principles of justice and virtue support, if not require, compensating research subjects who are harmed as a result of participating in research.”⁶⁸⁵

Given the difficulties of proving that an injury to a child was the result of a drug given as part of a clinical trial in which the child’s mother participated whilst she was pregnant (see Chapter 7.9), perhaps consideration should be given to reversing the presumption, such that unless certain conditions were satisfied, the injury would be considered to be the result of the pregnant woman’s participation in the trial but only for the purposes of providing compensation, and not for establishing causation in a legal or regulatory sense. This would be consistent with the way in which no-fault compensation was first envisaged.⁶⁸⁶ Its application specifically to clinical trials of investigative drugs in pregnant women could be construed as a policy-based response to the difficulties trial participants will have in establishing that the injury to the child was related to the trial treatment, similarly to the Fairchild exception.

Such trials will rely upon pregnant women volunteering to participate. Many of these are likely to be pharmacokinetic trials, and therefore of no foreseeable benefit to participants. Trials of this type are considered as ‘Phase I’ trials, and so participants will be paid for participating, and will (probably) come within the ABPI Compensation Guidelines. As matters stand at present, pregnant women will not be considered differently to male and non-pregnant female participants – yet they are taking a greater risk. The risk to the pregnant woman is increased as a consequence of pregnancy-related physiological and biochemical changes, but she assumes these risks knowingly. The acute risk to the foetus is increased over the risk of the pregnant woman not participating, and the foetus does not assume these risks knowingly, but the pregnant woman bears the responsibility for

⁶⁸⁵ Mariner, W.K. *Compensation for Research Injuries in: Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Vol. 2. Workshop and Commissioned Papers. Mastroianni, A.C., Faden, R., Federman, D (Eds). Washington D.C.: National Academy Press, 1994, pp113-126.

⁶⁸⁶ Ehrensweig, A. (1964) Compulsory ‘hospital accident’ insurance: a needed first step toward the displacement of liability for ‘medical malpractice’. *Univ.Chicago L.Rev.*, **31**, 279–91.

participating. Accordingly, the participation of pregnant women in such trials is supererogatory in nature, a behaviour which merits recognition and - arguably - reward. Addressing the greater risk by increasing payments to participants seems inappropriate; it engages the notion of employing a financial incentive to encourage trial participation, contrary to every ethical code under which clinical research is conducted. It would also mean that a flat rate of payment was given to all participants, whether the potential risk was realised or not. For most, the risk will not be realised, but for the very small number of cases in which it is, or it may have been, an increased participant payment is unlikely to meet the resultant costs, leaving the mother and injured child in the same position they are at present regarding the recovery of compensation.

If the pregnant woman sustains an iatrogenic injury herself, and the foetus is unharmed, she can engage the, admittedly imperfect, systems to gain compensation for herself, just like any other trial volunteer. The route to compensation for a child born injured is both less clear and less certain, and, leaving aside the causation issue, the injury may have resulted from the pregnant woman's supererogatory behaviour of participating in a clinical trial. A child born injured through no fault of its own should not be disadvantaged if the injury is the result of the pregnant woman's supererogatory act - an act which will generate information which will be of use to many others. Establishing causation for teratogenic injury is fraught with difficulty, as described in Chapters 7.8.4 and 7.9; as a result, the prospects for recovery of compensation by the injured are not good. If the issue of compensation for injury in such trials is not addressed, participation will almost certainly be adversely affected when the first few possible cases occur, in which case the advantages from such trials will not be realised. The option of suppressing the challenges regarding the prospects for compensation in the event of injury during the consent process is not an appropriate or defensible approach. A change of approach to the payment of compensation for foetal injury in such trials offers the advantage that compensation is paid only should a foetal injury arise. The moral basis for a different approach to compensation for foetal injury in such trials is that the injury was the result of a supererogatory act by the pregnant woman. Harris's and others' 'duty to participate' arguments and the payments to other Phase I participants differentiate male and non-pregnant female participants from pregnant participants.

There are a number of arguments which support consideration of such a system. A simple consequentialist case would be that this would remove a potential impediment to pregnant

women participating in such trials, with a consequent increase of knowledge which would be to the benefit of the pregnant population in particular. Children who are born with congenital abnormalities often require significantly more care than their 'normal' counterparts, which can impact on the quality of life and earning capacity of the family unit, which in turn may lead to additional financial support requirements from central funds.

From a non-consequentialist perspective, it may be argued that where society conducts, supports or sponsors research, it voluntarily assumes an obligation to compensate those who are injured in its enterprise. The Clinical Trials Directive, Regulation 536, and the review and approval systems for the RECs and the MHRA all constitute evidence that the UK and the European Union, i.e., one definition of the society in which we live, support research of this type. A 'no-causation' approach may be considered reasonable on the basis of fairness to those who voluntarily risk personal harm, and that of their foetuses, for the benefit of the community, or by a social desire to reward behaviour that is perceived as virtuous; as discussed earlier in this chapter, the participation of pregnant women in clinical trials is supererogatory, and such behaviour surely merits recognition. A strong version of this argument would postulate that a community which benefits from an individual's altruistic act has a moral obligation to provide restitution to the individual; a weaker version would simply assert that although compensation may not be morally required, it is morally desirable as a charitable act.

Many countries have implemented compensation schemes for vaccine injuries as an expression of solidarity.⁶⁸⁷ In some countries, the schemes reflect a broader social judgment that all medical risks should be shared. In others, vaccine injuries were viewed as special due to their severity, complexity, and propensity to befall children and others who would not qualify for benefits under processes.⁶⁸⁸ Given the extent of similarities between vaccine damage and teratogenic injury arising in clinical trials in pregnant women, particularly the fact that the party most likely to be injured is the one least able to look after his or her own interests, there seems merit in extending the rationale from vaccines to clinical trials in pregnant women.

⁶⁸⁷ W.K. Mariner, W.K. (1987). Compensation Programs for Vaccine-Related Injury Abroad: A Comparative Analysis. *St. Louis Univ. Law J.*, **31**, 599–654.

⁶⁸⁸ Evans, G. (1999). Vaccine injury compensation programs worldwide. *Vaccine*, **17**, S25–35

Under the current regulations, one of the definitions of a serious adverse event is a congenital abnormality or birth defect occurring after exposure to an investigational medicinal product.⁶⁸⁹ Thus, the occurrence of such events, if detected during or after a clinical trial involving an investigative drug, must be reported to the relevant authorities, and becomes part of the corpus of information relating to that drug. This currently does not connote an admission of liability by the sponsor, nor would it do so under this ‘no-causation’ proposal. However, such a report would be sufficient to trigger a payment to the (now) mother; payment would be a response to occurrence rather than causation. The trial sponsor would not be responsible for making the payment; it would be made from the national insurance scheme described previously and specified within Regulation 5.3.6. Accordingly, the sponsor would not be liable for costs which may not have arisen as a result of any error or wrongdoing on the part of the sponsor. The member state would meet the cost on the basis that, analogous to one of the justifications put forward in the Pearson Report for vaccine damage compensation,⁶⁹⁰ this is the very occasional price that society pays for the benefit of defeating disease in this patient group.

One of the criticisms of the ABPI Compensation Scheme is that it does not make payment in the event the trial subject is randomised to comparator or placebo (Chapter 7.5.3); children born injured or who are subsequently found to be impaired need to bring a claim in negligence. Under this proposal, payment from the insurance fund would be made regardless of the treatment group to which the pregnant woman was randomised. In this way, all subjects entering a clinical trial would be managed in the same way regarding recompense for teratogenic injury. This also seems fair, as the Government’s representative, the MHRA, may have specified the trial design, or at least approved it.

A pre-requisite would, of course, be that the injury was not present prior to the clinical trial, and specifically the administration of trial treatment, and was present subsequently. Akin to the process which preceded the VDMA 1979, an appropriate Expert Group would need to be established to define the pre-trial information to be assembled to provide a baseline against which assessments could be made of whether an injury had, in fact, occurred, in the process almost defining a set of ‘exclusion criteria’ - factors which, if

⁶⁸⁹ ICH Topic E 2 A. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002749.pdf, accessed 5th May 2016.

⁶⁹⁰ This is addressed in Chapter 7.8.4.

present, would exclude a child from ‘automatic’ recompense, but would not necessarily exclude the pregnant woman from the clinical trial. As of the consent process, the pregnant woman would be informed regarding the antenatal finding, and its implication regarding payment in the event the child is subsequently born injured. Those providing the ‘special expertise’ to the RECs required under Regulation 536 may be credible candidates for such a Group, although the Group would also require particular legal expertise. The criteria could be formally reviewed and updated on a regular basis as new evidence emerges.

The pre-trial information requirement would lessen the risk of exploitation of pregnant women and reduce the prospect of a mother with an already-damaged foetus participating in a clinical trial. A system such as this would avoid the accusation of bribery which would inevitably follow any suggestion of paying trial participants; under this option, payments would be made only to children born injured. Thus trial participants are not being ‘compensated’ for being exposed to the risk of a teratogenic effect, but for such effect should it arise, given the challenges of establishing causation, especially in the ‘first case’. This would result in a degree of selection bias, but such a bias is inherent in the selection criteria for any clinical trial; the point of these criteria is to define a reasonably homogeneous study sample which will generate transportable information to the population of which it is representative, with an ethically-acceptable risk:benefit ratio.

On the premises that the appropriately-informed autonomous pregnant woman may make whatever decisions she pleases regarding trial participation (Chapter 6.4), and the overall ethical issues have been considered prior to the approval of the trial (Chapter 6.3), the restrictions regarding an automatic entitlement to recompense in the event of a possible teratogenic injury should be made known within the consent process. If the pre-trial information indicates that the child is highly likely to be born with some form of congenital abnormality, then it seems reasonable to exclude such an abnormality from the ‘no-causation’ process. Such pre-trial information might include, *inter alia*, the results of scans, blood and genetic tests, the current medical history of the pregnant woman, e.g., is she taking anything which is associated with teratogenic injury in humans, and family history. Given that payments would be made from the national insurance scheme, it would seem not unreasonable for the Government to protect its interests by specifying as condition of protocol approval by the MHRA that particular information was generated within the pre-trial process, always provided the generation of the information did not pose

a risk in itself, e.g., amniocentesis, or was excessive, i.e., going significantly beyond the usual level of baseline data collection in a clinical trial.

The threshold for exclusion would need to be set high, or the threshold for causation set low, to avoid the types of arguments which have proven so difficult in vaccine-damage cases. For the same reason, the level of disability would need to be set low; the prospect of a mother being denied recompense in respect of a child whose disabilities had been assessed at, say, 58% is unattractive, and will do little to reassure other pregnant trial participants. As part of this structure, criteria would need to be defined by the Expert Group regarding the age at which injury becomes apparent in order to qualify; visual impairment may not become noticeable until the child is many months old, and developmental abnormalities, such as speech and learning, may take considerably longer to become obvious. Provision would also need to be made for consideration of *novus actus interveniens*, the most likely of which is, ironically, vaccination. Nonetheless, starting from a rebuttable presumption that the injury was the result of the pregnant woman's participation in the trial, an approach such as this should do much to accelerate the payments to and reduce the distress and potential financial hardship of mothers who find themselves in this situation.

Rather than the fixed sums which exist under the Vaccine Damage Compensation Scheme, a sliding scale of disability would avoid the issues posed by pre-defined thresholds. Such a scale should, ideally, reflect the type of injury commonly found in congenital injuries, and reference might usefully be made to Vaccine Injuries Compensation Programme in the USA or the Criminal Injuries Compensation Scheme in the UK.

Capturing all such cases in the proposed registry of pregnant women participating in such studies will enable more complete tracking of potential teratogenic injury, and support the MHRA and EMA in the conduct of analyses which may move the balance of probabilities away from favouring congenital abnormalities as being spontaneous towards being causally-related to a particular drug, a structural moiety within the drug, or an excipient. In the event that the collection and analysis of such information identified such a link, this would be notified to all drug manufacturers and trial sponsors, and the appropriate steps would then be taken, including the addition of relevant warnings on patient information leaflets and package inserts, consent documents for clinical trials, and so on, relating to the suspect entity.

If that entity was an investigative drug, then the manufacturer would already have all of the relevant information, and may be called to explain the reasons that an Agency, rather than the manufacturer, identified the link. If the entity identified as being teratogenic was a comparator drug in a clinical trial, it is possible that the drug was produced by multiple manufacturers, and so all of the relevant information may not have been available to any of them, but it would be available to the Agencies. However, under the requirements of Good Manufacturing Practice,⁶⁹¹ the source of all materials employed in clinical trials must be documented, and so the identifies of the manufacturers which made the drug can be discovered. Should the entity be a moiety within a molecular structure, or an excipient, then the number of drugs and formulations which could be implicated would be substantial; none of the manufacturers would have had access to all of the information which would have enables them to come to such an assessment, and resolving issues of liability would be a prolonged process. However, under this proposed ‘no-causation’ scheme, any party who suffered suspected teratogenic injury after participating in a clinical trial would already have been recompensed, regardless of the cause of the injury.

As noted previously, far fewer pregnant subjects will be enrolled into clinical trials annually than the twelve million children vaccinated every year. Assuming that the numbers of clinical trials in pregnant women would be relatively low, and the size of many of these trials, assuming they were intended to generate pharmacokinetic data, would be relatively small, then the number of children born with congenital disabilities would also be low, and although the costs per child could be significant, the overall costs would be relatively modest, particularly if a sliding scale was employed. Certainly, the costs would be low when compared to the costs of managing medical conditions in pregnant women cited in Chapter 1.1,⁶⁹² an unknown proportion of which may be attributable to the mismanagement of these conditions by under- or over-dosing pregnant patients.

If the UK adopted such an approach unilaterally, that might constitute an incentive for sponsors to bring such trials preferentially to the UK; the potential risks to the sponsor of becoming embroiled in protracted litigation with families seeking recompense would be

⁶⁹¹ See

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000154.jsp&mid=WC0b01ac0580027088, accessed on 5th May, 2016, and Commission Directive 2003/94/EC, available at http://ec.europa.eu/health/files/eudralex/vol-1/dir_2003_94/dir_2003_94_en.pdf, accessed on 5th May, 2016.

⁶⁹² Lopez, A.D., Mathers, C.D., Ezzati, M., Jamison, D.T., Murray, C.J. (2006). Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet*, **367**, 1747–1757; Gill, K., Pande, R., Malhotra, A. (2007). Women deliver for development. *Lancet*, **370**, 1347–1357.

much-reduced. However, the potential costs to the national insurance scheme of such a 'no-causation' could be met or at least offset by increased trial fees to all sponsors to meet costs, or a higher fee for studies of this nature.

It would seem reasonable that potential liability under a conventional system would be prospective from the point at which the link was identified, always accepting that such a link does not satisfy the legal test of causation. Capturing an appropriate level of information on such cases in a pre-approval setting, which should not prejudice approval *per se*, would, however, provide information against which any later cases might be compared, and may serve to provide evidence of a causative relationship.

8.5.3 A Fair Solution?

This 'no-causation' approach would prevent victims' claims being thwarted through no fault of their own by the lack of scientific knowledge regarding the cause of an injury. Of course, (almost) any congenital injury could arise spontaneously, and there may appear to be an inherent unfairness if one child with such an injury received compensation because the mother had participated in a clinical trial, whilst another child with an identical congenital injury did not, because the mother did not participate in a trial - the same argument as arose when the Vaccine Damage Payment Act was under discussion. As suggested earlier, perhaps as a society we need to find ways in which to reward those who 'go first' - without them, there will be no progress in this, as in many other areas, of medical research.

Children born with a congenital injury and whose mothers did not participate in a clinical trial would be no worse off than they would otherwise have been. The wider issues regarding the causes of and compensation for congenital injury certainly merit investigation, but are beyond the scope of this thesis. For those born with a congenital injury after their mothers had taken part in a clinical trial, a causation-based approach entails the risk of reaching a decision not to pay compensation, or delaying payment for a significant period of time - witness the thalidomide example - which in hindsight is proven to have been erroneous. Such children would be worse off than they would otherwise have been - their interests have clearly been 'set back' both by incurring the injury and by being denied compensation to which they were entitled. Providing compensation in such circumstances positively reinforces the pregnant woman's supererogatory behaviour, and seems likely to alleviate one of the concerns of others who might contemplate trial

participation, but without creating an exploitative situation: participants are not being paid for participation *per se* - the futures of their children are being protected in the event of injury, which may not, of course, arise.

The principle of corrective justice requires that an individual or an organisation should be liable only for harm that he/she has wrongfully caused. The inability to establish that a particular harm is caused by a particular drug means that an organisation can avoid liability for harm which its drug has, in fact, caused. However, the failure to establish the case means that the victims are denied recompense. The ‘no-causation’ approach proposed would mean that organisations were not found liable in the absence of evidence, and victims were not denied recompense.

This approach would do much to address the restorative issues noted in the introduction to this chapter, and it would bring the regulatory authority, the REC and the NHS more clearly into the preventative aspects. The approach does not require any further resolution of foetal status than currently exists, nor does it require rationalisation of the appropriate model of the relationship between the pregnant woman and her foetus; the REC will already have considered the particular risk to the foetus when approving the trial, and so the pregnant woman’s consent is all that is then required. Finally, such an approach would require extensive revision of the ABPI Guidelines, or the development of a Guideline for use with pregnant women, removing the lack of clarity described in Chapter 7.5.

8.6 Additional Legislative Reforms

In addition to the major changes proposed in the preceding two sections, a number of other changes could contribute to an increased level of protection for the foetus and the interest of the child the foetus will become.

8.6.1 Defining the Investigator-Subject Relationship

The introduction of legislation to clarify the legal nature of the relationship between Investigator and Subject would be helpful. This would also define the Investigator’s responsibilities, in terms of adherence to the protocol, thereby recognising that, in effect, the Investigator may not be ‘treating’ the subject; the responsibility has become one of minimising harm. Whilst it is tempting to suggest that the opportunity might be taken to define the relationship between the pregnant woman and the foetus (see Chapter 4.4), or the status of the foetus as a trial participant (see Chapter 6.3.1), given the long list of UK

and European cases in which that opportunity has not been taken, such a suggestion may be overly-ambitious.

8.6.2 Removal of Contributory Negligence

Under the proposals in the sections above, the contributory negligence provision in the CDCLA 1976 would also be removed specifically for clinical trials in pregnant women, for three reasons. The first is that this provision has, apparently, been so rarely used for 40 years that its need must now be considered as questionable in any setting. Secondly, since the injured child cannot sue the (now) mother, the child may be left with no recourse, which effectively denies justice to the child. The third reason is that the philosophy behind the maternal exemption, described in Chapter 3.5, was that if a child could sue the mother for damage suffered *in utero*, this would disrupt family harmony and create an adversarial atmosphere between the two; it seems difficult to conclude that a child whose compensation was abated due to the mother's negligence during the course of a clinical trial would not feel similarly aggrieved.

8.6.3 Application to Comparators and Placebo

The same non-differentiated approach would be taken for injuries sustained following randomisation to an active comparator or placebo in a clinical trial under the proposals above. Pregnant women may not know, do not choose, and cannot control, the treatment to which they are assigned, other than by declining participation in the trial, although they will be aware of the options and, if properly informed, the risks. The trial sponsor chose - or the regulatory agency specified - the comparator treatment, and the dose, when designing the trial, and both are better-placed than the trial subject to understand the potential risks associated with the comparator. If the comparator damages, or may have damaged, the foetus, why should the trial subject or the injured child need to instigate an action in negligence with all its attendant challenges to seek compensation from the manufacturer of the comparator? Arguably, whoever selected the comparator should be responsible for the consequences of their actions. A similar argument arises in respect of placebo. Although placebo treatment will not precipitate teratogenic injury (although constituent excipients are not subject to the same testing as investigational drugs, so the possibility exists that any of these has undiscovered teratogenic potential), allocation to placebo treatment engages the risk that the subject will not receive treatment which is medically-indicated; as a result, the untreated condition may result in teratogenic injury.

Of course, the REC should not approve trials with such inherent risks, but as discussed in the previous chapter, there is not an obvious method by which to hold the REC accountable for its decisions. This probably represents a greater challenge for the recovery of compensation, as the complainant needs to establish that something would have been better than nothing.

8.6.4 Relevant Degree of Proximity

Should trial subjects reasonably be in the contemplation of the regulatory authorities and the sponsors when designing the trial? Precedent appears to indicate that the regulatory authority is considered as being too far removed from the subjects to owe a duty of care, although the possibility has not been excluded (see Chapter 7.7.2). If the MHRA stipulates the use of a particular comparator in a clinical trial, and that comparator then expresses teratogenic effect, it would seem difficult to hold the MHRA to a different standard to that of the sponsor. Precedent indicates that sponsors are considered as having a sufficient relationship with trial participants to enable them to answer in negligence, so if the cause of the injury is a comparator agent required by the MHRA, this would seem not to fall easily within the categories of discretionary or policy decisions.

8.6.5 Insurance coverage

The requirement in Regulation 536 for member states to establish some form of insurance for trial participants fits well with these proposals. As stated in the previous chapter, countries would be expected to be better-placed to meet the potentially substantial costs associated with congenital injuries than sponsors, although sponsors might reasonably be expected to contribute to the funding of such a scheme by a system of user fees. In conjunction with a no-fault construction, children born injured would be able to seek appropriate compensation from the national system. By linking the two in this way, the compensatory damages paid in a specific country would be appropriate and proportional for that country, rather than, for example, a subject born injured in the UK seeking to bring an action in the USA. Should the injury be related to the investigational drug, to the comparator specified by the regulatory authority, or to the inclusion of placebo at the behest of the regulatory authority, then the sponsor and the authority can subsequently negotiate or litigate regarding some apportionment of these costs, but they can do so in

their own time, and avoid forcing the injured party to wait many years for compensation, as mentioned by Howells and Weatherill (Chapter 7.8.3).⁶⁹³

Obviously, this approach would bring the MHRA, the regulatory authority in the UK, into the compensation process. Although possibly not directly answerable to trial subjects, involving the regulatory authority in this way would create a chain of indirect liability. If a number of cases of teratogenic injury were found to be the result of comparators included at the insistence of the regulatory authority, presumably, the Governmental provision for such payment would come under pressure, and the regulatory authority may then be prevailed upon to reconsider the basis upon which such decisions were made. In this way, the regulatory authority would face greater accountability than is currently the case for the decisions it made, and the greater scrutiny seems likely to result in the authority providing a more detailed rationale for its decision. If this were to be the case, then, potentially, it would increase the preventative protection for the foetus. Such an approach would provide a framework within which all cases of teratogenic injury could be considered and which may set precedent for future cases; this would seem preferable to the current case-by-case arbitration scheme described within the ABPI Compensation Guidelines.

8.6.6 Creating a National Registry

The introduction by Regulation 536 of an obligation upon member states of the European Union to provide insurance for trial participants provides a foundation for an integrated process which could resolve many of the issues identified with the current processes. One might assume that, like any other insurance undertaking, the provider of the insurance would wish to know who is being insured, and so it would not seem unreasonable for the identities of those participating in clinical trials to be collated, perhaps by the MHRA. This could provide the basis for a national Registry for pregnant women enrolling to clinical trials.

Once women had agreed to participate in a trial, details which would enable their information to be recovered at a future date, such as name, N.I. Number, and NHS Number could be captured in the Registry. This would enable the same type of process to be followed which prevents volunteers from participating in an excessive number of trials, as

⁶⁹³ Howells, G., Weatherill, S. *Consumer Protection Law*. Ashgate Publishing, 2005 at p249; see Chapter 7.8.3 for a discussion of this point.

described in Chapter 8.1.1,⁶⁹⁴ and so provide preventative protection for the foetus. Requiring the capture within the Registry of the identity of the drug to which the pregnant subject was randomised, and recording the outcome of the pregnancy, would provide a longitudinal database which the MHRA could monitor to detect associations between particular drugs, or specific moieties, and suspected teratogenic effect. This would provide an additional preventative protection for future foetuses, allowing the MHRA to advise companies of any emerging patterns related to particular moieties which might guide future drug designs. In the event that an investigational drug was approved, and subsequently suspected of being teratogenic, the pre-approval information would be available for examination, which may enable a level of restorative justice for any subjects who participated in clinical trials, gave birth to an injured child, but were denied compensation at the time due to uncertainty regarding an association between the injury and any of the drugs in the trial.

8.7 Conclusions

For the first time ever we are about to undertake the intentional, ethical, systematic administration of investigational drugs to pregnant women in a research rather than therapeutic setting. The practice of ‘avoiding’ the associated risks by excluding or withdrawing pregnant women from clinical trials will become progressively less acceptable, just as has happened with paediatric research. Few of those involved in any aspect of the clinical trial process will not be aware of thalidomide, and all will be determined that such a situation will not recur. As described in Chapter 2 and 4, for moral reasons, the foetus *is* considered to ‘deserve’ protection, and as described in Chapter 3, the law has given effect to that in various ways. However, as our processes stand at present, that protection seems to be significantly lacking in three distinct areas regarding clinical trials: consent, causation and compensation.

The *lacunae* in the protective network start before the consideration of specific trials by the relevant authorities. The ICH Guidelines, with the exception of ICH-E6, have no legal authority, and so sponsors are free to decide not to conduct preclinical assessments defined in these Guidelines. The MHRA is apparently empowered to approve the conduct of clinical trials despite the absence of the information which those assessments would

⁶⁹⁴ Health Research Authority National Health Service The Over-volunteering Prevention System (TOPS), available at <http://www.hra.nhs.uk/about-the-hra/our-committees/the-over-volunteering-prevention-system/>, accessed 19th September, 2015.

provide. The MHRA, and the EMA, have the authority to specify the agents to which an investigational drug must be approved, as a condition of eventual approval of the drug. Yet the MHRA appears to bear no liability for the consequences of its decisions. Similarly, the RECs appear to be immune to suit, but could do much to improve the content and wording of consent documents and require that periodic re-assessment of the level of understanding of trial subjects was conducted. Moreover, the RECs could take a position on the ABPI Compensation Guidelines, requiring that a clearer explanation be given regarding the scope for payment in the event of injury; whilst the RECs are not in a position to require changes to these Guidelines, they are in a position to stipulate the way in which they are described in documents shown to prospective trial subjects. Finally, the NHS document retention schedules are such that key documents can be destroyed within the limitation period for a personal injury claim; although the number of potential claims which could be frustrated in this way is probably small, this seems an unnecessary situation, with present day document-retention technology. Thus, one must question whether, when patients give their consent, they have all the information they need upon which to base that, and, in some, possibly many, cases, patients will simply be unaware of the information which might - or ought - to be available.

In the UK, in contrast to the USA, the consent process is confounded because many of our legal approaches to clinical trials remain founded on a 'Doctor-Patient' rather than 'Investigator-Subject' relationship. This seems particularly marked in the area of obstetrics, where, as in many other areas, it seems likely that physicians will recruit their own patients into clinical trials. The physicians' conflict of interest seems obvious, but many patients will probably not consider the consequences of the physician becoming an investigator, and the duty changing from that of doing the best for the patient to one of minimising harm. This, when compounded by therapeutic misconception, must raise questions regarding the validity of the consent process.

Of course, many, if not all, of these criticisms could be levelled against any clinical trial, involving any target population. However, additional complexities arise in clinical trials involving pregnant women because of the inconsistent approaches regarding the status of the foetus and the unique relationship between women and foetus, highlighted in particular in Chapter 4. The implications of the pregnant woman's consent 'for' the foetus and whether that precludes a child born injured seeking compensation if the pregnant woman is adjudged to have assumed the risk, need to be clarified. Compensation is currently

predicated upon causation, which is uniquely difficult in this population, as injuries may not become apparent for many months or years after the clinical trial, by which time the relevant records may no longer exist.

The challenge of establishing whether a teratogenic injury in a particular child can be linked to a drug the child's mother took while she was pregnant is significant. The requirement to establish causation is implicit within the ABPI Compensation Guidelines, and explicit within tort, where the balance of probabilities approach will always work against the first few children who sustain injury *in utero*, unless the injury has distinctive characteristics, as was the case with thalidomide. Given the background rate of spontaneous congenital abnormalities, a drug-related teratogenic effect in a very low proportion of children, particularly if, like thalidomide, a small 'window of opportunity' exists for it to do so, may never be proven. Returning to the issue of consent, how many pregnant women are made aware of these difficulties when being asked to consider participation in a clinical trial?

Pregnant women constitute a unique - and necessary - population in which to conduct clinical trials of new drugs, and a population which was never in contemplation when the current processes for consent, trial conduct, assessment of causation and mechanisms for seeking compensation were being developed. Until we find ways in which to eradicate the diseases we currently treat using drugs, the protection of future generation of pregnant women and their foetuses from iatrogenic, teratogenic injury is best-served by the proper conduct of research in that population. We must ensure that these benefits are not gained at the expense of the people and future people they are intended to protect. Regulation 536, the successor to the Clinical Trials Directive, is the first legislative instrument applicable to the UK which specifically addresses clinical trials in this population, but it focuses, appropriately, on a small number of general principles. It does not address the issues identified in this thesis related to consent, causation or compensation; these issues are under the purview of national Governments, rather than the European Union and its Agencies. Therefore, the changes need to be driven from within the UK. Nearly 40 years have passed since the CDCLA 1976 and the VPDA 1979 came into effect. During that time medical research and clinical trials have changed in ways inconceivable when these laws were enacted, and particularly the intent to conduct clinical trials of investigational drugs in women who are pregnant. The time has now come to consider the introduction of legislation to increase the protection of the foetus whose mother enrolls into a clinical trial.

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