A MIXED METHODS STUDY OF THE RELATIONSHIP BETWEEN ILLNESS PERCEPTIONS AND THE CASCADE GENETIC SCREENING PROCESS IN HYPERTROPHIC CARDIOMYOPATHY AND CLINICAL RESEARCH PORTFOLIO

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CHAPTER 1 - SYSTEMATIC REVIEW

Factors associated with first degree relative uptake of genetic testing in Hypertrophic Cardiomyopathy: A systematic review.

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Abstract

Hypertrophic Cardiomyopathy (HCM) is a relatively common inherited cardiac condition. Uptake of genetic screening in HCM reportedly ranges from 39 to 66%. This leaves a significant proportion of individuals and their potentially at-risk relatives without appropriate assessment or treatment. The current review synthesises the available literature evaluating the evidence for systemic, demographic and psychological factors linked to uptake of genetic screening by first degree relatives. This review included studies where the relationship between HCM proband first degree relative uptake of genetic screening and any systemic, demographic or psychological factor was either quantitatively measured or assessed using formal qualitative research methodology. A systematic search of the Medline, Embase, Web of Science and PsychInfo databases was conducted on the 20th September 2019. Bibliographies of related reviews and included articles were also examined. Five relevant studies were included in the final narrative data synthesis. Quality of included studies was assessed using the adapted AXIS tool for quality assessment for cross sectional studies and a standardised questionnaire derived from the National Institute for Clinical Excellence methodology checklist for qualitative studies. Overall quality of included studies was rated as satisfactory by two researchers. The findings of the current review suggest there is currently insufficient evidence to make definitive conclusions about the relationship between systemic, demographic or psychological factors and first degree relative uptake of genetic screening in HCM. However, access to professional advice, perceived benefits of testing and parental status emerged as the factors most closely associated with uptake. The overall quality of the studies and how their findings relate to research on uptake of genetic screening in other conditions are discussed and recommendations for future research are made.

1. Introduction

1.1 Hypertrophic Cardiomyopathy (HCM)

Advances in the understanding of the genetic heterogeneity of some cardiac conditions in combination with reductions in costs of DNA sequencing have led to increased use of genetic testing as a means of identifying, diagnosing and treating individuals and their relatives (Garcia *et al.,* 2016). HCM is an autosomal dominant inherited cardiac disease where the myocardium is thickened making the heart muscle stiff and reducing its ability to efficiently pump blood around the body (Maron *et al.,* 1995). Many people with HCM live without observable symptoms however symptoms can include breathlessness, palpitations, chest pain and more rarely, sudden cardiac death (SCD). In addition to risk of SCD some subgroups are at greater risk of progressive heart failure, stroke and atrial fibrillation (Maron, 2002). The severity of symptoms is usually determined by the specific area of the heart affected and the level of associated stiffening. Treatment is conditional on the presentation and symptomatology but can include longitudinal monitoring, drug treatments and surgical interventions (Maron, 2002). Diagnosis is most commonly through echocardiography but can be confirmed by DNA testing (Maron, 2002).

1.2 Genetic screening and HCM

Approximately 50% of individuals with HCM carry a gene variant associated with the condition and children of these individuals have a 50% chance of inheriting this gene (Khouzam *et al.,* 2015). Genetic screening for the gene associated with HCM is usually offered through a process called "*cascade genetic screening"* where individuals with an existing diagnosis of HCM who have first degree relatives (FDRs) that may be at risk are offered genetic testing to ascertain whether they carry the associated gene. These individuals, often referred to as "*proband*" patients, are asked to distribute information to FDRs with a view to them coming forward for either genetic testing or cardiac screening depending on the proband gene status. This process enables services to identify, monitor or treat at risk individuals as required. Asymptomatic relatives with the associated gene are likely to be offered more intensive testing, monitoring or preventative

treatments. Asymptomatic relatives who do not carry the gene can be ruled out of future monitoring (Garcia *et al.,* 2016). This process also increases the identification of individuals most at risk of SCD where more intensive preventative strategies can be employed (Marteau & Kinmonth, 2002).

1.3 The relationship between systemic or demographic factors and screening decisions

Although the cascade screening structure remains consistent across different conditions a growing number of studies have sought to understand if variations in service approaches such as how information is delivered or how probands are supported has an influence on FDR screening uptake (Finlay *et al*, 2008; Forrest *et al*, 2008). Due to the small number of studies across different genetic conditions the evidence for any particular service approach is currently sparse. There is however an abundance of literature concerned with the relationships between demographic factors and genetic testing decisions. A review of predictors of genetic testing decisions across a range of conditions highlighted that demographic factors tend to be included in most studies concerned with genetic testing decisions irrespective of the main focus but that this has led to a large but often contradictory literature (Sweeney *et al*, 2014).

1.4 The psychology of genetic screening

In addition to systemic and demographic factors there have been attempts in recent years to understand genetic screening through the application of psychological models (Aatre & Day, 2011; Marteau & Weinman, 2006; Sweeny *et al,* 2014). One of the most commonly used models is the Health Belief Model (HBM) which incorporates an individual's perceptions of their susceptibility, seriousness, cues to action, demographic factors and perceived benefits and barriers of the illness or treatment concerned (Rosenstock, 1996; Janz, Champion, & Strecher, 2002). In one study investigating uptake of genetic screening in colorectal carcinoma the HBM explained 36% of variance in individual screening uptake (Cyr & Haynes, 2010). Leventhal's common-sense model (CSM) of self-regulation has also been highlighted as a potentially useful

tool for exploring patient beliefs around genetic risk and using findings to shape services and tailor the information individuals are given (Leventhal, Nerenz & Rachman, 1980; Petrie *et al.,* 2007).

1.5 Rationale for review

Genetic testing in HCM is increasingly available however reported overall uptake to date has been suboptimal ranging between 39-66% (Charron *et al.,* 2002; Christiaans *et al.,* 2008; Miller *et al.,* 2013; Khouzam *et al.,* 2015). This leaves a significant proportion of individuals and their FDRs without access to potential monitoring or treatment. Synthesising the available literature investigating the factors associated with uptake of genetic testing by FDRs may inform service understanding of FDR uptake and direct future research.

1.6 Review Aims

This review aims to address the following questions:

- Are systemic factors associated with uptake of genetic screening by FDRs of probands with a diagnosis of HCM?
- Are proband or FDR demographic factors associated with increased uptake of genetic screening by FDRs of probands with a diagnosis of HCM?
- Is there a relationship between psychological factors and uptake of genetic screening by FDRs of probands with a diagnosis of HCM?

In addition to addressing these questions the review sought to:

- Evaluate the quality of current research in these areas.
- Evaluate findings in the context of factors associated with uptake of genetic testing in other populations
- Make recommendations for future research, based on an appraisal of the extant evidence.

2. Method

2.1 Search Strategy

Initial scoping searches identified potentially relevant studies and associated indexing keywords including Medical Subject Headings (MeSH). These were used to inform the terms used in the systematic literature searches conducted on the 20th of September 2019 (Appendix 1.1). Databases included in the search were: Medline, Embase, Web of Science and PsychInfo. Strategies for each of these varied slightly because of their respective individual search tools. Results were limited to publications available in English. Bibliographies of articles that underwent full text review were also checked to identify additional studies.

2.2 Inclusion and exclusion criteria

Studies were included if the relationship between HCM proband FDRs' uptake of genetic testing and any systemic, demographic or psychological factor was quantitatively measured and reported or qualitatively assessed using formal qualitative research methodology. Systemic factors were defined as those linked to the practical process of cascading genetic screening. Demographic factors referred to individual characteristics. Psychological included beliefs related to the genetic screening process or healthcare. Studies were excluded if they met any of the following criteria: Single n case studies, conference abstracts, book chapters and non-peer reviewed studies.

2.3 Data selection

Data selection for the current review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Studies identified through the search strategies were screened for duplicates using reference management software. The reviewer then screened titles and abstracts of the remaining papers and excluded those that clearly did not meet the inclusion criteria. Studies that potentially met the eligibility criteria underwent a full text review. Studies that underwent full text review and met the inclusion criteria were then included for quality review and data extraction.

2.4 Data extraction

For each article included in the study key data were extracted using a bespoke data extraction form (Appendix 1.2).

2.5 Quality assessment

The quality of cross-sectional studies was assessed using the adapted AXIS tool for quality assessment for cross sectional studies (Downes *et al.,* 2016) (Appendix 1.3). The tool focuses on three areas of assessment: Quality of reporting, Study design and Bias. All included articles were rated either "*Yes*", "*No*", "*Partial*" or "*Unclear*" against items under these categories by two researchers. Inter-rater reliability for the quality assessment of cross-sectional studies was 91%. The quality of the qualitative articles was assessed using a standardised questionnaire derived from the National Institute for Clinical Excellence methodology checklist for qualitative studies (Appendix 1.3) (NICE Quality Appraisal Checklist-Qualitative Studies, 2012). Only one study that was included in the final review used qualitative methodology. Interrater reliability for this quality assessment was 100%.

2.6 Data synthesis

Due to the heterogeneity of methodologies employed in the included studies quantitative meta-analysis was deemed unfeasible therefore a qualitative assessment and narrative synthesis of the available data was conducted. Recommended guidelines for this process were followed (Popay *et al.,* 2006).

3. Results

3.1 Search results

Figure 1 illustrates the study selection process. After removal of duplicates and applying the eligibility criteria 5 of the 9266 studies identified in the initial searches were reviewed. Two of the five studies included in the final review used the same sample population but with different

methodologies (Christiaans *et al.,* 2008; Christiaans *et al.,* 2009). These two papers are therefore summarised as one larger study. One further potentially suitable article was identified for full-test assessment through manual searches of reference lists however this was then excluded as it did not meet the review inclusion criteria (Charron *et al.,* 2002).

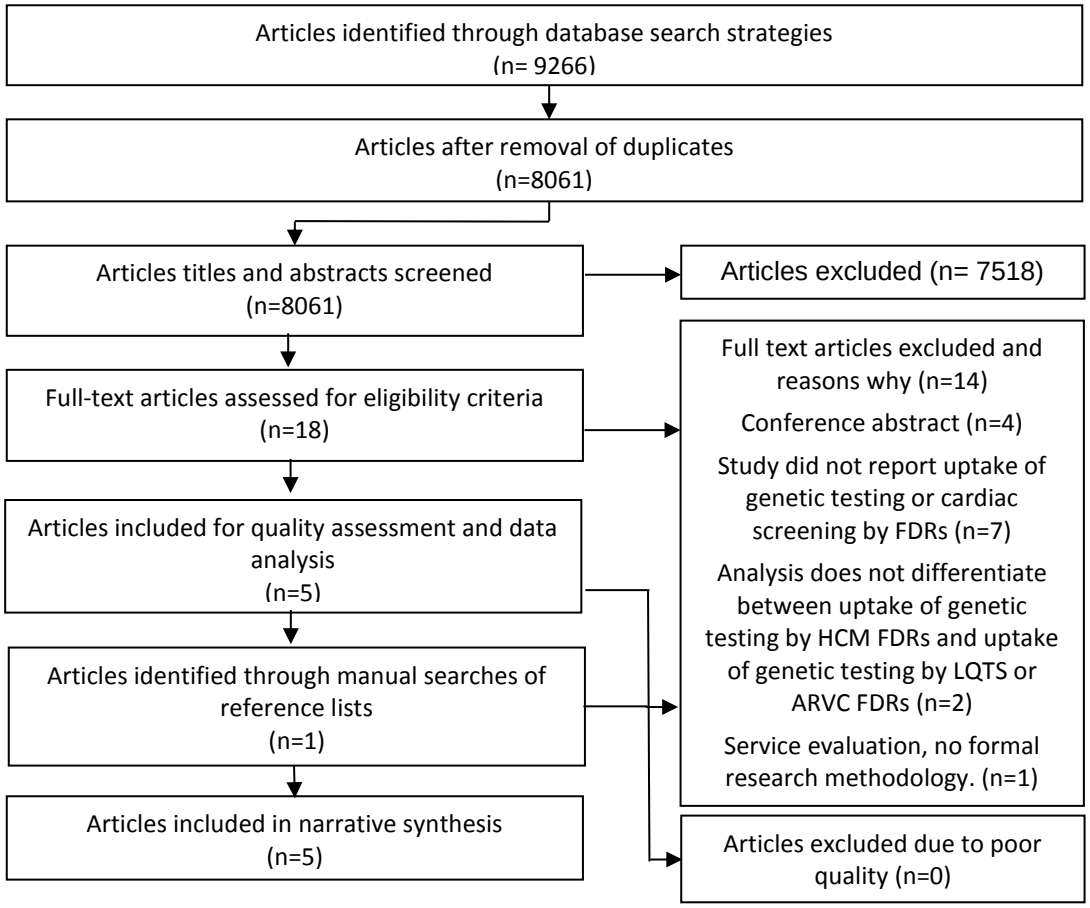

Figure 1 Participant flow diagram.

3.2 Overview of included studies

A summary of the five studies included in the review is outlined in Table 1. Research designs varied across the five studies; three adopted retrospective cross-sectional designs, one used an online questionnaire and one used qualitative interviews. Within these research approaches differences in genetic testing processes were reflected in variances in how the proband and FDR uptake of genetic testing was assessed specifically the stage at which factors associated with FDR uptake of genetic testing were measured. In terms of the three review questions all five studies included analysis reported on demographic factors, three of these also included systemic factors and the remaining two included psychological factors.

3.3 Quality assessment

The full results of the quality assessment for all included articles are presented in Appendix 1.4. Notably none of included studies included justification of sample size and only one reported effect sizes alongside p values (Miller *et al.,* 2012). The methodological limitations of all the studies were well defined and linked to caution in interpreting findings. There was no evidence that the quality of the studies was associated with the reported outcomes. Nor was there evidence of a difference in the quality of the papers between those that addressed systemic, demographic or psychological factors.

Table 1: Table of results

Quantitative studies

Author, Year, Region	Sample	FDR uptake %	Factors measured and associated with uptake	Factors measured and not associated with uptake	Study design	Key findings	Quality assessment
Christiaans *et al.,* 2008 & 2009. The Netherlands	97 HCM Probands & 507 HCM FDRs	38.6%	Attendance of genetic counselling: 233 of the 235 (99%) FDRs who attended genetic counselling went on to undergo genetic testing. Wanting to know due to hereditary nature n=108 (90%) Wanting to know for self n=104 (87%) Because of children n=57 (64%)	Factors associated with uptake of genetic counselling as a proxy to uptake of genetic testing. Proband gender (p=0.80) FDR gender (p=0.97) FDR age 10-18 vs 18+ (p=0.09) SCD family history (p=0.14)	Cross sectional, Single centre retrospective review of records and retrospective questionnaire.	Uptake of predictive genetic testing in FDRs was 38.6%. Uptake of genetic counselling was 40.4% in FDRs, this did not differ significantly by proband's or relative's gender, age of the relative or a family history of SCD. Of those that attended genetic counselling 99% underwent predictive genetic testing. Further research into determinants of uptake prior to genetic counselling was indicated. 70% of FDRs learned about the possibility of genetic testing through a family member. 85% agreed the information the test provided was sufficient.	14/16 & 17/18
Khouzam *et al.,* 2015. USA	270 English speaking individuals aged over 18 years with a diagnosis of HCM and 36 individuals aged over 18 years with a FDR with a diagnosis of HCM	N/A	*Bonferroni-adjusted significance level of 0.00125 used accounting for multiple comparisons.* Genetic testing discussed or offered by healthcare provider (p<0.001) Individual seen by genetics professional in relation to HCM (p<0.001) Genetic testing recommended by healthcare provider (p<0.001) Requests from family members to take up testing (p<0.001) Genetic mutation identified in the family (p<0.001) Perception testing would help stratify risk to family members (p<0.001) Perception testing would improve family healthcare decisions (p<0.001) Perception testing would provide reassurance (p<0.001)	*Bonferroni-adjusted significance level of 0.00125 used accounting for multiple comparisons.* Gender (p=0.021) With/Without children (p=0.119) Diagnosis of HCM (p=0.363) Perceived susceptibility (p=0.097) SCD family history (p=0.122) Perception genetic testing would negatively impact on health insurance (p=0.011) Perceived utility of testing (p=0.003) Perceived impact on active lifestyle (p=0.009)	Self-report online survey distributed via email mailing list.	Factors measured against uptake were clustered into broad categories informed by the Health Belief Model. Factors under" cues to action", "perceived benefits" and "barriers" were most associated with uptake of genetic testing. Further research into how best to educate and promote awareness around genetic testing for HCM.	14/18
Miller *et al.,* 2013. USA	46 HCM & 11 DCM* probands & 177 FDRs	39%	Number of living affected relatives(p=0.04) (cardiac screening only)	Proband gene mutation status (p=0.48) SCD family history (p=0.09) for cardiac screening and (p=0.020) for genetic testing	Cross sectional, Single centre Retrospective, single centre, review	Only the number of living affected relatives was associated with uptake of cardiac screening. No factors were associated with FDR uptake of genetic testing. Overall FDR uptake of genetic testing was 39%, like other studies despite differences in the healthcare	16/18

			Proband age at diagnosis (p=0.27) for cardiac screening and (p=0.10) for genetic testing Number of living affected relatives(p=0.90) (genetic testing) Time of proband testing for cardiac screening (p=0.15) and (p=0.85) for genetic testing	of records	systems. .	

Qualitative studies

Author, Year, Region	Sample	FDR uptake %	Themes identified	Study design	Key Findings	Quality
Ormondroyd *et al.*, 2014. UK	18 HCM & 4 LQTS**	N/A	Thematic analysis produced the following themes associated with uptake: *Perception of risk* – Interviewees generally reported low perceived risked and came forward for testing only to "rule out" risk. *Perceived meaning of genetic testing* – This theme focused on individuals "need to know" both for themselves and their children and highlighted potential barriers around the perceived utility of testing. *Managing risk to children* – For interviewees that were parents perceived risk to children was frequently reported as the main reason for undergoing testing. Concerns about insurance and psychological impact were highlighted by parents who had yet to have their children tested *Communication of risk to wider family* – Complexity of family relationships and not wanting to raise undue alarm were the main factors associated with uptake within this theme.	Qualitative interviews of FDRs who had previously undergone pre-symptomatic genetic testing for HCM or LQTS	Perceived risk in FDRs appeared to be low even in case where SCD was present in family history. Knowledge and perception of value of testing was reportedly linked to non-uptake. Additionally, the complexities of family communication were also raised as potentially significant barriers to uptake. The dependence on effective communication between healthcare provider and proband then proband and FDRs is highlighted as having high potential for failure. The case for direct contact between healthcare providers and FDRs is discussed.	Nearly all checklist criteria met: ++

KEY: *DCM – Dilated Cardiomyopathy, **LQTS - Long Q-T syndrome

3.4 Narrative Synthesis

3.4.1 Are systemic factors associated with uptake of genetic screening by FDRs of probands with a diagnosis of HCM?

The evidence for whether systemic factors potentially influence uptake was addressed in three studies (Christiaans *et al.,* 2008; Khouzam *et al.,* 2015; Ormondroyd *et al.,* 2014). Christiaans *et al*. (2008) reported that 233 out of 235 FDRs who attended genetic counselling went on to undergo genetic testing. This 99% conditional uptake was reflected in the authors' decision to use uptake of genetic counselling as a proxy for uptake of genetic testing when assessing the influence of other factors. Khouzam *et al*. (2015) also reported that three similar factors were significantly linked to uptake of genetic testing: genetic testing discussed or offered by healthcare provider ($p<0.001$), individual seen by genetics professional in relation to HCM ($p<0.001$) and genetic testing recommended by healthcare provider ($p<0.001$). Requests from family members to take up testing also was significantly linked to uptake of genetic testing by family members ($p<0.001$) (Khouzam *et al.,* 2015). Similarly, Ormondroyd *et al*'s (2014) qualitative study suggested that their sample held positive opinions about being been told by a relative about their own risk or hypothetically being informed by a healthcare provider directly. Conversely however participants in Ormondroyd's study were conflicted about telling other relatives and reported the practical difficulties of family communication, highlighting this as a potential barrier to uptake.

3.4.2 Are there proband or FDR demographic factors that are associated with increased uptake of genetic screening by FDRs of probands with a diagnosis of HCM?

The evidence for specific demographics associated with increased FDR uptake was assessed to some extent in all of the included studies. The results for this section are separated by the evidence identified for each demographic factor.

3.4.2.1 Gender

The influence of gender on uptake of genetic testing by FDRs was partially assessed in two of the included studies (Christiaans et a, 2008; Khouzam *et al.,* 2015). Christiaans *et al*. (2008) reported that the FDRs' gender did not significantly influence uptake of genetic counselling (38.7% in males and 39.6% in females, p=0.97). Similarly, the gender of the proband did not influence uptake of genetic counselling by respective FDRs (38.2% in males and 40% in females, p=0.09). Khouzam *et al*. (2015) found 59% of males and 46% of females in a mixed group of probands and FDRs reported undergoing testing (p=0.021) however with statistical adjustments for multiple comparisons this finding was not significant.

3.4.2.2 Age

Age, as a potential moderator, was assessed in two of the included studies (Christiaans *et al.,* 2008; Miller *et al.,* 2012). In Christiaans *et al*. (2008), the influence of age on uptake of genetic counselling as a proxy to genetic testing was investigated by evaluating difference in uptake by FDRs aged 10-18 years and FDRs aged 18 years or over. No significant differences in uptake were reported (56.1% in 10-18 range and 37.2% in the 18+ range, p=0.09). Miller *et al*. (2012) evaluated whether the age at which the proband was diagnosed influenced FDR uptake of genetic testing or cardiac screening reporting it did not have a significant influence on either (p=0.27 for cardiac screening and p=0.10 for genetic testing).

3.4.2.3 Number of living affected relatives

The relationship between uptake of genetic testing by FDRs and the total number of living affected relatives was assessed in Miller *et al*. (2012). Miller *et al*. (2012) found a weak association with the number of affected relatives and uptake of cardiac screening (p=0.04, r=27) but no association with uptake of genetic testing (p=0.9, r = 0.02)

3.4.2.4 Family history of SCD

Family history of SCD was measured against uptake of genetic testing in four studies (Christiaans *et al.,* 2008; Khouzam *et al.,* 2015; Miller *et al.,* 2012; Ormondroyd *et al.,* 2014). Khouzam *et al*. (2015) reported that family history of SCD was not associated with uptake of testing (p=.0122) in a mixed group of both probands and FDRs. Similarly, Miller *et al*. (2012) also found family history of SCD was not associated with uptake of either cardiac screening (p=0.09) or genetic testing (p=0.2). Although measured against uptake of genetic counselling as a proxy to genetic testing uptake Christiaans *et al.,* 2008 found that uptake of genetic counselling did not differ between individuals with (49.2%) or without (35.3%) a family history of SCD (p=0.14). The influence of SCD history also formed part of a "perception of risk" theme in Ormondroyd *et al*'s (2014) study. Participants indicated that family history of SCD had little influence on the decision to undergo genetic testing.

3.4.2.5 Proband gene status

Khouzam *et al.,* (2015) and Miller *et al*. (2012). explored the relationship between FDR uptake of genetic testing and respective proband gene status. Khouzam *et al*. (2015) reported FDRs with knowledge of gene mutation in the family were more likely to undergo genetic testing (p=0.001). However, Miller *et al*. (2012) found no link between uptake of cardiac screening and proband gene status (p=0.48).

3.4.2.6 Children

The influence of children on uptake of genetic testing by FDRs was explored in three studies (Khouzam *et al.,* 2015; Christiaans *et al.,* 2009; Ormondroyd *et al.,* 2014). Khouzam *et al.,* 2015 reported no differences in uptake of testing between those with and without children in a population of both probands and FDRs, 83 % and 76 % (p=0.119), respectively. Conversely, Christiaans *et al*. (2009) reported 64% of FDRs with children agreed with a statement that they had done so in their children's interest. This finding was also reflected in the Ormondroyd *et al's*. (2014) study where coping with children's risk emerged as a key theme and perceived risk to children was frequently reported by FDRs as the primary reason for undergoing testing.

3.4.3 Is there a relationship between psychological factors and uptake of genetic screening by FDRs of probands with a diagnosis of HCM?

Psychological factors were assessed in two of the studies (Ormondroyd *et al.,* 2014; Khouzam *et al.,* 2015). Khouzam *et al*. (2015) found three separate perceptions were linked to uptake in a mixed sample of probands and FDRs. These were: perception testing would help stratify risk to family members ($p<0.001$), perception testing would improve family healthcare decisions ($p<0.001$) and perception testing would provide reassurance ($p<0.001$). Ormondroyd *et al*'s (2014) thematic analysis yielded a theme of "Perception of risk" where participants mostly reported low perceived risk and the decision to undergo testing was based on "ruling out" any risk.

4. Discussion

The primary aim of this review was to evaluate the evidence base for systemic, demographic and psychological factors that influence uptake of genetic screening by FDRs in HCM. In addition to the three main review questions the review aimed to contrast findings with existing literature in other genetic conditions and make recommendations for future research. The results of the review indicate that although few studies have investigated this area to date, numerous factors have been considered for their influence on FDR uptake. The small number of studies and differences in healthcare systems make definitive conclusions as to which factors are likely to influence uptake by FDRs difficult. Despite this, several factors were associated with uptake of genetic testing by FDRs, the implications of these findings are discussed below.

4.1 Factors associated with FDR genetic screening uptake

4.1.1 Are systemic factors associated with uptake of genetic screening by FDRs of probands with a diagnosis of HCM?

Contact with a health professional in relation to HCM or genetic screening was one of the few factors reportedly linked to genetic screening uptake in more than one of the studies (Christiaans *et al.,* 2008; Khouzam *et al.,* 2015; Ormondroyd *et al.,* 2014). In two of these studies there was a significant association between FDR contact with a health professional in relation to HCM and subsequent uptake of genetic testing (Christiaans *et al.,* 2008; Khouzam *et al.,* 2015). Both studies point out that an emphasis on understanding what determines whether FDRs encounter health professionals in relation to HCM might be important to increase FDR uptake. These studies also highlight that the cascade genetic screening process is highly reliant on effective communication both initially between the health professional and proband and latterly the proband and their FDRs. Ormondroyd *et al*'s (2014) study explored this idea by evaluating participant attitudes to the alternative of direct contact from healthcare providers as means of reducing the barriers associated with family mediated contact finding all participants had favourable opinions of this approach. Despite this and although direct contact has been linked with higher screening uptake rates in other genetic conditions there is an ongoing debate regarding the data protection and ethical implications of this approach where individuals might receive correspondence from a healthcare provider without prior knowledge of familial risk (Suthers *et al.,* 2006). The evidence identified by this review is insufficient to conclusively answer the question of whether specific systemic factors are associated with FDR uptake. However, it is apparent that once FDRs have contact with relevant health professional uptake is significantly improved.

4.1.2 Are there proband or FDR demographic factors that are associated with increased uptake of genetic screening by FDRs of probands with a diagnosis of HCM?

Most demographic factors were not associated with uptake of screening by FDRs including gender of the FDR or proband, age of FDR, age of proband diagnosis and family history of SCD studies (Christiaans *et al.,* 2008; Christiaans *et al.,* 2009; Khouzam *et al.,* 2015; Miller *et al.,* 2012;

Ormondroyd *et al.,* 2014). Several demographic factors had mixed evidence. Miller *et al*'s (2012) study indicated that the number of living affected relatives had a small but significant influence on uptake of cardiac screening in FDRs but not on genetic screening. Khouzam *et al.* (2015) similarly reported FDRs with knowledge of gene mutation in the family were more likely to undergo genetic testing. However, Miller *et al*. (2012) also found no link between either uptake of cardiac or genetic screening and knowledge of proband gene status. The ambiguous nature of these results are in keeping with the findings of a broader review of predictors of genetic testing uptake across multiple conditions which suggested such predictors are unlikely to be reliable but may act as mediators to more consistent indicators of uptake (Sweeny *et al.,* 2014). Parental status also had mixed evidence across the studies (Khouzam *et al.,* 2015; Christiaans *et al.,* 2008; Ormondroyd *et al.,* 2014). Two of the studies indicated a positive relationship between being a parent and uptake of testing (Christiaans *et al.,* 2008; Ormondroyd *et al.,* 2014) whereas Khouzam *et al*. (2015) found no relationship between parental status and FDR or proband uptake of testing. Research investigating the influence of parental status on genetic testing in other conditions has yielded a range of findings. In BRCA 1/2 having children has consistently been associated with increased interest in pursuing testing (Foster *et al.,* 2004) whereas in testing for Huntington's Disease the evidence is more contradictory (Binedell, Soldan & Harper, 1998). Further research is required to better define the relationship between FDR genetic screening uptake and parental status in HCM. Overall, the current reviews findings suggest, in keeping with previous literature, that there is currently no evidence to support a link between any demographic factors and increased FDR uptake of genetic screening.

4.1.3 Is there a relationship between psychological factors and uptake of genetic screening by FDRs of probands with a diagnosis of HCM?

Psychological factors were linked to increased rates of FDR uptake in two studies (Ormondroyd *et al.,* 2014; Khouzam *et al.,* 2015). Ormondroyd *et al*'s (2014) theme of "Perception of risk" linked participants' desire to assess and negate risk with uptake of testing. Discussing this theme further

they draw attention to a potentially important difference between genetic screening in HCM and similar screening in other conditions such as Huntington's disease or some cancers. In these conditions screening typically provides an easily interpretable binary outcome in terms of risk and prognosis. In inherited cardiac conditions including HCM the prognostic value of test outcome is more ambiguous (Cirino *et al.,* 2019). Ormondroyd *et al*'s (2014) suggest that this is addressed early in the process of encouraging individuals to undergo testing and the screening process is framed as the first step in a longer "*risk stratification*" process. This links with Khouzam *et al*'s (2015) finding that perceptions that genetic screening would stratify risk, inform family healthcare choices and provide reassurance were associated with uptake. Ormondroyd *et al* (2014) also suggest that perceived risk relating to HCM is likely moderated by pre-existing beliefs about causation, inheritance and prognosis. If these perceptions are understood to be positively linked with improved uptake further research into how they are formed and influenced may be beneficial. Like Khouzam *et al*'s (2015) study, research in other genetic conditions has used the Health Belief Model (HBM) (Rosenstock, 1966; Glanz, Rimer & Lewis, 2002) to cluster influencing factors. To date the perceived benefits and perceived barriers constructs within the HBM appear to be the most reliable predictors of broad genetic testing choices (Sweeny *et al.,* 2014) and this appears to be, in part, true for HCM. Conversely, Leventhal's CSM can be used to understand why even well-informed illness perceptions may lead to non-compliance with recommendations from healthcare professionals (Marteau & Weinman, 2006). Marteau and Weinman (2006) suggest where an illness is seen as hereditable, personal actions to minimise risk are more limited and where treatment options are not clear or seen as unnecessary compliance is lower. Whilst healthcare professionals facilitating the cascade genetic screening process for HCM may justly aspire to maximise the screening uptake rate a proportion of FDRs may actively be choosing not to undertake screening as a reasoned choice that makes sense in their personal context. To understand the prevalence of this in HCM, services might be best advised to facilitate expression of these perspectives within the cascade screening process or through qualitative research (Donovan & Blake, 1992). As only two studies, using very different methodologies, were identified

by the current review it would be inadvisable to make definitive conclusions about the role of psychological factors. However, both of these studies indicate the potential role of risk perception in the screening process which warrants further investigation.

4.2 Study quality and recommendations for future research

The overall quality of the studies included in the review was good, although some studies did not meet all the quality assessment criteria these omissions were deemed too minor to have influenced reported outcomes. However, given the low number of studies identified by this review and small overall sample captured across the included studies and review questions there is an apparent need for further research in this area. The evidence accumulated within this review indicates that once individuals have access to accurate information delivered by a relevant health professional they are highly likely to undergo testing if its recommended. Within the cascade genetic screening process FDRs access to this information is likely to be facilitated by the proband therefore research into the communication process between proband and FDR may beneficial. Given the emerging evidence that health beliefs about the benefits and barriers to testing might be linked to FDR uptake (Ormondroyd *et al.,* 2014; Khouzam *et al.,* 2015) consideration should be given to how these beliefs are influenced by the proband and the information provided when discussing HCM and genetic screening. Notably, no studies were identified that actively sought to improve uptake through intervention. Further investigation of how the factors that have been linked to increased uptake might be enhanced and whether doing this improves uptake might be beneficial. The findings from this is review suggest that factors to focus on enhancing would be; access to professional advice (Christiaans *et al.,* 2008; Khouzam *et al.,* 2015) and the perceived benefits of testing (Ormondroyd *et al.,* 2014; Khouzam *et al.,* 2015).

4.4 Review limitations

The current review has several limitations that should be noted. Firstly, the small number of studies identified by the review both indicates a dearth of research in this area and limits this review's ability to provide conclusive evidence based on synthesis of such a relatively small

amount of data. Secondly, the differences in how uptake of genetic testing was measured and how proband, FDR and other relatives were group in each of the included studies made direct comparison problematic again limiting generalisability of findings across different healthcare systems.

5. Conclusion

No substantive conclusions can be drawn from the small number of studies identified. However, some factors appear to show more consistent links with improved rates of uptake by FDRs. This review highlights the current lack of evidence for specific service approaches associated with uptake, however, it does indicate that once FDRs have contact with relevant health professionals they are highly likely to undergo testing. In terms of the evidence for specific demographic factors associated with FDR uptake the review indicates that despite being the most researched area there is no evidence that supports the link between uptake and any given demographic factor. Finally, the evidence for psychological factors associated with FDR uptake was sparse but where it was found was of a good quality and suggested FDRs who perceived genetic screening as a means of risk stratification or allaying concerns were more likely to undergo screening. These findings indicate that focus on demographic factors may not be productive however exploration of systemic or psychological approaches may be warranted. Pragmatically, focus may best be placed on factors that can be influenced through changes in healthcare processes or information provision with a view to improving uptake and providing appropriate care to as many at risk individuals as possible.

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CHAPTER 2 – MAJOR RESEARCH PROJECT

A mixed methods study of the relationship between illness perceptions and the cascade genetic screening process in Hypertrophic Cardiomyopathy

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Plain English Summary

A mixed methods study of the relationship between illness perceptions and the cascade genetic screening process in Hypertrophic Cardiomyopathy

Background

Hypertrophic Cardiomyopathy (HCM) a relatively common inherited cardiac condition where the heart muscle is thickened which can make it harder to pump blood around the body. HCM occurs in approximately 1 in 500 people in the UK, symptoms include breathlessness, palpitations, chest pain and more rarely, sudden cardiac death. Approximately half of individuals with HCM will carry an associated gene mutation. Genetic screening is an increasingly viable means of both confirming those who carry this gene mutation and using this information to identify and treat their first-degree relatives who may also be at risk. This is done through a 'cascade' genetic screening process where individuals confirmed as carrying the gene mutation distribute self-referral forms to their first-degree relatives who then choose whether or not to take up testing. Uptake of such testing by first degree relatives is suboptimal and the reasons for this are not well understood. There is a lack of research concerned with the requirement of family members who first undergo testing to distribute referral forms to their first-degree relatives and how this may influence the process and uptake of testing by relatives.

The way in which individuals experience and understand a given health condition such as HCM are sometimes called 'illness perceptions'. These are understood to be comprised of five main factors; the identity individuals' associate with the illness, the perceived cause, how much perceived control individuals feel they have over the condition, the perceived consequences of having the condition and how long they expected it to last. Studies suggest that these factors can influence how individuals manage their condition through behaviours including whether they take up genetic testing. Less is known about whether these perceptions influence how individuals communicate information about conditions to others.

Aims and Questions

The study aimed to explore whether the illness perceptions about HCM of those who first undergo genetic testing for the gene mutation predicts uptake of genetic testing by their respective first-degree relatives.

Methods

Fifty-seven individuals diagnosed with HCM who had been asked to communicate genetic risk to first degree relatives were recruited from the West of Scotland Inherited Cardiac Conditions and to complete questionnaires assessing their illness perceptions of HCM, subjective closeness to family members and confidence in being able to distribute self-referral forms to at-risk first-degree relatives. Six of these individuals also took part in semi-structured interviews to explore these areas in more depth. Statistical analyses indicated that relatives of individuals who perceived HCM to be a more acute condition were more likely to have undergone genetic screening however the small number of participants limits how relevant this finding is.

Practical Implications

The tentative finding in this study that some illness perceptions held by individuals tasked with communicating genetic risk to relatives are associated with subsequent relative uptake both merits further research in this area and emphasises the need for individuals given this task to be equipped with robust information on both HCM and the genetic screening program.

Abstract

Background
Hypertrophic Cardiomyopathy (HCM) a relatively common inherited cardiac disease, symptoms include breathlessness, palpitations, chest pain and more rarely, sudden cardiac death. Cascade genetic screening where individuals already diagnosed with HCM are tasked with communicating genetic risk to relatives is an increasingly viable means of confirming HCM associated gene carriers and identifying their at-risk relatives, however uptake of such testing is suboptimal. The common-sense model of illness perceptions has frequently been used to understand behaviours linked to health within individuals (Leventhal *et al.,* 1980). Less is understood about how these perceptions may influence communication of health information to others.

Aims
The primary aim of the study was to explore whether illness perceptions of those who first undergo genetic testing for the HCM gene mutation predict uptake of cascade genetic screening by at-risk first-degree relatives.

Methods
A mixed method, single centre, cross-sectional design was employed. Fifty-seven individuals with HCM undergoing genetic testing completed measures of illness perceptions, closeness to relatives and perceived self-efficacy. Data on uptake of cascade screening by respective first-degree relatives was obtained from the host clinic. Semi-structured interviews were conducted on a sub-group of six individual focusing on those who had low associated illness identity. Transcripts were explored using Thematic Analysis (TA).

Results
Overall first-degree relative uptake within the sample was 65%. A linear regression indicated that relatives of individuals who perceived HCM to be a more acute condition were 13% more likely to have undergone genetic screening. Thematic analyses of interview transcripts yielded three superordinate themes: The confusing HCM experience, the reasons for testing and doubts about testing.

Conclusions
The findings of this study should be considered with caution due to the limits placed on the analysis as a result of the small sample recruited. However, the findings of the analysis indicating a link between the illness perceptions of the individual tasked with communicating risk to relatives and subsequent relative uptake merits further investigation.

1. Introduction

1.1 Hypertrophic Cardiomyopathy (HCM)

Hypertrophic Cardiomyopathy (HCM) is an inherited cardiac disease affecting approximately one in 500 people in the UK (Maron *et al.,* 1995). Symptoms are most commonly minor or unobservable however some individuals with HCM carry an increased risk of developing an abnormal heart rhythm and are therefore at risk of sudden cardiac death (SCD) (Gersh *et al.,* 2011). There is no cure for HCM however medications are offered to control symptoms and mitigate risk associated with abnormal heart rhythms and in cases at increased risk of life threatening arrythmia a pacemaker or implantable cardiac defibrillator may be fitted (Maron, 2002). Initial identification of HCM within families usually relies on a symptomatic individual seeking medical advice and having their diagnosis confirmed through cardiac screening. Around half of these individuals most commonly referred to as "probands" will carry a gene variant associated with HCM and their first-degree relatives (FDRs) will also have a 50% risk of having this same gene variant.

1.3 Cascade genetic testing in HCM

The identification and treatment of FDRs within a family is necessary to manage the risk associated with HCM especially as asymptomatic individuals with HCM are unlikely to be aware they have the condition. This is done through a process called "*cascade genetic screening*". This process starts with genetic testing being used to identify the gene status of probands, this information is then used to determine whether FDRs should be sought for either genetic testing or cardiac screening. Genetic testing is then recommended for FDRs of gene positive probands and cardiac screening for FDRs of gene negative probands. Proband patients are asked to communicate this recommendation to FDRs. In HCM uptake of genetic testing by FDRs using this method reportedly ranges from 39-66% leaving a significant proportion of FDRs without

appropriate assessment or treatment (Charron *et al.,* 2002; Christiaans *et al.,* 2008; Miller *et al.,* 2013; Khouzam *et al.,* 2015).

1.4 Decision making in genetic testing

Research investigating patient experience and decision making in genetic testing in a range of conditions has grown in recent years (Sweeny, *et al* 2014). In parallel there is growing research specifically investigating these areas in HCM (Charron *et al.,* 2002; Christiaans *et al.,* 2008; Miller *et al.,* 2013; Hickey *et al.,* 2014**;** Ormondroyd, *et al* 2014; Khouzam *et al.,* 2015; Wynn *et al.,* 2017). However, studies concerned with investigating factors that influence uptake remain sparse and vary in focus and quality (Charron *et al.,* 2002; Christiaans *et al.,* 2008; Fitzgerald-Butt, 2010; Miller *et al.,* 2013; Khouzam *et al.,* 2015). Factors implicated to date include perceived utility of testing (Miller *et al.,* 2013; Khouzam *et al.,* 2015), age (Fitzgerald-Butt, 2010), level of education (Fitzgerald-Butt, 2010), family history of sudden cardiac death or HCM diagnosis (Miller *et al.,* 2013; Khouzam *et al.,* 2015), knowledge that HCM is hereditary (Fitzgerald-Butt, 2010) and HCM specific health beliefs (Khouzam *et al.,* 2015). Sweeny *et al* (2014) emphasise the need for future research to draw on both medical and psychological perspectives with a view to generating theoretical models that can inform what influences decision making in genetic testing.

1.5 The health belief model and illness perceptions

There is an abundance of literature concerned with the understanding of how an individual's beliefs about a given condition may influence their behaviours. Leventhal's (1980) Common Sense Model (CSM) of illness representations supposes that when faced with an illness, individuals form beliefs about the illness which can be captured under five areas: cause, consequences, controllability, time-line and identity (Leventhal *et al.,* 1980). These representations combined with existing schemata allow individuals to make sense of their condition and guide coping mechanisms. The influence of these representations in a range of conditions including HCM (Christiaans *et al.,* 2008; Hickey *et al.,* 2014**;** Khouzam *et al.,* 2015) has been increasingly

investigated since the development of the Illness Perception Questionnaire (IPQ) which captures beliefs across Leventhal's five areas (Weinman *et al.,* 1996). Similarly, the Health Belief Model (HBM) (Rosenstock, 1966; Glanz, Rimer & Lewis, 2002) has frequently been used to predict health behaviours across a range of conditions including individual uptake of genetic testing in HCM (Khouzam *et al.,* 2015). The HBM suggests that an individual's perceptions of an illness and associated behaviours are modified by "*cues to action*" such as education and symptoms, the perceived benefits and barriers of the behaviour and perceived self-efficacy. Cues to action such as requests to undergo testing from family and perceived benefits and barriers have both previously been implicated as having influence on the uptake of genetic testing in HCM (Khouzam *et al.,* 2015). However, the influence of perceived self-efficacy on the cascade process does not yet appear to have been investigated.

1.6 Rational for the current study

Although illness perceptions and the HBM have been shown to model how individuals make behavioural choices about healthcare generally and in HCM (Petrie *et al.,* 2007; Christiaans *et al.,* 2008; Hickey *et al.,* 2014**;** Khouzam *et al.,* 2015) less is understood about whether they influence communication of health information to others in genetic testing. The cascade genetic model used to identify at risk FDRs relies on proband patients communicating the recommendation that genetic screening should be pursued to FDRs. The qualitative experience of communicating genetic risk of HCM within families has rarely been studied, one qualitative study has highlighted a theme of ambivalence and concerns about the communication process held by probands (Smart, 2010). In other genetic conditions such as Huntington's disease and Ovarian cancer, studies have highlighted the complexity of the communication process within families and the need to be sensitive to individual family dynamics (Forrest *et al.,* 2003). Research indicates that once an individual has contact with a genetics specialist professional they are highly likely to undergo testing and that the short fall in uptake lies with uptake of testing by the FDRs being recruited by probands (Christiaans *et al.,* 2008; Aatre & Day, 2011; Miller *et al.,* 2013; Khouzam *et*

al., 2015). Given the central role proband patients have in the cascade genetic testing process it is possible that their experience of, and beliefs about HCM may influence how they communicate the importance of testing to relatives which may subsequently influence FDR uptake of genetic testing.

1.7 Research aims

The primary aim of this study was to use questionnaires and interviews to explore the relationship between the illness perceptions of proband patients with diagnosis of HCM and the uptake of genetic screening by their respective FDRs. As a secondary aim, the study also aimed to explore whether perceived self-efficacy and subjective closeness to FDRs are associated with uptake of genetic screening by FDRs.

1.8 Research questions

a) Do the illness perceptions of HCM probands significantly correlate with the uptake of genetic screening by their respective FDRs.
b) Does the perceived self-efficacy of HCM probands significantly correlate with the uptake of genetic screening by their respective FDRs.
c) Does subjective closeness to respective FDRs of HCM probands significantly correlate with the uptake of genetic screening by their respective FDRs.

2. Method

2.1 Design

A cross-sectional, mixed methods design was used.

2.1 Ethics

Ethical approval was initially granted by the South West – Central Bristol Research Ethics Committee (Appendix 2.1) and NHS Greater Glasgow and Clyde Research and Development department (Appendix 2.2). Approval for a subsequent substantial amendment to accommodate

retrospective recruitment was also approved by these bodies allowing for this to be implemented in the present study.

2.3 Participants and sample size

The study sought to recruit as many probands who had, or were in the process of, taking part in the cascade genetic screening process at the West of Scotland inherited cardiac conditions clinic (WSICC) at the Queen Elizabeth University Hospital Glasgow (QEUH). An a priori power calculation indicated a sample of 123 would be required to achieve (β=.80), with a medium effect size of f^2 = 0.15 for the multiple regression with 10 predictors. In addition, a sub-sample of six of these individuals was sought to take part in the interview element of the study. Inclusion criteria for participation were: Diagnosis of HCM and age 18. Exclusion criteria were: English language proficiency below level required to understand written information and questionnaires, individuals considered too vulnerable by clinical team and probands who declined genetic testing.

2.4 Recruitment procedure

Recruitment began in January 2019 and ended in May 2019. Two recruitment sources were used.

i. Prospective recruitment of individuals attending the weekly WSICC at the QEUH. Individuals attending the WSICC identified as potentially suitable by the clinic team were given information regarding the study (Appendix 2.3). Individuals then had the option to come forward during their WSICC appointment and express interest in participating. Those that did were directed to a member of the research team in attendance at the clinic. Potential participants were given the opportunity to ask questions before indicating whether they would consent to participation. Each participant was also given the option of consenting to take part in only the questionnaire element or both questionnaire and interview elements of the study. Six clinics were attended by the researcher.

ii. Retrospective recruitment of probands who were already taking part in the cascade genetic screening process. The WSICC team identified 250 probands who either had completed or were in the process of completing the cascade genetic screening process. These individuals were contacted by the clinic team by letter. The covering letter from the WSICC (Appendix 2.4) included an overview of the study and what participation would involve and what to do should the individual wish to take part as well as contact details for the researcher. Included alongside this correspondence was a study pack containing a study information sheet, separate consent forms for the questionnaire and interview elements (Appendix 2.5), the three questionnaires (Appendix 2.6) and a free post return envelope.

2.5 Part one: Questionnaires

Participants completed three self-report questionnaires (Appendix 2.5.1). The age and gender of participants was also recorded. Participants taking part at the WSICC handed questionnaires back to the researcher whereas participants taking part by post returned completed questionnaires via free post. Individuals who expressed an interest in taking part in the interview element were asked to provide contact information and informed that should they be selected to take part they would be contacted to arrange an interview in the following two weeks.

2.5.1: Measures

The *Revised- Illness Perception Questionnaire (IPQ-R)* (Moss-Morris *et al.,* 2002) was used to measure proband illness perceptions. The individual's view is comprised of 28 items which can be grouped into eight factors. Each factor is scored out of thirty. In the identity, timeline acute / chronic, consequences and timeline cyclical factors high scores indicate strongly held perceptions about symptoms attributed to the condition, its chronicity, its negative consequences and its cyclical nature. High scores in the personal control, treatment control and coherence factors

indicate positive perceptions about the controllability and personal comprehension of the condition. The authors report good internal reliability with Cronbach alphas for each of the subscales ranging from 0.79 to 0.89: Identity (α=.75), Consequences(α=.79), Personal control(α=.81), Treatment control(α=.80), Illness coherence(α=.87), Timeline cyclical(α=.79), Timeline acute/chronic (α=.89) and Emotional representations (α=.88). Cronbach alpha's for test-retest reliability range slightly more between .46 and .88.

The *Generalised Self-Efficacy Scale (GSES)* (Schwarzer & Jerusalem, 1995) is a ten-item scale that captures an individual's general sense of perceived self-efficacy, higher scores indicate greater perceived self-efficacy. Internal reliability is reported as good with Cronbach alpha's ranging between .76 and .90.

The *Inclusion of others in the self-scale (IOS)* (Gächter, Starmer & Tufano, 2015) is a visual tool for measuring the perceived closeness of a given relationship. Closeness is scored on a scale of one to seven with one representing the least close relationships and seven the closest. The IOS correlates highly with other more time-consuming measures of relationship closeness (Gächter, Starmer & Tufano, 2015).

2.6 Part two: Interviews

For the interview element of the study a sample of six was sought based on guidelines for qualitative research in postgraduate research (Smith & Eatough, 2007). A purposive sampling method was used, participants scoring 5 or below on the IPQ-R Illness Identity item were sought. Eligible participants then contacted by the researcher to arrange a suitable time and date for the interview at the QEUH until the desired number of six was achieved. Each participant was interviewed once with interviews lasting between 30 and 70 minutes. A semi-structured interview schedule was used a guide in each interview (Appendix 2.7). Participants were asked to give an account of their own experience of receiving a diagnosis of HCM, their experience of living with

the diagnosis and their experience of being involved in the cascade genetic screening process for HCM. Throughout the interview participants were encouraged to expand on their descriptions through use of open prompts, in doing so the interviewer aimed to facilitate an open discussion of their experiences without being led by the interviewer's expectations.

2.7 Data analysis

Part one: quantitative analysis

Data were analysed using SPSS v21 software. Anonymised FDR uptake data were obtained from the WSICC. This dataset was comprised of the total number of FDRs who had come forward for testing and the expected total number of FDRs who should be screened for each proband. To standardise the different numbers of FDRs between each proband, FDR uptake was converted into a three-point scale one denoting no uptake, two partial uptake and three complete uptake. To assess suitability for correlation and regression analyses assumptions of normality, linearity and homoscedasticity were carried out using box plots, scatter plots, histograms and Shapiro-Wilks tests. These tests indicated the assumption of normality was violated for several IPQ-R factors: Identity, Timeline Acute-Chronic, Consequences, Personal control, Timeline Cyclical as well as FDR uptake. Non-parametric testing was adopted to account for these findings. Spearman's rank correlations were used to inform the selection for inclusion in subsequent regression analysis. As regression is a robust parametric test, it was conducted in the potential multivariate analyses. Test assumptions were checked through examination of P-P and residual scatter plots which indicated these were met. As only one variable correlated with FDR uptake a univariate linear regression was used in place of the planned multiple regression analysis. A post hoc power calculation based on a medium effect size ($f^2 = 0.15$) indicated a minimum sample of 55 would be required to achieve adequate power ($\beta=.80$) for this regression.

Part two: qualitative analysis

Qualitative data were analysed using Thematic Analysis (TA). This approach gave the flexibility necessary to explore participants' views and experiences without being tied to a particular theoretical base. TA is driven by the data and guided by the themes that emerge from the interviews (Braun & Clarke, 2006). All interviews were recorded then transcribed verbatim except for personally identifiable information which was omitted or modified. Transcripts were listened to and read multiple time to allow the researcher to develop an overall sense of each interview. Throughout this process early notes on language choice, conceptual and descriptive content were taken within each transcript. Individual analysis of each transcript then developed emerging themes which were subsequently compared for connections between these themes. This process was repeated for each transcript. Emergent themes identified were then considered for similarities and developed into superordinate themes that were represented across each of participant's experiences. These superordinate themes were then retrospectively cross checked back against individual transcripts and quotations from each participant relating to each theme were collated an example of this can be found in appendix 2.8. Quotations were then selected that best represented the theme discussed or provided specific insights.

2.6.1: Reflexivity

The IPA framework for qualitative data analysis acknowledges the potential influence of the researcher's personal and professional beliefs and experiences during both the interview and analysis stages. Prior to involvement in the present study I had limited knowledge of HCM or genetic screening processes however my knowledge of both had developed during the planning of the study. Prior experience of working as both an Assistant Psychologist and Trainee Clinical Psychologist in cardiac health settings had developed my interest in the psychological experiences of individuals with cardiac conditions. As a means of reducing assumptions associated with my position examined what I brought to the process through a process of reflexivity by keeping a brief reflective account throughout the data collection stage as a means of helping to recognise and limit the influence of my emotional responses and subjective views. In doing so I aimed to

separate my own beliefs and expectations to the best of my ability from the unique experiences of those interviewed. Through this process I was able to observe how my prior experiences and interactions with the WSICC team initially drew me towards the clinical perspective which prioritised improving FDR uptake. However, in carrying out the six interviews I reflected on the range of individual experiences and different level of importance placed on the cascade screening process by the individuals. It is therefore possible that these prior experiences and subsequent reflections influenced the qualitative analysis in the present study.

3. Results

3.1 Part one results: Questionnaires

3.1.1 Questionnaire sample characteristics

A total of 57 participants were recruited, one from the WSICC directly and 56 from the 250 participants informed of the study by post. Twenty-nine (51%) were female and twenty-eight (49%) were male, age ranged from 29-82 (mean = 57 years, SD =11.50). T-test analysis indicated that gender significantly affected four of the IPQ-R elements; Identity *(t(55)* = 2.75, p = 0.08*)*, Consequences *(t*(55) = 2.60, p = 0.012*)*. and timeline cyclical *(t*(51) = 2.02, p = 0.049*)* and emotional representation *(t*(51) = 2.64, p = 0.011*)* however due to the small sample conducting gender analysis was not feasible. There were 184 FDRs linked to probands where genetic screening was indicated, WSICC data indicated 119 of these underwent screening yielding a 65% rate of FDR genetic screening uptake at the time of reporting. Data provided by the WSICC on FDR uptake did not identify individual FDRs therefore analysis of the IOS closeness data which related to specific individual FDRs was not possible and is therefore omitted from subsequent reporting of findings.

3.2 IPQ-R factors and Self-efficacy as predictors of FDR uptake

The main research question was to assess whether the illness perceptions of probands were associated with FDR uptake of genetic testing. Secondary to this perceived self-efficacy was also to be tested a predictor of FDR uptake.

3.2.1 Correlations

The relationship between each of the eight IPQR-R domains, GSES scores and FDR uptake was initially assessed using Spearman's rank correlation analyses. Results are presented in table 1.

Table 1: Correlations, medians and inter-quartile ranges (n=57)

Variable	*Median & Inter=quartile range*	*FDR Uptake 1 (1-3)*
Identity	*2 (0-12)*	*.033*
Timeline Acute / Chronic	*29 (18-20)*	*.395***
Consequences	*18.50 (8-28)*	..033
Personal control	*19.50 (6-28)*	-.176
Treatment control	*15 (5-26)*	-.200
Coherence	*20 (5-25)*	.092
Timeline cyclical	*9 (4-30)*	.029
Emotional representation	*17 (6-30)*	.213
GSES	*34 (23-43)*	.183

**p=<.05, **p=<.01*

3.2.2 Regression

As timeline acute / chronic factors was the only IPQR variable to be significantly correlated with FDR uptake a univariate linear regression was used in place of a multiple regression to evaluate the relationship between the IPQR factor timeline acute / chronic and FDR uptake. The scatterplot showed a weak linear relationship between the two variables, confirmed by the Spearman's rank correlation coefficient of .395. The scatter plot indicated assumptions of homogeneity of variance and linearity were met. The IPQR factor timeline acute /chronic significantly predicted FDRs genetic screening uptake (n=57): r^2=0.13, f = 7.18, df=1, p=0.010. 13% of variance in FDR uptake was explained by the IPQR factor timeline acute /chronic. The equation of the regression line was FDR genetic screening uptake = .845 (95% CI: -2.73-1.05) + .091 (95% CI: 0.02-0.16) (IPQR timeline acute /chronic).

3.3 Part two results: Interviews

3.3.1 Qualitative sample characteristics

Fifty-one out of fifty-seven participants provided provisional consent to take part in the qualitative element. Fifty met the criteria of having low illness identity as measured by the Illness

identity element of the IPQR. Of these 6 participated in an interview. Three were male and three were female, age ranged from 37-67 (mean= 56.5, SD=11.96). Questionnaire data for interview participants are provided in table 3

Table 3 – Interview sample characteristics

Pseudonym	Age	FDRs	Uptake	IPQ-R Domains								GSES
				Identity	Acute / Chronic	Consequences	Personal control	Treatment control	Illness Coherence	Timeline Cyclical	Emotion representation	
Harry	57	5	5/5	0	18	24	24	22	20	9	19	33
Rose	48	3	3/3	0	30	13	26	15	20	8	13	42
Oscar	67	5	5/5	1	30	15	24	21	21	18	6	34
Nancy	63	2	2/2	4	22	15	18	21	20	8	14	30
Megan	37	2	2/2	5	25	18	20	20	13	13	19	39
Simon	67	4	2/4	0	30	13	24	17	25	4	9	37

3.3.2 Thematic analysis

The interviews aimed to explore participant's individual experience of HCM and their involvement as an 'proband' patient in the cascade genetic screening process for their respective FDRs. Three superordinate themes and five related subthemes emerged, these are illustrated in table 4.

Table 4: Superordinate and subthemes identified

Superordinate themes	**Subthemes**
The confusing HCM experience	"*Something on paper*" Low impact experience vs SCD
	"*You're middle-aged and you've got HCM*" Underlying vulnerability
Reasons for screening	"*We believe everything you tell us*" Compliance
	"*An instant killer*" Protecting children
	"*It's good to know*" Protective knowledge
Doubts about screening	

These themes essentially characterise how participants experienced HCM as individuals and how this related to their involvement in the cascade genetic screening process. Quotations from participant interviews are used to illustrate each theme. Notation is used when presenting some quotations: […] indicates small amount of confidential or irrelevant text has been omitted, ".." represents a small pause in speech and (pause) represents a more substantial pause in speech.

Theme one: The confusing HCM experience

The first superordinate theme reflected how participants characterised living with HCM and the associated gene. This theme was understood through two subthemes that emerged from the participant accounts: 1) Low impact experience vs SCD and 2) Underlying vulnerability

Low impact experience vs SCD

When reflecting on their experiences of living with HCM all six participants gave accounts of minimal interference as a consequence of either physical symptoms or associated worries about HCM. However, most participants also demonstrated an awareness of the potentially serious symptoms especially SCD. The following quote illustrates Harry's experience of this:

> *"In something like HCM there is quite a broad spectrum of possibilities, you've got that worst-case scenario of.. the sudden death which the media maybe blows up a bit but then for the vast majority is of people they might be non-symptomatic and that makes it quite confusing"* (Harry)

Harry's account illustrates this discrepancy between his lived experience of being mostly asymptomatic and his knowledge of its potentially serious implications. He rationalises this by suggesting that the risk of SCD is perhaps inflated by the media and indicates that he believes his experience is in keeping with that of most people with HCM. The confusion Harry describes appears to relate to how he should feel or behave in relation to his HCM.

Rose's account of living with HCM without significant symptoms was framed around comparisons with other conditions and the relative importance of HCM:

> "*I feel conflicted sometimes…that you know that you and members of your family have something on paper but in reality, you feel like you don't and sometimes you feel like you feel like you are wasting NHS time.*" (Rose)

Rose's description indicates that her asymptomatic experience of HCM has diminished the importance she places on it to the extent that she questions the need for involvement from the National Health Service. Like Harry she references a sense of uncertainty about how seriously it should be taken and whether it is something worth addressing. This experience was mirrored in Oscar's account:

> "*I sort of feel doctors have got enough on their plate without people like me ringing up when I don't have anything bothering me.*" (Oscar)

Underlying vulnerability

All six participants gave accounts of uncertainty about interaction between HCM, age and lifestyle choices. Each participant's account indicated that even where no symptoms were present it often still felt like something that should inform lifestyle choices especially in older age which was frequently linked to potential increase in symptoms. The following quote from Rose's account demonstrates her experience of this:

> *"I'm approaching 50 and the HCM thing is making me think […] a bit.. it's like you do know smoking is bad for you, you're middle-aged and you've got HCM."* (Rose)

Rose places HCM alongside age as a reason to stop smoking suggesting that that this is how she conceptualises the condition and uses her knowledge of having it to inform health choices. Despite being asymptomatic she is conscious of it as a potential vulnerability.

Oscar described similar views when considering his weight in relation to having a diagnosis of HCM:

> "*I guess I would be concerned if I was putting on a lot of weight and had a heart condition so in that sense perhaps I'm more weight conscious than I otherwise would be. And yeah, I guess that is interconnected a bit. I think if my weight continued to go up I might be concerned about strain on the heart, being conscious that you know I've some weaknesses in that respect.*" (Oscar)

Oscar's description of having "*weaknesses*" suggests that despite not experiencing symptoms he feels having HCM makes his heart vulnerable and that this is a motivator to make healthy lifestyle choices. However, his language indicates this is not something he feels certain about in his use of "*I guess*" "*perhaps*", "*a bit*", "*I might*".

> "*I would imagine it's going to have and affect at some point but I've nearly 70 now […] I think because you're not terribly overweight you don't smoke you don't have a lot you're quite healthy diet so I think all these things help as well you know […] so if I put on 5 pounds I deal with it right away and that hopefully will continue to be like that because […] part of the reason is because I know I put extra strain on my heart which I can't have.*" (Harry)

Harry's account indicated similar attitudes towards HCM being a motivator to make healthy lifestyle choices to avoid "*strain*" on his heart but with a little more certainty. He also talks about the sense despite being currently asymptomatic this might not always be the case especially as he gets older:

Theme two: The benefits of screening

This theme captures participants' motives to undergo initial testing and their perceived benefits of having been screened. Three subthemes were captured under this broader theme: 1) Compliance with medical advice, 2) Seeking to protect children and 3) Feeling protected through understanding.

Compliance

Between the participants there was a shared account of having little or no prior knowledge of HCM prior to diagnosis but also a willingness to trust and act on advice from health professionals where screening was recommended in relation to the diagnosis. The following quote from Nancy's account of discovering she had HCM highlights her own trust in doctors:

> "*When I was about 55 I started getting short of breath but just let it go because I was a smoker […] but as it went on and on and I was still getting shortness of breath so I went to my doctor and the doctor says I think you may have what your mother had so he sent me for a cardiograph and a scan and there it was HCM*" (Nancy)

Nancy's describes her response to worsening shortness of breath in a matter of fact way signifying her perception of its normality and in her willingness to comply with medical advice despite her own beliefs about the causes of her symptoms. Her use of the word "*sent"* about going for tests suggests an external health locus of control in this situation.

Simon alluded to a similar attitude:

> *"My cardiologist and said look. It comes to it just take them. So I have got Bisoprolol or I think you call it, I think I take that and that doesn't do anything."* (Simon)

Although he states his medication "*doesn't do anything"* and portrays a dismissive attitude towards it "*I think you call it*" he complies with the prescription regardless as this was the instruction he was given by the cardiologist.

Protective knowledge

When discussing life after diagnosis and screening, participants alluded to a sense of protection from knowing about the condition and its symptoms.

> "*As my cardiologist, […] said. People who know they're got it don't really die of it. You know so, it's good to know. I was pleased it had been picked up…because if it hadn't been…if I hadn't had that test then you know…who knows what might have happened.*" (Simon)

Simon's statement is powerful in that he implies that he believes knowledge of his diagnosis through having had genetic test protects him from risk of death linked to the HCM. The way he describes "*what might have happened*" suggests a hesitancy to contemplate the reality of his risk of SCD.

> "*I suppose then in terms of if I ever started to experience symptoms I could…I would now probably be able to pinpoint that a lot quicker and go and get it seen to and I know my dad is on medication for it so then I hope that then I could be medicated as well to reduce symptoms.*" (Megan)

The positives Megan attributes to knowing differ slightly from Oscar but also indicate that despite not being affected presently, knowledge of what symptoms to look for would hasten her response to these enabling quicker access to medication and ultimately reduce her risk.

Protecting children

For the 5 participants with children, screening was frequently talked about in reference to minimising their risk, especially of SCD.

> *"Should you find out just keep it quiet because your gonna die of something one day. Hypertrophic Cardiomyopathy it is, it's an instant killer. Right, you don't even, people who*

die don't even know they've got it. It's not like cancer where you deteriorate. So we took the decision to get them tested." (Simon)

Simon's language when talking about why he chose to get his children screened emphasises the threat he perceives HCM as an "*instant killer*" something that can't be stopped unless you know about HCM. He links this threat directly to his choice to have his children screened.

"*It worried me because he played at football at the time and at that time it was all these young footballers dropping dead, I mean obviously they didn't know they had it.. but because he's getting monitored now, he goes every two or three years for a heart scan and whatever, so we know it's not got any worse.*" (Nancy)

Nancy uses similarly abrupt language talking about SCD and her children in "*dropping dead*" but links a sense of reassurance and safety from the fact he gets regular scans.

Theme three: Doubts about screening

Although all six participants expressed predominantly positive views about having been screened most also acknowledged doubts and concerns they had experienced during and after the process.

The excerpt below illustrates Rose's reaction after getting her genetic test results:

Rose: "I was annoyed, and I felt like I wish I hadn't bothered getting screened."

Interviewer: "What was the biggest factor in that?"

Rose: "Basically just because it's like I've come along and nobody is saying a definite yes or no.. I suppose learning a bit more about it.. thinking but I'm not unwell so just leave me alone to be not unwell." (Rose)

Rose's recollection of how she initially felt after getting an unclear result suggests she might have complied with the suggestion of testing with expectations of clarity and was left feeling frustrated when this wasn't achieved.

For Oscar, Rose and Harry doubts focused on the implications of having children screened.

> Oscar: "*We were very clear that you know there are moral issues both.. on all of this, you don't want to raise unnecessary concerns in your kids, but I think I discussed it with my wife and we decided it was the best thing to do so we told them. Individually*".
>
> Interviewer: "*Why was it the best thing to do*?"
>
> Oscar: "*Because I think they had a right to know for a start, secondly you know it was quite clear that there is medication, what I was told at the time was there are a variety of ways of dealing with all this but when my father died I think there was no way dealing with it*" *(Oscar)*

Oscar's account indicates his decision to have his children screened was not taken lightly. He references "unnecessary concerns" implying that for him the risk to them was low enough to consider not having them screened. Conversely felt that it was not his place to deny them the information "they had a right to know".

Concerns about labelling children and the impact of this were shared by Rose and Harry:

> *"You could start labelling them ones healthy ones sick even subconsciously you could do it" (Rose)*

"It was like well do you want to have your children tested because it was it was kind of should you tell them all should you get them tested because if you get them tested will you deal with them differently" (Harry)

Megan talked about separate concerns in her own ability to have the conversation about genetic screening with relatives:

"In terms of having conversations with family it probably.. I think it's probably something I get really anxious about doing but actually the anxiety wouldn't stop me doing I probably feel like I have more of a duty to do it rather than.. so I'd overcome my sort of anxiety in myself in terms.. to deliver that information.." (Megan)

This account highlights both the anxiety that the task provoked in Megan but also the importance she places on the information she has been asked to pass on.

4. Discussion

The primary aim of this study was to investigate the relationship between proband perceptions of HCM and FDR uptake of genetic screening through analysis of questionnaire and interview data. Analyses of questionnaire data demonstrated a significant correlation between the timeline acute /chronic illness representation and FDR uptake of genetic screening. The remaining seven IPQR factors and self-efficacy measured by the GSES were not significantly correlated with FDR uptake. Self rated self-efficacy measured by the GSES was high (mean=35.18, SD=4.54) suggesting this did not pose a barrier to probands in communicating with FDRs although a larger sample size would be necessary to infer significance to this relationship. The relationship between timeline acute / chronic and FDR uptake was explored further through a linear regression which indicated a significant proportion of the variance in FDR uptake could be explained by timeline acute / chronic

IPQR factor. FDR's of individuals that perceived HCM to be a more acute condition were more likely to have come forward for genetic screening. Illness perception and self-efficacy findings are discussed in the context of previous research. Thematic analysis of the accounts of living with HCM and being a proband involved with the cascade genetic screening process for HCM from the subset of six questionnaire participants yielded three superordinate themes: The confusing HCM experience, the reasons for testing and doubts about testing. Notably, these themes correspond with some of those identified in previous qualitative research in this area specifically distinguishing between perceived risk to self and perceived risk to children (Ormondroyd *et al.,* 2014). In the interests of conciseness only key findings from the thematic analysis are discussed in relation to the questionnaire findings.

4.1 IPQR factors and self-efficacy and FDR uptake

FDR uptake of genetic screening was 65% which is towards the higher end of the range of uptake percentages reported in previous studies (Charron *et al.,* 2002; Christiaans *et al.,* 2008; Miller *et al.,* 2013; Khouzam *et al.,* 2015). The timeline acute / chronic factor indicated most individuals viewed HCM as a chronic condition (mean=27.62, SD=3.01) however it was the FDRs of those who viewed the condition as more acute that were significantly more likely to have undergone genetic screening. Given the small sample size it would be inadvisable to over-interpret this finding. However, a possible explanation may be that individuals who perceived HCM as a more acute condition placed more emphasis on the need for prompt action when advising relatives of genetic screening. This appeared to reflect the subtheme of "*low impact experience vs SCD*" and correspond with the "*protecting children"* subtheme which focused on the acute nature of the SCD element of HCM being a strong motivator to have children pursue genetic screening. This could also be framed as a "*cue to action*" using the HBM which in previous research has been linked to increased FDR screening uptake (Khouzam *et al.,* 2015). In keeping with timeline acute

/chronic the timeline cyclical factor was consistently low (mean=10.52, SD=4.56) suggesting most probands perceived the HCM experience as consistent on a day to day basis.

Across the sample illness identity scores were consistently low (mean=2.77, SD=3.01) indicating the sample did not have a strong sense that HCM defined their identity and symptomatology was low. This was in keeping with the subtheme around the low impact of HCM where interview participants described HCM as a peripheral consideration. Low identity in other conditions such as chronic fatigue syndrome has been linked to avoidant coping styles which reduces active assistance seeking (Heijmans, 1998). Moreover, illness identity measured by symptomatology has been shown to be a strong predictor of illness outcomes in patients with other chronic conditions such as rheumatoid arthritis, chronic obstructive pulmonary disease and psoriasis (Scharloo, *et al.,* 1998). Framed through Leventhal's CSM it may be in HCM where symptomatology is often unobservable, individuals rely on other illness stimuli including lay and professional information to inform their illness representations and subsequent actions. This theory is supported by previous findings highlighting the importance of contact with health professionals as well as the TA findings in the present study within the theme of "*compliance*" where participants indicated a high degree of compliance with advice from health professionals relating to their actions (Christiaans *et al.,* 2008; Khouzam *et al.,* 2015; Ormondroyd *et al.,* 2014).

A previous review of the influence of illness perceptions across a range of conditions suggested that controllability factors within the IPQR were significantly linked to active coping strategies (Hagger & Orbell, 2003). Within the current study perceptions of personal control (mean=18.62, SD=5.13), treatment control (mean=14.75, SD=4.13) and consequences (mean=19.11, SD=5.42) were low. With the caveat of the small sample these findings may reflect the broad range of disease expression within HCM and varying personal experiences of perceived personal and treatment control within the sample. A larger sample size may have allowed for comparison between subgroups such as those that had experienced different symptoms or treatments.

Illness coherence (mean=19.20, SD=4.51) was also low given probands contact with health professionals in relation to HCM and their role in communicating genetic risk to FDRs. The subtheme of "*the confusing HCM experience*" illustrated participants experience of ambiguity around their personal experience HCM. This sense of ambiguity was identified in a previous qualitative study which investigated impediments to genetic testing in HCM and Long QT syndrome. This study identified a disjuncture between patients seeking more certainty through testing but the tests available not always being able to provide this (Smart *et al.,* 2010). Correspondingly, research on factors associated with uptake of genetic testing across a range of conditions suggests that perceptions of test-related factors (e.g., perceived test utility) rather than disease-related factors (e.g., perceived consequences of condition) may be stronger predictors of uptake by relatives (Miller *et al.,* 2013; Khouzam *et al.,* 2015; Sweeny *et al.,* 2014). These findings highlight the need for probands to be equipped with clear information on the purpose and merits of testing to support them with the communication of genetic risk to FDRs.

4.2 Strengths and limitations

The TA element of this study represents a strength in that it provided insight into the personal experiences of probands with HCM and enabled additional analysis of the link between probands personal experiences and views and FDR uptake complementing quantitative findings. Sweeney at al. (2014) advocate the use of qualitative methodology alongside quantitative approaches for research concerning genetic testing decisions based on their systematic review that suggested qualitative findings provide the best means of identifying ways to practically promote genetic screening. This approach was not without its limitations. The sample is relatively small for a TA analysis. Although thematic saturation was evident within the sample interviewed the broad range of experiences suggests additional themes may be present if recruitment was centered on something other than illness identity, for example, gender or symptomatology. It is also important to note that the themes extracted were a result of one researcher's interpretation of the data and

these were not cross checked. Finally, it should also be noted that given the methodological change which led to recruitment of both prospective and retrospective participants, the accuracy of individual recall of the cascade genetic screening process may have varied depending on how recent this was.

In addition to the limitations of the TA analysis there are some limitations to the main quantitative element of the study. Firstly ,it was originally hoped that participants would be recruited from a consistent time-point within the cascade genetic screening process (i.e. shortly after being asked to recruit FDRs) however poor recruitment uptake from the WSICC meant retrospective recruitment of probands at different stages in the process was necessary. This meant that although participants were recruited from the same broad part of the cascade process some variation in how long they had been given the information would have been introduced. For the purposes of replication, an outline of the cascade genetic screening process and where participants were recruited from is included in appendix 2.9. Future research would benefit from obtaining greater access to this information as this might provide additional information on the effect of time on the cascade screening outcomes. Secondly , a larger sample obtained through a longer recruitment window would not only provide a sample from a consistent timepoint in the screening process but also enable more detailed and robust analysis of different subgroups within the sample. A further limitation is the potential for sampling bias because of the methodology employed: as initial contact regarding the study was conducted by the WISCC, it is likely that probands' views of their experience at the clinic will have informed their decision to participate or not. This is a particularly important consideration given the studies interest in their perspectives of their condition and healthcare received related to it. Facilitating expression of these views within questionnaire data might allow for this to be controlled for. Finally, omission of the IOS data in the current study also represents a limitation in that it meant exploration of the influence of perceived closeness was not possible. Family communication in genetic screening has been explored qualitatively in numerous studies however quantitative assessment of its influence is

sparse (Gaff, *et al.,*2007; Batte *et al.,* 2014). Obtaining individual FDR data for each proband would enable greater understanding of the potentially important influence of family dynamics on the cascade genetic screening process.

4.4 Clinical Implications

The limitations outlined above mean the clinical implications of the study are restricted however the findings around low illness identity and mixed perceptions around controllability highlight the necessity for probands to be equipped with unambiguous information regarding HCM as well as the intended function of the genetic screening process that captures the range of potential outcomes for FDRs. Furthermore, although the value of the quantitative data in this study was limited by small numbers, clinics involved in the cascade screening process are best placed to collate similar information on proband perceptions and experiences. Contrasting this data with subsequent FDR uptake could contribute to a greater understanding of proband profiles that may influence subsequent FDR uptake.

4.5 Conclusion

The cascade genetic screening process relies on the effective communication of health information between family members. Models such as the CSM and HBM traditionally relate to individuals and their health-related actions however less is understood about how they can be used to understand the communication of health information such as genetic risk between individuals. With the caveat of a small sample the current study's finding suggests a probands perception of HCM as either an acute or chronic condition has a relationship with subsequent FDR uptake of genetic screening. Moreover, there appear to be consistencies in illness perceptions relating to HCM in some areas such as identity and understanding of it as a chronic condition. Further research is warranted to better understand the role of illness perceptions in the cascade genetic screening process with a view to informing clinicians on how best to prepare and support individuals for the task of communicating genetic risk to family members.

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Appendices

Appendix (1.1): Search strategies

Searches conducted 20/09/2019
Database: Ovid Medline (R) <1946 to December Week 4 2018> = 1403
Search strategy:
1. Cardiomyopathy, Hypertrophic/ (13845)
2. (hypertrophic adj3 cardiomyopath*).tw. (14803)
3. hcm.tw. (4690)
4. hocm.tw. (792)
5. 1 or 2 or 3 or 4 (19614)
6. exp "Patient Acceptance of Health Care"/ (143526)
7. (satisf* or dropout* or drop out).mp. (395931)
8. (compliance or complie* or comply*).mp. (169909)
9. (encourage* or improve* or improving or increas* or promot*).mp. (7502185)
10. (uptake or particip* or nonattend*).mp. (1504665)
11. (accept* or attend* or attitude* or utilisation or utilization).mp. (1186410)
12. (refus* or respon* or reluctan* or nonrespon*).mp. (3736019)
13. 6 or 7 or 8 or 9 or 10 or 11 or 12 (10974219)
14. genetic services/ (484)
15. genetic screening/ (35983)
16. genetic predisposition to disease/ (130430)
17. ((gene or genes or genetic* or genotyp*) adj3 (test* or assess* or risk* or susceptibility or disease* or screen*)). ti,ab. (206862)
18. (familial or inherit$ or heredit$ or predispos$ or susceptib$).mp. (861674)
19. 15 or 16 or 17 or 18 or 19 (995271)
20. 5 and 13 and 20 (1403)

Searches conducted 20/09/2019
Database: Embase <1996 – 2019 Week 16> = 2533
Search strategy:
1. Cardiomyopathy, Hypertrophic/ (13097)
2. (hypertrophic adj3 cardiomyopath*).tw. (22161)
3. hcm.tw. (8807)
4. hocm.tw. (1306)
5. 1 or 2 or 3 or 4 (27370)
6. exp "Patient Acceptance of Health Care"/ (384316)
7. (satisf* or dropout* or drop out).mp. (520126)
8. (compliance or complie* or comply*).mp. (331079)
9. (encourage* or improve* or improving or increas* or promot*).mp. (9856095)
10. (uptake or particip* or nonattend*).mp. (1972666)
11. (accept* or attend* or attitude* or utilisation or utilization).mp. (1599553)
12. (refus* or respon* or reluctan* or nonrespon*).mp. (5028251)
13. 6 or 7 or 8 or 9 or 10 or 11 or 12 (14381236)
14. genetic services/ (886)
15. genetic screening/ (79857)
16. genetic predisposition to disease/ (46713)
17. ((gene or genes or genetic* or genotyp*) adj3 (test* or assess* or risk* or susceptibility or disease* or screen*)). ti,ab. (289355)
18. (familial or inherit$ or heredit$ or predispos$ or susceptib$).mp.(1289557)
19. 15 or 16 or 17 or 18 (1486690)

20. 5 and 13 and 19 (2533)
Searches conducted 20/09/2019
Database: Web of science <1990 – 2019 > = 5269
Search strategy:

1. TS=((cardiomyopath* AND hypertroph*)) (30027)
2. TS=((HCM or HOCM)) (5757)
3. TI=((cardiomyopath* AND hypertroph*)) (12937)
4. TI=((HCM or HOCM)) (630)
5. TS=((patient acceptance of health care or satisf* or dropout* or compliance or complie* or comply or encourage* or improve* or improving or increas* or promot* or uptake or particip* or nonattend* or accept or attend or attitude or utilisation or utilization or refus* or respon* or reluctan* or nonrespon*)) (17399941)
6. TI=((patient acceptance of health care or satisf* or dropout* or compliance or complie* or comply or encourage* or improve* or improving or increas* or promot* or uptake or particip* or nonattend* or accept or attend or attitude or utilisation or utilization or refus* or respon* or reluctan* or nonrespon*)) (3131569)
7. TS=((genetic service* or genetic screen* or genetic predisposition to disease or gene* or genotyp* or genetic test* or genetic assess* or genetic risk* or genetic screen or familial*)) (9626285)
8. TI=((genetic service* or genetic screen* or genetic predisposition to disease or gene* or genotyp* or genetic test* or genetic assess* or genetic risk* or genetic screen or familial*)) (2283227)
9. #4 OR #3 OR #2 OR #1 (31726)
10. #6 OR #5 (1739941)
11. #8 OR #7 (9626285)
12. #11 AND #10 AND #9 (5605)
13. #12 *AND* **LANGUAGE:** (English) *Timespan=1980-2019 Timespan=1980-2019 [excluding]* ***DOCUMENT TYPES:*** *(MEETING ABSTRACT OR NOTE OR DATA PAPER OR EDITORIAL MATERIAL OR LETTER OR EARLY ACCESS OR PROCEEDINGS PAPER OR BOOK CHAPTER OR RETRACTED PUBLICATION)* (5269)

Searches conducted: 20/09/2019
Database: Psychinfo = 61
Search strategy:

1. TX Cardiomyopathy, Hypertrophic (96)
2. TX HCM or HOCM (101)
3. TX patient acceptance of health care or satisf* or dropout* or compliance or complie* or comply or encourage* or improve* or improving or increas* or promot* or uptake or particip* or nonattend* or accept or attend or attitude or utilisation or utilization or refus* or respon* or reluctan* or nonrespon* (2555570)
4. TX genetic service* or genetic screen* or genetic predisposition to disease or gene* or genotyp* or genetic test* or genetic assess* or genetic risk* or genetic screen or familial* (1037487)
5. S1 OR S2 (175)
6. S3 AND S4 AND S5 **Narrow by Language:** - English (61)

Appendix (1.2): Data extraction form

Data extraction form

Paper title	
Authors	
Location	
Year	
Journal	
Sample characteristics	
FDR % uptake	
Factors measured against uptake	
Study design	
Key findings	

Appendix (1.3): Quality assessment tools

1.3.1 AXIS – Quality appraisal tool.

		Question	Yes	No	Partially	Unclear / Comment
Introduction						
QR	1	Were the aims/objectives of the study clear?				
Methods						
SD	2	Was the study design appropriate for the stated aim(s)?				
SD	3	Was the sample size justified?				
QR	4	Was the target/reference population clearly defined? (Is it clear who the research was about?)				
SD	5	Was the sample frame taken from an appropriate population base so that it closely represented the target/reference population under investigation?				
B	6	Was the selection process likely to select subjects/participants that were representative of the target/reference population under investigation?				
B	7	Were measure undertaken to address and categorise non-responders?				
SD	8	Were the outcome variables measured appropriate to the aims of the study?				
B	9	Were the risk factor and outcome variables measured correctly using instruments/measurement that had been trialled, piloted or published previously?				
QR	10	Is it clear what was used to determined statistically significant and/or precision estimates?				
QR	11	Were the methods (including statistical methods) sufficiently described to enable them to be repeated?				
Results						
QR	12	Were the basic data adequately described?				
B	13	Does the response rate raise concerns about non-response bias?				
B	14	If appropriate, was information about non-responders described?				
B	15	Were the results internally consistent?				
B	16	Were the results presented for the analyses described in the methods?				
Discussion						
SD	17	Were the authors discussions and conclusions justified by the results?				
QR	18	Were the limitations of the study discussed?				
Other						
N/A	19	Were there any funding sources or conflicts of interest that may affect the authors interpretation of the results?				
N/A	20	Was the ethical approval or consent of participants attained?				

1.3.2 Standardised questionnaire derived from the National Institute for Clinical Excellence methodology checklist for qualitative studies

1. Is a qualitative approach appropriate? • Does the research question seek to understand processes or structures, or illuminate subjective experiences or meanings? • Could a quantitative approach better have addressed the research question?	Appropriate Inappropriate Not sure	Comments:
2. Is the study clear in what it seeks to do? • Is the purpose of the study discussed – aims/objectives/research question/s? • Is there adequate/appropriate reference to the literature? • Are underpinning values/assumptions/theory discussed?	Clear Unclear Mixed	Comments:
Study design		
3. How defensible/rigorous is the research design/methodology? • Is the design appropriate to the research question? • Is a rationale given for using a qualitative approach? • Are there clear accounts of the rationale/justification for the sampling, data collection and data analysis techniques used? • Is the selection of cases/sampling strategy theoretically justified?	Defensible Indefensible Not sure	Comments:
Data collection		
4. How well was the data collection carried out? • Are the data collection methods clearly described? • Were the appropriate data collected to address the research question? • Was the data collection and record keeping systematic?	Appropriately Inappropriately Not sure/inadequately reported	Comments:
Trustworthiness		
5. Is the role of the researcher clearly described? • Has the relationship between the researcher and the participants been adequately considered? • Does the paper describe how the research was explained and presented	Clearly described Unclear Not described	Comments:

to the participants?		
6. Is the context clearly described? • Are the characteristics of the participants and settings clearly defined? • Were observations made in a sufficient variety of circumstances • Was context bias considered	Clear Unclear Not sure	Comments:
7. Were the methods reliable? • Was data collected by more than 1 method? • Is there justification for triangulation, or for not triangulating? • Do the methods investigate what they claim to?	Reliable Unreliable Not sure	Comments:
Analysis		
8. Is the data analysis sufficiently rigorous? • Is the procedure explicit – i.e. is it clear how the data was analysed to arrive at the results? • How systematic is the analysis, is the procedure reliable/dependable? • Is it clear how the themes and concepts were derived from the data?	Rigorous Not rigorous Not sure/not reported	Comments:
9. Is the data 'rich'? • How well are the contexts of the data described? • Has the diversity of perspective and content been explored? • How well has the detail and depth been demonstrated? • Are responses compared and contrasted across groups/sites?	Rich Poor Not sure/not reported	Comments:
10. Is the analysis reliable? • Did more than 1 researcher theme and code transcripts/data? • If so, how were differences resolved? • Did participants `feedback` on the transcripts/data if possible and relevant? • Were negative/discrepant results addressed or ignored?	Reliable Unreliable Not sure/not reported	Comments:
11. Are the findings convincing? • Are the findings clearly presented? • Are the findings internally coherent? • Are extracts from the original data included?	Convincing Not convincing Not sure	Comments:

• Are the data appropriately referenced? • Is the reporting clear and coherent?		
12. Are the findings relevant to the aims of the study?	Relevant Irrelevant Partially relevant	Comments:
13. Conclusions • How clear are the links between data, interpretation and conclusions? • Are the conclusions plausible and coherent? • Have alternative explanations been explored and discounted? • Does this enhance understanding of the research topic? • Are the implications of the research clearly defined? • Is there adequate discussion of any limitations encountered?	Adequate Inadequate Not sure	Comments:
Ethics		
14. How clear and coherent is the reporting of ethics? For example: • Have ethical issues been taken into consideration? • Are they adequately discussed e.g. do they address consent and anonymity? • Have the consequences of the research been considered i.e. raising expectations, changing behaviour? • Was the study approved by an ethics committee?	Appropriate Inappropriate Not sure/not reported	Comments:
Overall assessment		
As far as can be ascertained from the paper, how well was the study conducted? (see guidance notes)	++ + –	Comment

Appendix (1.4): Summary of quality assessment

		Quality of reporting						Study Design					Bias							Other	
		1	4	10	11	12	18	2	3	5	8	17	6	7	9	13	14	15	16	19	20
Cross Sectional – AXIS appraisal tool.																					
Christiaans *et al.,* 2008. The Netherlands	R1	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	N/A	N/A	Y	Y	N	U
	R2	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	Y	N	Y	N	N/A	Y	Y	N	U
Christiaans *et al.,* 2009. The Netherlands	R1	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	U
	R2	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	U
Khouzam *et al.,* 2015. USA	R1	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	P	Y	Y	Y	N	Y	Y	N	Y
	R2	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N	Y	N	Y	Y	N	Y
Miller *et al.,* 2013. USA	R1	Y	Y	Y	Y	Y	Y	Y	P	Y	Y	Y	Y	N	Y	N/A	N/A	Y	Y	N	Y
	R2	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N/A	N/A	Y	Y	N	Y

Qualitative - NICE Quality Appraisal Checklist-Qualitative Studies.																
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Ormondroyd *et al.,* 2014. UK	R1	Appropriate	Clear	Defensible	Appropriate	Clear	Clear	Not clear	Rigorous	Rich	Reliable	Convincing	Relevant	Adequate	Appropriate	++
	R2	Appropriate	Clear	Defensible	Appropriate	Clear	Clear	Not clear	Rigorous	Rich	Reliable	Convincing	Relevant	Adequate	Appropriate	++

Appendix 2.1: *NHS Ethics approval*

Appendix 2.1.1: *Initial approval letter.*

Health Research Authority

South West - Central Bristol Research Ethics Committee
Whitefriars
Level 3, Block B
Lewin's Mead
Bristol BS1 2NT
Email: nrescommittee.southwest-bristol@nhs.net

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

05 September 2018

Professor Rory O'Connor
Institute of Health & Wellbeing, University of Glasgow
Mental Health & Wellbeing, Academic Centre, Gartnavel Royal Hospital
Glasgow
G12 0XH

Dear Professor O'Connor

Study title:	**A mixed methods study of the influence of illness perceptions on the cascade genetic testing process in Hypertrophic Cardiomyopathy.**
REC reference:	**18/SW/0209**
Protocol number:	**4**
IRAS project ID:	**244547**

The Proportionate Review Sub-committee of the South West - Central Bristol Research Ethics Committee reviewed the above application in September 2018.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact hra.studyregistration@nhs.net outlining the reasons for your request. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Ethical opinion

On behalf of the Committee, the sub-committee gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Approved documents

The documents reviewed and approved were:

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [University insurance - In addition to NHS sponsor]		27 July 2017
Interview schedules or topic guides for participants [Interview schedule]	2	10 July 2018
IRAS Application Form [IRAS_Form_16082018]		16 August 2018
Letters of invitation to participant [Letter of invitation]	2	10 July 2018
Participant consent form [Questionnaire consent form]	1	10 July 2018
Participant consent form [Interview consent form]	1	10 July 2018
Participant information sheet (PIS) [Participant Information Sheet]	2	10 July 2018
Research protocol or project proposal [Project protocol/proposal]	4	10 July 2018
Summary CV for Chief Investigator (CI) [Chief Investigator CV]	1	21 June 2018
Summary CV for student [Student CV]	1	20 June 2018
Summary CV for supervisor (student research) [Academic Supervisor CV]	1	21 June 2018
Summary CV for supervisor (student research) [Clinical Supervisor CV]		
Validated questionnaire [IPQ-R]	N/A	
Validated questionnaire [GSES]		
Validated questionnaire [IOS]		

18/SW/0209	**Please quote this number on all correspondence**

Yours sincerely

Mr Brian Pixton
Chair
Email: nrescommittee.southwest-bristol@nhs.net

Enclosures: *List of names and professions of members who took part in the review*
"After ethical review – guidance for researchers"

Copy to. *Miss Emma-Jane Gault, Ms Elaine O'Neill, NHS Greater Glasgow & Clyde Lead Nation*

Appendix 2.1.2: *Amendment approval letter*

NHS
Health Research Authority

South West - Central Bristol Research Ethics Committee

Whitefriars
Level 3, Block B
Lewin's Mead
Bristol BS1 2NT
Email: nrescommittee.southwest-bristol@nhs.net

Please note: This is the favourable opinion of the REC only and does not allow the amendment to be implemented at NHS sites in England until the outcome of the HRA assessment has been confirmed.

12 December 2018

Mr Bruce Irvine
Institute of Health and Wellbeing
University of Glasgow
1st floor, Administration Building
Gartnavel Royal Hospital,
1055 Great Western Road
G12 0XH

Dear Mr Irvine

Study title:	**A mixed methods study of the influence of illness perceptions on the cascade genetic testing process in Hypertrophic Cardiomyopathy.**
REC reference:	**18/SW/0209**
Protocol number:	**4**
Amendment number:	**01**
Amendment date:	**13 November 2018**
IRAS project ID:	**244547**

The above amendment was reviewed at the meeting of the Sub-Committee held on 10 December 2018 by the Sub-Committee in correspondence.

Summary

This amendment sought approval to change the inclusion criteria.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Covering letter on headed paper [for PIS]	3.0	17 October 2018
Notice of Substantial Amendment (non-CTIMP)	01	13 November 2018
Participant consent form [Interview]	2.0	13 November 2018
Participant consent form [for Questionnaire]	2.0	13 November 2018
Participant information sheet (PIS)	3.0	17 October 2018
Research protocol or project proposal [Protocol]	5.0	17 October 2018

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

Working with NHS Care Organisations

Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our Research Ethics Committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

18/SW/0209:	**Please quote this number on all correspondence**

Yours sincerely

Dr Julie Woodley
Chair
E-mail: nrescommittee.southwest-bristol@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Ms Elaine O'Neill, NHS Greater Glasgow & Clyde,*

South West - Central Bristol Research Ethics Committee

Attendance at Sub-Committee of the REC meeting on 10 December 2018

Committee Members:

Name	*Profession*	*Present*	*Notes*
Dr Ian Davies	Consultant in Cardiac Anaesthesia & Intensive Care	Yes	
Dr Julie Woodley	Senior Lecturer/ Chair of Faculty Ethics Committee	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Ms Lidia Gonzalez	REC Assistant

Appendix 2.2: *NHS GG&C R&D approval*

Administrator: Mrs Elaine O'Neill
Telephone Number: 0141 232 1815
E-Mail: elaine.o'neill2@ggc.scot.nhs.uk
Website: www.nhsggc.org.uk/r&d

R&D Management Office
West Glasgow ACH
Dalnair Street
Glasgow G3 8SW

17 September 2018

Mr Bruce Irvine
Mental Health and Wellbeing
1st floor Admin Building
Gartnavel Royal Hospital
1055 Great Western Road
Glasgow G12 0XH

NHS GG&C Board Approval

Dear Mr B Irvine,

Study Title:	**A mixed methods study of the influence of illness perceptions on the cascade genetic testing process in Hypertrophic Cardiomyopathy.**
Principal Investigator:	**Mr Bruce Irvine**
GG&C HB site	**Queen Elizabeth University Hospital**
Sponsor	**NHS Greater Glasgow and Clyde**
R&D reference:	**GN18MH326**
REC reference:	**18/SW/0209**
Protocol no:	**V4; 10/07/18**

I am pleased to confirm that Greater Glasgow & Clyde Health Board is now able to grant **Approval** for the above study.

Conditions of Approval

1. **For Clinical Trials** as defined by the Medicines for Human Use Clinical Trial Regulations, 2004

    a. During the life span of the study GGHB requires the following information relating to this site
        i. Notification of any potential serious breaches.
        ii. Notification of any regulatory inspections.

It is your responsibility to ensure that all staff involved in the study at this site have the appropriate GCP training according to the GGHB GCP policy (www.nhsggc.org.uk/content/default.asp?page=s1411), evidence of such training to be filed in the site file.

2. **For all studies** the following information is required during their lifespan.
   a. Recruitment Numbers on a monthly basis
   b. Any change of staff named on the original SSI form
   c. Any amendments – Substantial or Non Substantial
   d. Notification of Trial/study end including final recruitment figures
   e. Final Report & Copies of Publications/Abstracts

Please add this approval to your study file as this letter may be subject to audit and monitoring.

Your personal information will be held on a secure national web-based NHS database.

I wish you every success with this research study

Yours sincerely,

Mrs Elaine O'Neill
Senior Research Administrator

Cc: Emma Jane Gault (University of Glasgow)

Appendix 2.3: *Participant Information Sheet*

Researcher contact information

Bruce Irvine,
Trainee Clinical Psychologist
University of Glasgow
1st floor, Administration Building
Gartnavel Royal Hospital
1055 Great Western Road
Glasgow G12 0XH
Email: b.irvine.1@research.gla.ac.uk

Rory O'Connor,
Professor of Health Psychology
Institute of Health & Wellbeing
University of Glasgow
Gartnavel Royal Hospital
1055 Great Western Road
Glasgow, G12 0XH
rory.oconnor@glasgow.ac.uk

Participant information sheet

Version: 3 Date: 17/10/2018

A mixed methods study of the influence of illness perceptions on the cascade genetic screening process in Hypertrophic Cardiomyopathy

We would like to invite you to take part in a research study. Before deciding if you would like to participate, it is important you understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish and please ask one of the researchers using the contact details above if there is anything that is not clear or if you would like more information.

Who is conducting the research?

The research is being carried out by Bruce Irvine, Trainee Clinical Psychologist, from the University of Glasgow. It is being supervised by Professor Rory O'Connor from the University of Glasgow, and Dr John Sharp from the Scottish National Advanced Heart Failure Service at the Golden Jubilee National Hospital.

What is the purpose of this study?

The purpose of the study is to try to improve our understanding of the relationship between how we think about illnesses and the actions we take in relation to them. We are particularly interested in whether the beliefs about Hypertrophic Cardiomyopathy held by those first undergoing genetic testing for the genes associated with the condition influence the uptake of their respective relatives coming forward for subsequent cascade screening.

Why have I been invited?

We are looking for people who are aged over 18 years old, who have a diagnosis of Hypertrophic Cardiomyopathy who are either due to attend, or have attended the West of Scotland Inherited Cardiac Conditions clinic at the Queen Elizabeth University Hospital. We are hoping to recruit as many people as possible who fit these criteria.

What does taking part involve?
For most people the study will involve completing a set of three brief questionnaires. These questionnaires should take 15 to 20 minutes to complete. How you completed these questionnaires will depend on whether you have already attended the West of Scotland Inherited Cardiac Diseases clinic at the Queen Elizabeth University Hospital.

- **If you have already attended the clinic:** We will have enclosed the three questionnaires along with a consent form and a pre-paid envelope. If you would like to take part, please complete the three questionnaires and consent form and then return them to using enclosed pre-paid envelope. The clinic may also contact you by telephone within 4 weeks to confirm whether you are interested in taking part and answer any questions you may have.
- **If you are due to attend the clinic:** You do not need to do anything until you attend your appointment at the West of Scotland Inherited Cardiac Diseases clinic at the Queen Elizabeth University Hospital. At this appointment you will have the opportunity to say whether you would like to take part. If you intend on participating you will be asked to sign a consent form then given time to complete the three questionnaires at the clinic.

For most people completing the questionnaires will be all that is involved with participating in the study. However, all participants will also be asked if they would be willing to take part in an hour-long one to one interview at a time and date convenient to them. Only a small number of people who indicate they would be willing to take part in an interview will be invited to do so. Interviews will take place at a date and time convenient to the individual at the Queen Elizabeth University Hospital and will be audio recorded, Travel expenses up to £20 will be available to those attending for an interview. Those selected take part in the interview element will receive an invitation to arrange an interview date within four weeks following completion of the questionnaires. Interviews will focus on your experience of Hypertrophic Cardiomyopathy and the healthcare you have received related to the condition.

Do I have to take part?
No. It is up to you to decide if you want to take part in the study. You are free to withdraw from the study at any time until the research is written up, without giving a reason. Withdrawing from the study would not affect the standard of care you receive or your future treatment in any way.

What happens to the information?
Your identity and personal information will be completely confidential and held electronically on NHS computers before being anonymised and transferred to computers at the University of Glasgow. All data will be held in accordance with the Data Protection Act, which means that we keep it safely and cannot reveal it to other people without your permission. This information will only be accessed by the research team and representatives of the study sponsor (NHS Greater Glasgow & Clyde) for audit purposes. The results of this study may be published in academic journals, conference proceedings and as a piece of work for a doctoral qualification in Clinical Psychology. If you take part in the interview some direct quotes from this may be included in these reports/publications, however all information will be anonymised and it will not be possible to personally identify you from this information. Should you wish to be informed of the study's findings, you will be given the opportunity to provide contact details for these to be sent on once completed.

What are the possible benefits of taking part?
Whilst taking part will not have any direct impact on your own care, it is hoped that it will help us to improve our understanding of the cascade screening process in Hypertrophic Cardiomyopathy and the information future patients and their relatives receive.

Who has reviewed the study?
The study has been reviewed by the South West - Central Bristol Research Ethics Committee.

What if you have any further questions or complaint about any aspect of the study?
If you would like further information or would like to discuss a complaint please contact one of the researchers detailed at the *top* of this letter in the first instance. However the normal NHS

complaint mechanism is also available to you and if you would like to speak to someone from the University of Glasgow who is *not* closely involved in the study, then you can contact:

Professor Andrew Jahoda
Institute of Health and Wellbeing, University of Glasgow, Gartnavel Royal Hospital, 1055 Great Western Road, Glasgow, G12 0XH
Email: Andrew.Jahoda@glasgow.ac.uk

Thank you *for taking the time to read this information*.

Appendix 2.4: *Host clinic cover letter*

Inherited Cardiac Conditions Service
DEPARTMENT OF CARDIOLOGY
Level 4, Cardiac

Dr
Correspondence address:

Dr
Correspondence address:

Correspondence address:
Laboratory Medicine Building
Southern General Hospital
1345 Govan Road
Glasgow
G51 4TF
Tel: 0141 354 9201

Genetic Counsellor - Contact No.
Specialist Nurse - Contact No.

Document version: 3 Date: 17/10/2018

Dear *POTENTIAL PARTICIPANT NAME*,

I am writing to invite to you take part in the following research study: *A mixed methods study of the influence of illness perceptions on the cascade screening process in Hypertrophic Cardiomyopathy.*

This research is being completed by a final year Trainee Clinical Psychologist, Bruce Irvine, working in NHS Greater Glasgow and Clyde, who is completing the research study as part of his doctoral degree at the University of Glasgow. I am inviting you to take part in this study as you are either due to attend, or have attended, the West of Scotland Inherited Cardiac Diseases Clinic and meet the eligibility criteria.

Please find enclosed an information sheet which contains all the details concerning the research. Please take the time to read this, and consider whether or not you would be happy to take part. If you have any questions regarding this research, contact details for the principal investigator are provided below:

Bruce Irvine,
Trainee Clinical Psychologist
University of Glasgow
1st floor, Administration Building
Gartnavel Royal Hospital
1055 Great Western Road
Glasgow G12 0XH

Email: b.irvine.1@research.gla.ac.uk

Thank you for taking the time to read this letter.

Yours sincerely,

Dr
Consultant Clinical Geneticist

Dr
Consultant Cardiologist

Appendix 2.5: *Consent forms*

Appendix 2.5.1: *Participant consent form (Questionnaire)*

Participant Consent form 1 – Questionnaires

Version: 2 Date: 13/11/2018

Title of Project: A mixed methods study of the influence of illness perceptions on the cascade screening process in Hypertrophic Cardiomyopathy.

Name of researcher: Bruce Irvine
Identification number for this study:

Please *initial* each item

1. I confirm that I have read and understand the participant information sheet (Version: 3 Date:17/10/2018) for the above study. ◯

2. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ◯

3. I give permission to be contacted by the researcher in the future to be invited to take part in an interview at the Queen Elizabeth University Hospital, if I am selected. ◯

4. I give permission for the information that I provide to be used as part of this research project. ◯

5. I understand that the information that I provide will be kept strictly confidential and my identity will not be revealed in any reports, publications or presentations. ◯

6. I give permission for my personal information to be viewed by representatives of the study sponsor, NHS Greater Glasgow & Clyde, for audit purposes. ◯

7. I agree to take part in this study. ◯

Name of Participant: Signature: Date:

Name of Researcher: Signature: Date:

Thank you for agreeing to take part in this research

Appendix 2.5.2: *Participant consent form (Interview)*

Participant Consent form 2 – Interview

Version: 2 Date: 13/11/2018

Title of Project: A mixed methods study of the influence of illness perceptions on the cascade screening process in Hypertrophic Cardiomyopathy.

Name of researcher: Bruce Irvine

Identification number for this study:

Please *initial* each item

1. I confirm that I have read and understand the participant information sheet (Version:3 Date:17/10/2018) for the above study. ◯

2. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ◯

3. I consent to the interview being audio-recorded. ◯

4. I give permission for the information that I provide to be used as part of this research project. ◯

5. I understand that the information that I provide will be kept strictly confidential and my identity will not be revealed in any reports, publications or presentations. ◯

6. I understand that anonymised direct quotations from my interview may be used in reports, publications or presentations ◯

7. I give permission for my personal information to be viewed by representatives of the study sponsor, NHS Greater Glasgow & Clyde, for audit purposes. ◯

8. I agree to take part in this study. ◯

Name of Participant:	Signature:	Date:
Name of Researcher:	Signature:	Date:

Thank you for agreeing to take part in this research

Appendix 2.6: *Questionnaires*

Appendix 2.6.1: *Revised - Illness Perception Questionnaire (IPQ-R)*

Illness Perception Questionnaire

Moss-Morris, R., Weinman, J., Petrie, K. J., Horne, R., Cameron, L.D., & Buick, D. (2002). The Revised Illness Perception Questionnaire (IPQ-R). *Psychology and Health. 17*, 1-16.

Participant ID: **Date:**

Listed below are several symptoms that you may or may not have experienced since your illness. Please indicate by circling Yes or No, whether you have experienced any of these symptoms since your illness, and whether you believe that these symptoms are related to your illness.

Symptoms	**I have experienced this symptom *since my illness***		**This symptom is *related to my illness***	
Pain	Yes	No	Yes	No
Sore Throat	Yes	No	Yes	No
Nausea	Yes	No	Yes	No
Breathlessness	Yes	No	Yes	No
Weight Loss	Yes	No	Yes	No
Fatigue	Yes	No	Yes	No
Stiff Joints	Yes	No	Yes	No
Sore Eyes	Yes	No	Yes	No
Wheeziness	Yes	No	Yes	No
Headaches	Yes	No	Yes	No
Upset Stomach	Yes	No	Yes	No
Sleep Difficulties	Yes	No	Yes	No
Dizziness	Yes	No	Yes	No
Loss of Strength	Yes	No	Yes	No

We are interested in your own personal views of how you now see your current illness. Please indicate how much you agree or disagree with the following statements about your illness by ticking the appropriate box.

	Views about your illness	**Strongly Disagree**	**Disagree**	**Neither Agree nor Disagree**	**Agree**	**Strongly Agree**
1	My illness will last a short time					
2	My illness is likely to be permanent rather than temporary					
3	My illness will last for a long time					
4	This illness will pass quickly					
5	I expect to have this illness for the rest of my life					
6	My illness is a serious condition					
7	My illness has major consequences on my life					
8	My illness does not have much effect on my life					
9	My illness strongly affects the way others see me					
10	My illness has serious financial consequences					
11	My illness causes difficulties for those who are close to me					
12	There is a lot which I can do to control my symptoms					

13	What I do can determine whether my illness gets better or worse					
14	The course of my illness depends on me					
15	Nothing I do will affect my illness					
16	I have the power to influence my illness					
17	My actions will have no affect on the outcome of my illness					
18	My illness will improve in time					
19	There is very little that can be done to improve my illness					
20	My treatment will be effective in curing my illness					
21	The negative effects of my illness can be prevented (avoided) by my treatment					
22	My treatment can control my illness					
23	There is nothing which can help my condition					
24	The symptoms of my condition are puzzling to me					
25	My illness is a mystery to me					
26	I don't understand my illness					
27	My illness doesn't make any sense to me					
28	I have a clear picture or understanding of my condition					
29	The symptoms of my illness change a great deal from day to day					
30	My symptoms come and go in cycles					
31	My illness is very unpredictable					
32	I go through cycles in which my illness gets better and worse					
33	I get depressed when I think about my illness					
34	When I think about my illness I get upset					
35	My illness makes me feel angry					
36	My illness does not worry me					
37	Having this illness makes me feel anxious					
38	My illness makes me feel afraid					

We are interested in what you consider may have been the cause of your illness. As people are very different, there is no correct answer for these questions. We are most interested in your own views about the factors that caused your illness rather than what others including doctors or family may have suggested to you. Below is a list of possible causes for your illness. Please indicate how much you agree or disagree that they were causes for you by ticking the appropriate box.

	Possible causes	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
1	Stress or worry					
2	Hereditary - it runs in my family					
3	A Germ or virus					
4	Diet or eating habits					
5	Chance or bad luck					
6	Poor medical care in my past					
7	Pollution in the environment					
8	My own behaviour					
9	My mental attitude e.g. thinking about life negatively					
10	Family problems or worries caused my illness					
11	Overwork					
12	My emotional state e.g. feeling down, lonely, anxious, empty					
13	Ageing					
14	Alcohol					
15	Smoking					
16	Accident or injury					
17	My personality					
18	Altered immunity					

Finally, please list in rank-order the three most important factors that you now believe caused YOUR illness. You may use any of the items from the box above, or you may have additional ideas of your own. The most important causes for me:-

1. _____

2. _____

3. _____

Appendix 2.6.2: *Generalised Self-efficacy Scale (GSES)*

Generalised Self Efficacy Scale

Schwarzer, R., & Jerusalem, M. **(1995)**. Generalized Self-Efficacy scale. In J. Weinman, S. Wright, & M. Johnston, *Measures in health psychology: A user's portfolio. Causal and control beliefs* (pp. 35-37). Windsor, UK: NFER-NELSON.

Participant ID: Date:

		Not at all true	Hardly true	Moderately true	Exactly true
1	I can always manage to solve difficult problems if I try hard enough.				
2	If someone opposes me, I can find the means and ways to get what I want.				
3	It is easy for me to stick to my aims and accomplish my goals.				
4	I am confident that I could deal efficiently with unexpected events.				
5	Thanks to my resourcefulness, I know how to handle unforeseen situations.				
6	I can solve most problems if I invest the necessary effort.				
7	I can remain calm when facing difficulties because I can rely on my coping abilities.				
8	When I am confronted with a problem, I can usually find several solutions.				
9	If I am in trouble, I can usually think of a solution.				
10	I can usually handle whatever comes my way.				
11	I am confident in my ability to distribute self referral forms to my relatives.				

Appendix 2.6.1: *Inclusion of Others in Self Scale (IOS)*

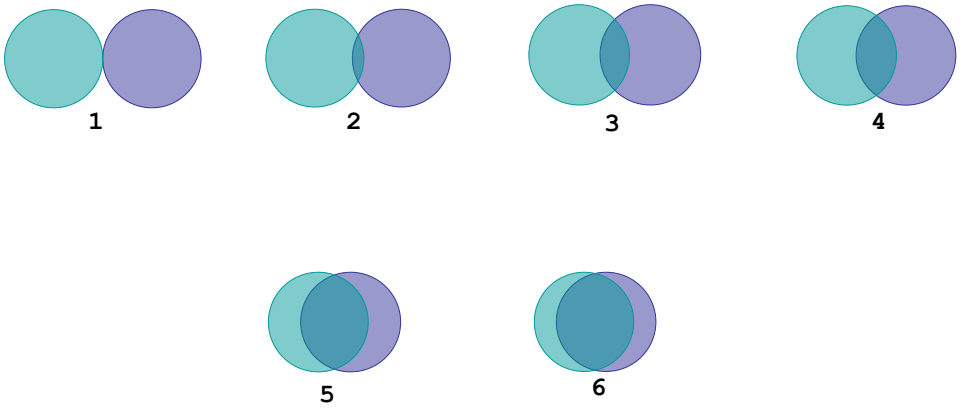
Inclusion of others in the self scale

Aron, A., Aron E. N., & Smollan, D. (1992). Inclusion of other in the self scale and the structure of interpersonal closeness. *Journal of Personality and Social Psychology, 63*, 596-612.

Questionnaire guidance

These questions relate to any first-degree relatives you may have been asked to discuss genetic screening with. You do not have to provide their names. If there are more than five, please add more columns.

Participant ID: **Date:**

	Person 1	**Person 2**	**Person 3**	**Person 4**	**Person 5**
Please indicate which pair of circles best describes your relationship using the corresponding number.					
					
Additional questions					
	Person 1	**Person 2**	**Person 3**	**Person 4**	**Person 5**
What relation is the person to you? *For example: Mother/Sister/Son*					
Do you currently live with the person?					
In the last *year* how regularly have you been in contact with this person? 1. Never 2. Less than monthly 3. Monthly 4. Weekly 5. Daily or almost daily					
How likely do you think this person is to come forward for genetic testing for Hypertrophic Cardiomyopathy if asked? 1. Very likely 2. Somewhat likely 3. Somewhat unlikely 4. Unlikely					

Appendix 2.7: *Interview schedule*

Interview schedule

Version no: Date:

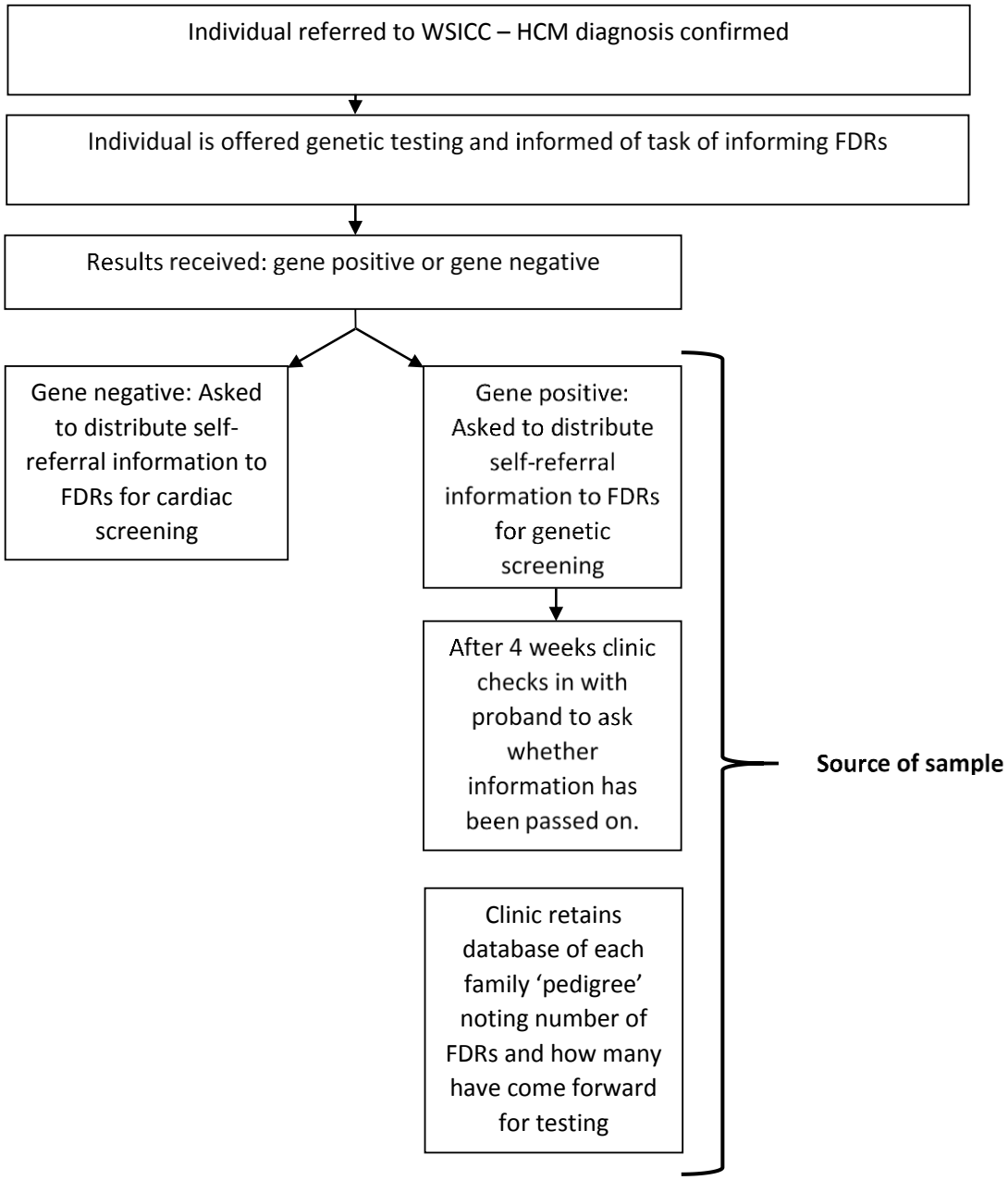
1	**Can you tell me about your experience of receiving a diagnosis of Hypertrophic Cardiomyopathy?**
Prompts	• What has been your experience of the healthcare related to the diagnosis? • Was there anything that could have been done differently or you would want to change?
Notes	
2	**Can you tell me about your experience of living with a diagnosis of Hypertrophic Cardiomyopathy?**
Prompts	• Did it make you think about your symptoms differently? • Have you made any changes because of the condition?
Notes	
3	**What was your reaction to being asked to distribute referral forms to your relatives who might be at risk of the condition?**
Prompts	• Do you think there is anything that would influence whether others take up testing or not? • Is there anything the service could do to improve this process?
Notes	

Appendix 2.8: *Sample Subthemes and exemplars*

Superordinate theme	Subtheme	Exemplars	Individual
The confusing HCM experience	Underlying vulnerability	*"I would imagine it's going to have and affect at some point but I've nearly 70 now […] I think because you're not terribly overweight you don't smoke you don't have a lot you're quite healthy diet so I think all these things help as well you know […] so if I put on 5 pounds I deal with it right away and that hopefully will continue to be like that because […] part of the reason is because I know I put extra strain on my heart which I can't have."* *"There was no guarantee at all that they would have any symptoms it was just the way that we are the same as like myself and my brother the heart is.. is deformed if you like and different."*	Harry
		"I'm approaching 50 and the HCM thing is making me think […] a bit.. it's like you do know smoking is bad for you, you're middle-aged and you've got HCM." *"we were aware that there were heart issues in the family"* *"I can get quite tired quite easily but could be multiple reasons for that and I couldn't know because it's always been there"*	Rose
		"I guess I would be concerned if I was putting a lot of weight and had a heart condition so in that sense perhaps I'm more weight conscious than I otherwise would be. And yeah, I guess that is interconnected a bit. I think if my weight continued to go up I might be concerned about strain on the heart, being conscious that you know I've some weaknesses in that respect." *"I probably avoided strenuous exercise since this was diagnosed but apart from that and apart from the fact I take ..beta blockers…and have done ever since this was diagnosed…you know I really its not an issue for me other than the fact I know I've got it"*	Oscar
		"I have lived this long.. nothings happened to me but the fact that I think Dad thought that he had developed it as in later life as an adult so I suppose I kind of thought to be knowledge is power to be forearmed"	Megan
		"Never effected my mother. Never really affected me apart from the annoyance of these dizzy spells. My oldest brother hasn't really affected him. My middle brother Jasper has affected him greatly so much, so he had a heart transplant"	Simon
Reasons for screening	Protective knowledge	*I just Felt that that we had to tell everybody in the family and some friends as well but the family had to know in order for them to do what they wanted with the information* *I think it's better to know because then you can keep an eye*	Harry
		Interviewer: "How did you feel the time?" *Rose: " Really that that it would be useful just to clear it just to make things more definitive"* *"I think it was the information, that's what I'm saying over a period of time but different it's not like one cardiologist completely sort of converted me to this is useful different bits of information over time you get a clearer picture and you do start*	Rose

		to say well yeah there is some use to be being monitored."	
		"As my cardiologist, one of the previous ones said. People who know they're got it don't really die of it. You know so, it's good to know." *"It's better to know and have something done about it and not to know given the sudden death syndrome aspect to all of this, to be aware and have what treatment might be necessary."*	Oscar
		"I think its good the testing because like that if we didn't know we had and the likes of me going short of breath theres no way I wouldn't went to the doctor" *"If you don't know you've got the gene you don't know when your going to just drop. Or if you find out that you've got it then it can be monitored and you can sort of tail back what your doing like my son he can tail back his football"*	Nancy
		"I suppose then in terms of if I ever started to experience symptoms I could…I would now probably be able to pinpoint that a lot quicker and go and get it seen to and I know my dad is on medication for it so then I hope that then I could be medicated as well to reduce symptoms." *"I get heart palpitations and every now and then I kind of its weird sometimes I can be quite detached from it and every now and then I'd be like Ill get palpitations and be like ahhh that'll be that'll be that thing"*	Megan
		"As my cardiologist, […] said. People who know they're got it don't really die of it. You know so, it's good to know. I was pleased it had been picked up…because if it hadn't been…if I hadn't had that test then you know…who knows what might have happened." *"You don't have to get it checked out we did the reason is it's better to know than don't know. Especially if Hypertrophic Cardiomyopathy so it was a relatively straightforward decision for us.."*	Simon

Appendix 2.9: Summary of WSICC Cascade genetic screening process & sample source



Appendix 2.10: *Major research project proposal*

Major Research Project: Proposal

A mixed methods study of the influence of illness perceptions on the cascade genetic testing process in Hypertrophic Cardiomyopathy.

Matriculation number:

Date of submission: 29/01/2018

Version: 3

Total word count: 3490

Abstract

Background
Hypertrophic Cardiomyopathy (HCM) a relatively common inherited cardiac disease, symptoms include breathlessness, palpitations, chest pain and more rarely, sudden cardiac death. Cascade genetic testing is an increasingly viable means of confirming HCM associated gene carriers and identifying their at-risk relatives, however uptake of such testing is suboptimal.

Aims
The study aims to explore whether illness perceptions of those who first undergo genetic testing for the HCM gene mutation predicts uptake of cascade genetic testing by respective at risk relatives.

Methods
A mixed methods, single centre, cross-sectional design. 'Index' patients with HCM undergoing genetic testing will be asked to complete measures of their illness perceptions, closeness to relatives and perceived self efficacy. Uptake of cascade testing by respective first degree relatives will then be monitored. A multiple regression analysis will be used to explore the relationship between relative uptake and the index patient factors. Semi-structured interviews will be conducted on a sub-group of participants focusing on those who have low associated illness identity. Transcripts will be explored using Interpretive Phenomenological Analysis (IPA).

Applications
Identifying if specific index patient illness perceptions influence the uptake of cascade genetic testing in relatives may inform the way information is given to future patients.

1.0 Introduction

Hypertrophic Cardiomyopathy (HCM) is an inherited cardiac disease affecting approximately one in 500 people in the UK (Maron *et al.,* 1995). HCM can cause

symptoms such as breathlessness, palpitations, chest pain and more rarely, sudden cardiac death. With appropriate treatment most people with HCM are able to live without significant symptom burden (Gersh *et al.,* 2011). Approximately 50% of individuals with HCM will carry an associated gene mutation. Genetic testing is an increasingly viable means of both confirming gene carriers and using this information to identify at risk first degree relatives then provide risk minimising treatments (Khouzam *et al.,* 2015). Despite the potential benefits of genetic testing in HCM, uptake remains suboptimal, ranging from 39-66% in peer reviewed studies leaving a significant proportion of at risk relatives without any follow up (Charron *et al.,* 2002; Christiaans *et al.,* 2008; Miller *et al.,* 2013; Khouzam *et al.,* 2015).

Research investigating patient experience and decision making in genetic testing in a range of conditions has grown in recent years (Sweeny, *et al* 2014). In parallel there is growing research specifically investigating these areas in HCM (Charron *et al.,* 2002; Christiaans *et al.,* 2008; Miller *et al.,* 2013; Hickey *et al.,* 2014**;** Ormondroyd, *et al* 2014; Khouzam *et al.,* 2015; Wynn *et al.,* 2017). However studies concerned with investigating factors that influence uptake remain sparse and vary in focus and quality (Charron *et al.,* 2002; Christiaans *et al.,* 2008; Fitzgerald-Butt, 2010; Miller *et al.,* 2013; Khouzam *et al.,* 2015). Factors implicated to date include perceived utility of testing (Miller *et al.,* 2013; Khouzam *et al.,* 2015), age (Fitzgerald-Butt, 2010), level of education (Fitzgerald-Butt, 2010), family history of sudden cardiac death or HCM diagnosis (Miller *et al.,* 2013; Khouzam *et al.,* 2015), knowledge that HCM is hereditary (Fitzgerald-Butt, 2010) and HCM specific health beliefs (Khouzam *et al.,* 2015). Sweeny *et al* (2014) emphasise the need for future research to draw on both medical and psychological perspectives with a view to generating theoretical models that can inform what influences decision making in genetic testing.

There is an abundance of literature concerned with the understanding of how an individual's beliefs about a given condition may influence their behaviours. Leventhal's (1980) Common Sense Model (CSM) of illness representations supposes that when faced with an illness, individuals form beliefs about the illness which can be captured under five areas: cause, consequences, controllability, time-line and identity (Leventhal *et al.,* 1980). These representations combined with existing schemata allow individuals to make sense of their condition and guide coping mechanisms. The influence of these representations in a range of conditions including HCM (Christiaans *et al.,* 2008; Hickey *et al.,* 2014**;** Khouzam *et al.,* 2015) has been increasingly investigated since the development of the Illness Perception Questionnaire (IPQ) which captures beliefs across Leventhal's five areas (Weinman *et al.,* 1996). Similarly, the Health Belief Model (HBM) (Rosenstock,

1966; Glanz, Rimer & Lewis, 2002) has frequently been used to predict health behaviours across a range of conditions including individual uptake of genetic testing in HCM (Khouzam *et al.,* 2015). The HBM suggests that an individual's perceptions of an illness and associated behaviours are modified by "cues to action" such as education and symptoms, the perceived benefits and barriers of the behaviour and perceived self-efficacy. Cues to action such as requests to undergo testing from family and perceived benefits and barriers have both previously been implicated as having influence on the uptake of genetic testing in HCM (Khouzam *et al.,* 2015). However, the influence of perceived self-efficacy on the cascade process does not yet appear to have been investigated.

Although illness perceptions and the HBM have been shown to influence how individuals make behavioural choices about healthcare generally and in HCM (Petrie & Weinman, 2006; Petrie *et al.,* 2007; Christiaans *et al.,* 2008; Hickey *et al.,* 2014**;** Khouzam *et al.,* 2015) less is understood about whether they influence communication of health information to others in genetic testing. In the UK genetic testing in HCM is usually offered through specialist clinics using a cascade model which relies on an 'index' patient who has a confirmed diagnosis of HCM undergoing genetic testing then distributing self referral forms to their at risk first degree relatives with a view to them also undergoing genetic testing. The qualitative experience of communicating genetic risk of HCM within families has rarely been studied, one qualitative study has highlighted a theme of ambivalence and concerns about the communication process held by index patients (Smart, 2010). In other genetic conditions such as Huntington's disease and Ovarian cancer, studies have highlighted the complexity of the communication process within families and the need to be sensitive to individual family dynamics (Forrest *et al.,* 2003). Research indicates that once an individual has contact with a genetics professional they are highly likely to undergo testing and that the short fall in uptake lies with uptake of testing by the first degree relatives (Christiaans *et al.,* 2008; Aatre & Day, 2011; Miller *et al.,* 2013; Khouzam *et al.,* 2015). Given the central role index patients have in the cascade genetic testing process it is possible that their experience of, and beliefs about HCM may influence how they communicate the importance of testing to relatives which in turn may influence first degree relative uptake of genetic testing.

2.0 Aims and hypotheses

2.1 Aims

Through use of a mixed methods approach the study aims to explore the relationship between the illness perceptions of those with a diagnosis of HCM who are offered genetic testing for the HCM gene mutation and the uptake of cascade genetic testing by their

respective first degree relatives. As a secondary aim, the study also plans to explore whether perceived self efficacy and subjective closeness to first degree relatives also influences uptake of cascade genetic testing or cardiac screening in first degree relatives.

2.2 Hypothesis

2.2.1 Primary hypothesis: Higher reported HCM related symptoms and well informed beliefs about the cause, consequences, controllability and timeline of HCM in the index patient will predict increased uptake in first degree relative uptake of genetic testing.

2.2.2 Secondary hypothesis: Perceived self efficacy and subjective closeness to respective relatives will mediate the relationship between index illness perceptions and first degree relative uptake.

3.0 Plan of Investigation

3.1 Participants

The study sample will be comprised of a convenience sample of 123+ patients with a diagnosis of HCM offered genetic testing at the West of Scotland Inherited Cardiac Diseases (WSICD) clinic at the Queen Elizabeth University Hospital (QEUH) between late July 2018 and April 2019. **Inclusion criteria:** Diagnosis of HCM, age 18+ and consent to allow use of their data for the purposes of the study. **Exclusion criteria:** English language proficiency below level required to understand written information and questionnaires. Individuals considered too vulnerable by clinical team. Those who decline genetic testing.

3.2 Recruitment Procedures

All participants will take part in the quantitative element of the study with a sub-group also taking part in the qualitative element. The recruitment and research procedures are split into two parts detailing procedures for quantitative and qualitative elements separately.

3.2.1 Part one

As part of the WSICD clinic standard procedures patients are invited to attend the clinic by letter after which they received an additional letter requesting demographic data. To obtain informed consent an information sheet will be included in the second letter from the clinic informing prospective participants of the study and notifying them of the option to participate during their appointment at the clinic. This letter will provide a summary of the study including what participation would involve and the overall aims of the research with the option to contact the researcher for further information. Consent to participate in the study will be obtained from participants who indicate interest during their clinic

appointment either by the principle researcher or an appointed member of the clinic staff team who will have received basic training on the study purpose and procedures.

3.2.2 Part two

Participants will be purposively selected to the qualitative element from the broader quantitative sample to obtain a homogenous group. The interview sample will be based on characteristics gathered by the questionnaires, specifically those who indicated low HCM related symptoms/illness identity. Recruitment for this sample will take place following completion of questionnaires when suitable participants will be given the option to also take part in the interview component of the study. Participants that volunteer for this element will be given details of what this section will entail including returning at a later date for a one hour interview.

3.3 Data collection

Data collected will include age, gender, ethnicity, level of education, cardiac symptoms, date HCM diagnosis received, results of HCM genetic testing as well as the number of, and relationship to, frequency of contact with, each first degree relative and the proportion of these that go on to take up genetic testing or attend check up.

3.3.1 Instruments

The **Revised- Illness Perception Questionnaire (IPQ-R)** (Moss-Morris *et al.,* 2002) will be used to measure illness perceptions prior to genetic testing. The instrument is comprised on two main sections: individual's views of their condition and how it was caused. The individual's views section is comprised of 28 items which can be grouped into eight factors focusing on the persons views on: The Identity, Consequences, Personal control, Treatment control, Illness coherence, Timeline cyclical, Timeline acute/chronic and Emotional representations of the condition.

The **Inclusion of others in the self scale (IOS)** (Gächter, Starmer & Tufano, 2015) is a simple visual tool for measuring the perceived closeness of a given relationship. Responses are scored on a scale of one to seven with one representing the least close relationships and seven the closest. The IOS correlates highly with other more time-consuming measures of relationship closeness and is a reliable tool for measuring perceived closeness in relationships.

The **Generalised Self-Efficacy Scale (GSES)** (Schwarzer & Jerusalem, 1995) is a ten item scale that captures an individual's general sense of perceived self-efficacy.

3.4 Design

The study will use a mixed methodology, single centre, cross sectional design.

3.5 Research Procedures

3.5.1 Part one

Informed consent will then be obtained during prospective participant's appointment at the WSICD clinic from either the principle researcher or a trained designated member of the clinic team. This will be done after genetic testing has been offered but prior to actual testing. Following testing patients participating will then be directed to the study questionnaires by the researcher or the designated member of the clinic team who will be on hand to answer queries related to the study. Completion of questionnaires will take place in a private meeting room and should take approximately 10 to 20 minutes. For those not taking part in the interview element of the study this will end their active participation in the study however further data will later be obtained from the clinic to ascertain uptake of genetic testing by their respective first degree relatives.

3.5.2 Part two

Individuals suitable for the qualitative element will be invited to take part in a semi-structured interview at a later date. Those who opt in will be given additional information and asked to sign another consent form. These individuals will be recruited until the desired number of six is achieved. Semi – structured interviews will be used to gain further insight into these individuals' illness beliefs, perceived self-efficacy, family dynamics and experience of health care related to their condition. Interviews will follow a semi-structured guide and will take place at the QEUH lasting approximately 45 minutes.

All of the above proposed recruitment and research procedures have been discussed and provisionally agreed with the WSICD clinic lead.

3.6 Data Analysis

A multiple regression analysis will be used to explore the relationship between the proportion of first degree relatives taking up testing and the index characteristic variables. Predictors included in this analysis will be the eight components of the IPQ-R, GSES score and IOS score. Qualitative data will be analysed using Interpretive Phenomenological Analysis (IPA) which prioritises exploring the individual nature of experiences in combination with acknowledging the researchers interpretation of this facilitating detailed analysis of personal experiences (Smith, Flowers and Larkin, 2009). Identified themes across individual experiences will be cross-checked by a third party with IPA experience ensuring reliability.

3.7 *Justification of sample size*

As the predictive nature of illness perceptions has not yet been studied in this context a conservative estimated medium effect size was used to calculate the required sample size. To ensure the study is a suitably powered (β=.80), with a medium effect size of approximately $f^2 = 0.15$ a sample size of n = 123 will be required for the multiple regression with 10 predictors which will be used in the analysis of the quantitative data. The WSICD clinic is held weekly and sees between 3-8 patients suitable for the study each week. With a recruitment window of 40 weeks this would give a potential pool of between 120 and 320 patients to recruit from. The sample for the IPA analysis component is set at a minimum of six based on guidelines for doctoral research (Smith, Flowers and Larkin, 2009).

3.8 *Settings and Equipment*

Participant information sheet to be included in letter sent from clinic, consent form for quantitative element, clinic staff information sheet and protocol instructions for data collection, consent form for qualitative element and qualitative interview protocol. The research will take place in the WSICD clinic.

4.0 Researcher and Participant Health and Safety Issues

No significant issues anticipated at present. See appendix 6.

5.0 Ethical Issues

The study aims to recruit NHS patients therefore NHS research ethics (NRES) application will be required. Additionally, the study will require approval from the NHS GG&C research and development department. Precautions will be taken to ensure patients are aware participation is optional and that not participating will have no influence on their care.

6.0 Financial Issues Equipment, stationary costs etc.

No significant costs see appendix 5.

7.0 Timetable

Present – May 18	• Developing project proposal, final project proposal due on the 21/05/18. • Developing supporting paperwork & protocols.
May 18 – July 18	• Obtaining ethics
July 18 – April 19	• Data collection and follow up
April 19 – June 19	• Final participants recruited in early April 2019 to allow for follow up.
June 19 – July 19	• Analysis and write up

8.0 Practical Applications

- Identifying whether specific illness perceptions held by the index patient predict the uptake of cascade genetic testing in relatives might inform how or what type of information is given to future index patients and how they are supported to communicate it to relatives.

- Understanding the how illness perceptions interact with the communication of test results could inform changes to the process including developing the ethical debate on the pros and cons of direct and indirect contact with at risk relative by health professionals.

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Appendix 3: *Manuscript submission guidelines to the British Journal of Health Psychology*

AIMS AND SCOPE

The British Journal of Health Psychology publishes original research on all aspects of psychology related to health, health-related behaviour and illness across the lifespan including:

- experimental and clinical research on aetiology
- management of acute and chronic illness
- responses to ill-health
- screening and medical procedures
- psychosocial mediators of health-related behaviours
- influence of emotion on health and health-related behaviours
- psychosocial processes relevant to disease outcomes
- psychological interventions in health and disease
- emotional and behavioural responses to ill health, screening and medical procedures
- psychological aspects of prevention

MANUSCRIPT CATEGORIES AND REQUIREMENTS

The types of paper invited are:

- papers reporting original empirical investigations, using either quantitative or qualitative methods, including reports of interventions in clinical and non-clinical populations;
- theoretical papers which report analyses on established theories in health psychology;
- we particularly welcome review papers, which should aim to provide systematic overviews, evaluations and interpretations of research in a given field of health psychology (narrative reviews will only be considered for editorials or important theoretical discourses); and
- methodological papers dealing with methodological issues of particular relevance to health psychology.

Authors who are interested in submitting papers that do not fit into these categories are advised to contact the editors who would be very happy to discuss the potential submission.

Papers describing quantitative research (including reviews with quantitative analyses) should be no more than 5000 words (excluding the abstract, reference list, tables and figures). Papers describing qualitative research (including reviews with qualitative analyses) should be no more than 6000 words (including quotes, whether in the text or in tables, but excluding the abstract, tables, figures and references). In exceptional cases the Editor retains discretion to publish papers beyond this length where the clear and concise expression of the scientific content requires greater length (e.g., explanation of a new theory or a substantially new method). Authors must contact the Editor prior to submission in such a case.

All systematic reviews must be pre-registered. The pre-registered details should be given in the methods section but blinded for peer review (i.e., 'the review was preregistered at [BLINDED]'); the details can be added at proof stage. Registration documents should be uploaded as title page files when possible, so that they are available to the Editor but not to reviewers.

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The manuscript should be submitted in separate files: title page; statement of contribution; main text file; figures/tables; supporting information.

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For articles containing original scientific research, a structured abstract of up to 250 words should be included with the headings: Objectives, Design, Methods, Results, Conclusions. Review articles should use these headings: Purpose, Methods, Results, Conclusions. As the abstract is often the most widely visible part of your paper, it is important that it conveys succinctly all the most important features of your study. You can save words by writing short, direct sentences. Helpful hints about writing the conclusions to abstracts can be found **here**.

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Acknowledgments

Contributions from anyone who does not meet the criteria for authorship should be listed, with permission from the contributor, in an Acknowledgments section. Financial and material support should also be mentioned. Thanks to anonymous reviewers are not appropriate.

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All authors are required to provide a clear summary of 'what is already known on this subject?' and 'what does this study add?'. Authors should identify existing research knowledge relating to the specific research question and give a summary of the new knowledge added by your study. Under each of these headings, please provide 2-3 (maximum) clear outcome statements (not process statements of what the paper does); the statements for 'what does this study add?' should be presented as bullet points of no more than 100 characters each. The Statement of Contribution should be a separate file.

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- Title
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- Tables and figures (each complete with title and footnotes)
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Supporting information should be supplied as separate files. Tables and figures can be included at the end of the main document or attached as separate files but they must be mentioned in the text.

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Reference examples follow:

Journal article

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Book

Bradley-Johnson, S. (1994). *Psychoeducational assessment of students who are visually impaired or blind: Infancy through high school* (2nd ed.). Austin, TX: Pro-ed.

Internet Document

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Tables should be self-contained and complement, not duplicate, information contained in the text. They should be supplied as editable files, not pasted as images. Legends should be concise but comprehensive – the table, legend, and footnotes must be understandable without reference to the text. All abbreviations must be defined in footnotes. Footnote symbols: †, ‡, §, ¶, should be used (in that order) and *, **, *** should be reserved for P-values. Statistical measures such as SD or SEM should be identified in the headings.

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