EVALUATING A CUSTOM DESIGNED AID TO IMPROVE COMMUNICATION OF GENETIC RESULTS IN FAMILIES WITH HYPERTROPHIC CARDIOMYOPATHY: STUDY PROTOCOL FOR A RANDOMISED CONTROLLED TRIAL

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EVALUATING A CUSTOM DESIGNED AID TO IMPROVE COMMUNICATION OF GENETIC RESULTS IN FAMILIES WITH HYPERTROPHIC CARDIOMYOPATHY: STUDY PROTOCOL FOR A RANDOMISED CONTROLLED TRIAL

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ABSTRACT

Introduction: Genetic testing for hypertrophic cardiomyopathy (HCM) in the era of genomics brings unique challenges for genetic counselling. The number of genes routinely included in an HCM gene panel has increased markedly, many with minimal if any robust evidence of gene-disease association. Subsequently there is a greater chance of uncertain genetic findings. The responsibility of communicating this information with at-risk relatives lies with the index case (proband). We have developed a communication aid to assist with the delivery of genetic results to the proband. We have previously shown the aid is feasible and acceptable, and have now developed a study protocol for a randomised controlled trial of a genetic counsellor-led intervention incorporating the communication aid.

Methods and Analysis: This is a prospective randomised controlled trial. We will investigate the impact of a genetic counsellor-led intervention to return proband gene results using a custom designed communication aid. We aim to improve knowledge and empowerment. The primary outcome of this trial is the ability and confidence of the proband to communicate genetic results to at-risk relatives. Secondary outcomes will assess genetic knowledge, satisfaction with services, outcomes from genetic counselling and psychological adaptation to genetic information.

Ethics and Dissemination: This study has been approved by and is in strict accordance with the Sydney Local Health District Ethics Review Committee (X16-0030; 22/01/2016; version 1). Results from this trial will be prepared as a manuscript and submitted to peer-reviewed journals for publication as well as submission for presentation at national and international meetings.

Registration Details: This trial is registered with the Australian New Zealand Clinical Trials Registry: ACTRN12617000706370

STRENGHTS AND LIMITATIONS

- This study will assess the effectiveness of a communication aid to improve the ability and confidence of patients with hypertrophic cardiomyopathy (HCM) to communicate genetic test results with their at-risk relatives.
- The results of this trial will inform genetic counselling practice for HCM genetic testing, as well as be broadly applicable for other inherited heart diseases.
- Limitations include the generalisability of our findings, which are true for a specialised multidisciplinary clinic where the intervention was performed but may not be representative of the broader HCM population undergoing genetic testing.
- As genomic technologies continue to evolve, uncertainty and complexity of genetic findings will likely increase over time.

INTRODUCTION

Background and rationale

Genetic testing in the era of genomics brings unique challenges for the genetic counselling of families. Hypertrophic cardiomyopathy (HCM) is a clinically heterogeneous inherited heart disease characterised by unexplained left ventricular hypertrophy in the absence of a loading condition such as hypertension.[1] With a prevalence of 1 in 200-500, it is one of the most common inherited heart diseases and clinical manifestations can range from asymptomatic through to heart failure or sudden cardiac death.[2] In the setting of HCM, genetic testing of the index case (proband) can provide invaluable information by allowing at-risk relatives the opportunity to undergo cascade genetic testing to look for the presence or absence of the family-specific variants.[3] The first step is often the most challenging, requiring identification of a variant for which there is sufficient evidence of causation.

Genetic counselling is a critical aspect of the process, not just for genetic testing, but also for understanding inheritance risks, characterisation of the family history and information and emotional support.[4] Within a clinical setting, pre- and post-test genetic counselling should include discussion of inheritance risks and clinical screening guidelines for at-risk relatives.[5] This allows asymptomatic at-risk relatives to make proactive, informed decisions regarding their risk, including family planning decisions.

How a patient understands and communicates this genetic information to their at-risk relatives is critical to ensuring patients' get the most value out of genetic testing. This task of communication relies on the proband within the family. Current Australian practice and privacy laws dictate that in most cases the health care provider does not make contact with relatives to disclose risk information. Therefore, it follows that in order to communicate genetic results or risk information the proband must have adequate understanding of the

information they have received from their healthcare provider. Several studies indicate this may be problematic, and some individuals may not retain or understand the information presented to them.[6]

Existing knowledge

Currently literature estimates between 20-40% of relatives remain unaware of relevant genetic information and do not act on information even when they have reportedly been informed of their risk.[7-9] Many factors have been identified which influence family communication about genetic risk, including complicated family dynamics, guilt, anxiety and gender, however are difficult to target as areas for improvement within the context of one or two genetic counselling sessions.[7 8 10 11] There are stages within the genetic counselling process, where communication of genetic results and uptake of appropriate screening may be influenced.

Our group and others have shown some of the barriers that can negatively impact on family communication. In a qualitative study of HCM patients undergoing comprehensive genetic testing, many patients reported uncertain results to be conveyed less amongst families.[12] Further, these results are often misunderstood. For example, amongst this cohort, probands with uncertain results perceived these results as falsely reassuring or conversely suggests their disease is 'worse' or 'different'. This led to a misunderstanding that their result was not heritable and therefore communication with relatives did not occur.[12] Supporting these findings, the general genetics literature highlights that risk perception and understanding of results though varied, can be poor, inaccurate and incomplete.[13 14]

There is evidence for the effectiveness of a genetic counsellor in addressing some of the communication and knowledge barriers.[15-17] One key area for intervention is during the post-test genetic counselling session. Genetic and risk information can be difficult to understand and explain clearly and as a consequence, the patient may not gain sufficient knowledge and lack confidence to convey these key messages to at-risk relatives.[12] Further, it is recognised patients deliberate on the appropriate time to communicate genetic information and make decisions regarding which relatives the information is pertinent to, regardless of the recommendation of professionals.[7 18 19] Few resources exist which aim to facilitate effective communication to at-risk relatives. We therefore hypothesise that improving knowledge of an HCM genetic diagnosis will have a positive impact on communication to at-risk relatives, as well as genetic knowledge, satisfaction with services, outcomes from genetic counselling and psychological adaptation to genetic information.

Utility of a communication aid

When asked about family communication, most patients report families should communicate risk amongst themselves with varying levels of support from their healthcare providers.[14 17 20] In addition, there is evidence for the effectiveness of genetic counselling to assist with this process.[15 16 20] Hodgson et al. published a randomised controlled trial assessing the impact of a genetic counselling phone intervention on communication of genetic information within families.[21] They found no significant difference between the intervention and control group when measuring contact with genetic services, though in sub-analyses of the high-risk children group, the primary outcome was significantly improved. Importantly, the primary outcome measure was contact with a genetic service, which can be difficult to ascertain and may not be the most accurate measure of effectiveness or a direct reflection of communication efforts.

Resources such as decision and communication aids, or family letters, may provide additional support to this process, though more data is needed regarding efficacy.[15 19 21 22] Decision or communication aids are tools specifically designed to support patients with decision making and unmet information needs. There is evidence for the effectiveness of an aid with regard to improved knowledge and accuracy of risk perceptions.[23-25] Further, most health information is written which may not be the most effective health communication method. Communication and decision aids provide a format to include visual elements that may improve comprehension, recall and comfort with the information, particularly when health literacy may be an issue.

Need for a trial

Overall, the literature highlights that probands require additional support to understand and communicate genetic results. The rationale for this study is the critical gap in supporting patients' comprehension and consequent communication of genetic risk to at-risk relatives. Though genetic counsellors are specifically trained in delivering genetic information, information needs of patients are not always met and communication amongst at-risk relatives can be suboptimal. As genetic test results become increasingly complex, an evidence-based approach to supporting patients with genetic knowledge and risk communication should be explored.

STUDY AIMS AND OUTCOMES

The aim of this randomised controlled trial is to determine if a genetic counsellor-led intervention using a communication aid for the delivery of HCM genetic test results improves the ability and confidence of the proband to communicate genetic results to at-risk relatives compared with current clinical practice.

1. The primary outcome is the ability and confidence of the proband to communicate genetic results to at-risk relatives, measured at 2 weeks post-intervention.

2. Secondary outcomes will assess genetic knowledge, satisfaction with services, patient reported outcome of genetic counselling and psychological adaptation to genetic information, measured at 2 weeks post-intervention.

3. As a longer-term outcome, we will systematically assess and document family communication as reported by the proband measured by phone calls at one, three and six monthly intervals. The researcher conducting these phone calls will not be blinded to the treatment arm of the participant. These phone calls will be conducted and analysed after collection of the primary and secondary outcomes data. This is to prevent interference with results because the phone calls themselves may serve as a family communication intervention.

METHODS AND ANALYSIS

Trial design

This is a prospective randomised controlled trial. The protocol is reported in accordance with the SPIRIT statement, which provides recommendations for a minimum set of scientific, ethical and administrative elements that should be addressed within a clinical trial protocol.[26] All items from the World Health Organization Trial Registration Data Set are listed in Table 1. Consecutive HCM patients will be invited to participate when they are notified on the phone that their genetic result is ready to be returned. Once written consent is obtained they will be randomised to receive their genetic result via the intervention or control arm of the study (Figure 1).

Study setting

This trial will be carried out within a specialised multidisciplinary HCM clinic. This incorporates the expertise of specialist cardiologists and cardiac genetic counsellors.[27] Patients with HCM attending these clinics at Royal Prince Alfred Hospital will be invited to attend.

Eligibility criteria

HCM probands with a genetic result ready for return are eligible. Participants must be aged 18 years or older, with sufficient written English skills as nominated by the participant. Genetic testing is performed as part of a research study, or commercial laboratory as previously published.[28 29] All identified variants are classified in the same manner, as per current clinical standards and guidelines.[30] Recruitment commenced in November 2017 and is expected to end in November 2018. Participants will be invited to participate in the study during their routine pre clinic phone call conducted as normal

clinical process. Informed consent will be obtained by the cardiac genetic counsellor present at the participants clinic consultation (supplementary material).

Randomisation

A randomised list was prepared using the Excel (Microsoft Office) "Random" function and study participants who consent to the study are allocated the next number on the random list. This number is linked to either control or intervention. A researcher not involved in the study performs the randomisation.

Sample size and power calculations

Prior to commencement of the study, power calculations were performed using the results from our published feasibility study.[31] The primary outcome of this trial is the ability and confidence of the proband to communicate genetic results to at-risk relatives. Data from the feasibility study indicated 75% of participants communicated genetic results to at-risk relatives. Assuming the control group communicates in 50% of cases, at a significance level of 5% and 80% statistical power, a sample size of n=21 is required per group.

Development of the custom communication aid

We have developed a communication aid to assist with the delivery of genetic results to the proband and support family communication. A pilot study demonstrating feasibility and acceptability of this aid has been previously reported.[31] In brief, development of the aid involved review of the literature alongside multidisciplinary meetings. Development was a multistep process and on the basis of meeting outcomes, literature review and empirical evidence from the multidisciplinary team. The aid addresses:

1. Genetic test basic background information
2. Possible outcomes of genetic testing

3. Overview of the process involved in classification of a genetic variant
4. Implications for at-risk relatives including family screening recommendations

Control arm

Those within the control arm of the study will receive their result via normal clinical practice. There are currently no evidence-based guidelines for return of comprehensive genetic test results within the multidisciplinary clinic setting. Normal clinical practice typically involves return of a genetic result either by the cardiologist or genetic counsellor. Return of the result is usually performed following clinical cardiology review, which is often the primary purpose of the consult. In the majority of cases a genetic counsellor is present.

Intervention arm

Those randomised to the intervention arm will be allocated a separate appointment time after clinical review with their cardiologist, where they will see the cardiac genetic counsellor who will return their genetic result using the communication aid.

The communication aid covers the process of genetic testing and risk from diagnosis of HCM through to the implications of a genetic result for at-risk relatives (Figure 2). There is a section in the aid under 'Results', which goes through the meaning of each category of genetic result. These include an indeterminate result (no variant identified), a variant of uncertain significance and a likely pathogenic/pathogenic result (Figure 3). The genetic counsellor returning the genetic result will mark the appropriate category of result, which applies to the patient in front of them. The genetic counsellor will return the genetic result, and then go through the communication aid, referencing the individual result and specific recommendations for the rest of the family. There will be an opportunity to ask questions,

and the genetic counsellor will write the specific recommendations for each family member in the box provided at the end of the communication aid (Figure 4).

DATA COLLECTION AND OUTCOMES

Both the primary and secondary outcomes will be measured at a single time point (2-weeks post intervention) using a survey comprised of a number of previously published and validated scales. A number of demographic questions will also be asked within the survey. The survey will be available online via qualtrics (https://www.qualtrics.com/) with a direct link sent to participants. For those who prefer a hard copy it will be posted with a return envelope. The survey will be sent two weeks after return of genetic results. Evidence regarding the most appropriate time between genetic result disclosure and family communication is lacking. However, given the risk of arrhythmia and sudden death within the inherited heart disease context, two weeks post result disclosure was considered by the study team to be an appropriate time point to send the survey.[25] Return of the survey is followed up on a fortnightly basis.

Primary outcome

The primary outcome of this trial is the ability and confidence of the proband to communicate genetic results to at-risk relatives. This will be measured at a single time point, administered two weeks after return of genetic results. Ability and confidence will be assessed by two measures and then combined into a binary outcome. The certainty sub-scale of the Psychological Adaptation to Genetic Information (PAGIS) scale will measure confidence with genetic knowledge.[32] This sub-scale measures the patients' perception and confidence in their genetic knowledge and the items from this sub-scale are listed in Table 2. Subsequent ability to pass this information on will be measured by the number of at-risk relatives informed of genetic results by the proband. We will average the scores

from both measures to determine a final score. The calculations used to determine this cut-off are illustrated in Table 3. The final score will be converted to a binary outcome of fair versus poor ability and confidence to communicate genetic results to at-risk relatives. This outcome has been specifically designed for this study.

Factors that influence communication of genetic results to at-risk relatives are multidimensional. For this reason, we chose this combination approach to more broadly reflect the communication process. Many studies rely on single and linear measures of communication such as contact by relatives with genetics departments or self reported communication with at-risk relatives only. To overcome this, we aimed to incorporate a multidimensional approach that included the probands confidence regarding their knowledge of genetics alongside the action linked to this knowledge, being the communication to relatives. This will aim to determine consistency between the probands confidence with genetic information against their self-reported percentage of immediate family members informed

The certainty sub-scale of the Psychological Adaptation to Genetic Information Scale (PAGIS) will be used to measure confidence with genetic knowledge as described above.[32] Guided by grounded theory in patient perspectives of genetic counselling and the Roy Adaptation to Genetic Information Model, the 26-item PAGIS scale allows for evaluation of the efficacy of genetic counselling.[32 33] The scale aims to incorporate the multidimensional adaptation to genetic information and comprises of five domains which include; a) non-intrusiveness, b) support c) self-worth, d) certainty and e) self-efficacy.[32] Evidence for the utility of this scale has been published and illustrates its potential use for assessing genetic counselling interventions.[32]

Secondary outcomes

The survey comprises three additional scales to assess primary and secondary outcomes, a number of questions regarding communication with relatives, as well as a number of demographic questions.

Genetic knowledge will be assessed using an amended version of the Breast Cancer Genetic Counseling Knowledge Questionnaire (BGKQ).[33 34] This scale was originally developed to assess knowledge of information typically included in genetic counselling for breast cancer. The original scale was a 27 item questionnaire including statements regarding genetics such as '*50% (half) of your genetic information was passed down from your mother'* and participants were asked if the statement was true or false. Items in the original scale were empirically derived from detailed content analysis of breast cancer genetic counselling sessions. The original scale demonstrated a high content validity with cronbachs α = 0.92, with demonstrated ability to discriminate between patients before and after genetic counselling sessions.[34] We have amended questions to reflect the HCM context and 10 items were included.

Satisfaction with services received will be assessed using the widely used Satisfaction with Genetic Counseling Scale (SGCS).[35] The original questionnaire was designed to assess three dimensions of patient satisfaction: instrumental, affective and procedural.[33 35] This survey will use an amended version of the 12 item short form of the survey.

The genetic counselling outcome scale (GCOS-24) will be used to assess patient reported outcomes of genetic counselling.[36] The questionnaire was designed to be used pre and post genetic counselling, though we have used it in the post counselling setting. The

authors of this scale used the construct of empowerment to summarise the patient derived benefits from genetic counselling.

Data management

All data from the survey will be entered into Microsoft Excel. Patient identifiers will be removed with study codes allocated. The primary researcher will be blinded to treatment arm of the patient for analysis of the primary and secondary outcome data. A second senior researcher and supervisor will oversee data storage and analysis. Data will be stored in accordance with the Sydney Local Health District Ethics Review Committee and Centenary Institute.

Data analysis plan

Data will be analysed using Prism (version 7.0) and SPSS (Version 23.0). We will compare the primary outcome as a binary measure between the intervention and control group. We will use chi-square analyses using $p<0.05$ for statistical significance. For assessment of secondary outcomes we will be guided by published scoring systems for the validated scales to score genetics knowledge, satisfaction with services and genetic counselling outcomes. Mean scores for each scale will be compared between the intervention and control group and comparisons between the control and intervention group will be analysed using unpaired t-tests for continuous data and chi-square analysis for categorical data. Sub-group analysis will also be performed; specifically we will compare outcomes in the study groups stratified by the gene result (i.e. causative, uncertain or indeterminate results).

ETHICS AND DISSEMINATION

Ethics

All aspects of the study will be performed according to institutional human research ethics committee approval. This study has been approved by and is in strict accordance with the Sydney Local Health District Ethics Review Committee (X16-0030).

Dissemination

Results from this trial will be prepared as a manuscript and submitted to peer-reviewed journals for publication. In addition, it will form part of the first authors' PhD thesis. Results from the study will be submitted to international and national scientific sessions with the aim of being presented. We will make a copy of the aid available to a wider genetic audience for use in their clinical practice and study data will be available from the authors.

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AUTHOR STATEMENT

All authors contributed to the manuscript, specifically:

(1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work (CB, LY, CS, JI); AND

(2) Drafting the work or revising it critically for important intellectual content (CB, LY, CS, JI); AND

(3) Final approval of the version to be published (CB, LY, CS, JI); AND

(4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved (CB, LY, CS, JI).

REFERENCES

1. Maron BJ, Maron MS, Semsarian C. Genetics of hypertrophic cardiomyopathy after 20 years: clinical perspectives. Journal of the American College of Cardiology 2012;**60**(8):705-15.

2. Semsarian C, Ingles J, Maron MS, et al. New perspectives on the prevalence of hypertrophic cardiomyopathy. J Am Coll Cardiol 2015;**65**(12):1249-54.

3. Ingles J, Burns C, Barratt A, et al. Application of Genetic Testing in Hypertrophic Cardiomyopathy for Preclinical Disease Detection. Circ Cardiovasc Genet 2015;**8**(6):852-9.

4. National Society of Genetic Counselors' Definition Task F, Resta R, Biesecker BB, et al. A new definition of Genetic Counseling: National Society of Genetic Counselors' Task Force report. Journal of genetic counseling 2006;**15**(2):77-83.

5. Semsarian C, Ingles J. A clinical approach to genetic testing for non-specialists. BMJ 2017;**358**:j4101.

6. Burns C, James C, Ingles J. Communication of genetic information to families with inherited rhythm disorders. Heart rhythm 2018;**15**(5):780-86.

7. Burns C, McGaughran J, Davis A, et al. Factors influencing uptake of familial long QT syndrome genetic testing. Am J Med Genet A 2016;**170A**(2):418-25.

8. Christiaans I, Birnie E, Bonsel GJ, et al. Uptake of genetic counselling and predictive DNA testing in hypertrophic cardiomyopathy. Eur J Hum Genet 2008;**16**(10):1201-7.

9. Gaff CL, Clarke AJ, Atkinson P, et al. Process and outcome in communication of genetic information within families: a systematic review. European journal of human genetics. 2007;**15**(10):999-1011.

10. Claes E, Evers-Kiebooms G, Boogaerts A, et al. Communication with close and distant relatives in the context of genetic testing for hereditary breast and ovarian cancer in cancer patients. American journal of medical genetics Part A 2003;**116A**(1):11-9.

11. Barsevick AM, Montgomery SV, Ruth K, et al. Intention to communicate BRCA1/BRCA2 genetic test results to the family. Journal of family psychology. 2008;**22**(2):303-12.

12. Burns C, Yeates L, Spinks C, et al. Attitudes, knowledge and consequences of uncertain genetic findings in hypertrophic cardiomyopathy. Eur J Hum Genet 2017;**25**(7):809-15.

13. Patenaude AF, Tung N, Ryan PD, et al. Young adult daughters of BRCA1/2 positive mothers: what do they know about hereditary cancer and how much do they worry? Psycho-oncology 2013;**22**(9):2024-31.

14. Young AL, Butow PN, Vetsch J, et al. Family Communication, Risk Perception and Cancer Knowledge of Young Adults from BRCA1/2 Families: a Systematic Review. Journal of genetic counseling 2017;**26**(6):1179-96.

15. Forrest LE, Burke J, Bacic S, et al. Increased genetic counseling support improves communication of genetic information in families. Genetics in medicine : official journal of the American College of Medical Genetics 2008;**10**(3):167-72.

16. Fiallos K, Applegate C, Mathews DJ, et al. Choices for return of primary and secondary genomic research results of 790 members of families with Mendelian disease. European journal of human genetics. 2017;**25**(5):530-37.

17. Forrest K, Simpson SA, Wilson BJ, et al. To tell or not to tell: barriers and facilitators in family communication about genetic risk. Clinical genetics 2003;**64**(4):317-26.

18. Montgomery SV, Barsevick AM, Egleston BL, et al. Preparing individuals to communicate genetic test results to their relatives: report of a randomized control trial. Fam Cancer 2013;**12**(3):537-46.

19. Seymour KC, Addington-Hall J, Lucassen AM, et al. What Facilitates or Impedes Family Communication Following Genetic Testing for Cancer Risk? A Systematic Review and Meta-Synthesis of Primary Qualitative Research. Journal of genetic counseling 2010;**19**(4):330-42.

20. Healey E, Taylor N, Greening S, et al. Quantifying family dissemination and identifying barriers to communication of risk information in Australian BRCA families. Genetics in medicine. 2017;**19**(12):1323-31.

21. Hodgson J, Metcalfe S, Gaff C, et al. Outcomes of a randomised controlled trial of a complex genetic counselling intervention to improve family communication. European journal of human genetics. 2016;**24**(3):356-60.

22. Suthers GK, Armstrong J, McCormack J, et al. Letting the family know: balancing ethics and effectiveness when notifying relatives about genetic testing for a familial disorder. Journal of medical genetics 2006;**43**(8):665-70.

23. Stacey D, Legare F, Lewis K, et al. Decision aids for people facing health treatment or screening decisions. Cochrane Db Syst Rev 2017(4).

24. Wakefield CE, Meiser B, Homewood J, et al. Development and pilot testing of two decision aids for individuals considering genetic testing for cancer risk. Journal of genetic counseling 2007;**16**(3):325-39.

25. Vavolizza RD, Kalia I, Aaron KE, et al. Disclosing Genetic Information to Family Members About Inherited Cardiac Arrhythmias: An Obligation or a Choice? Journal of genetic counseling 2015;**24**(4):608-15.

26. Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Annals of internal medicine 2013;**158**(3):200-7.

27. Ingles J, Lind JM, Phongsavan P, et al. Psychosocial impact of specialized cardiac genetic clinics for hypertrophic cardiomyopathy. Genet Med 2008;**10**(2):117-20.

28. Bagnall RD, Weintraub RG, Ingles J, et al. A Prospective Study of Sudden Cardiac Death among Children and Young Adults. New Engl J Med 2016;**374**(25):2441-52.

29. Burns C, Bagnall RD, Lam L, et al. Multiple Gene Variants in Hypertrophic Cardiomyopathy in the Era of Next-Generation Sequencing. Circ Cardiovasc Genet 2017;**10**(4).

30. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genetics in Medicine 2015;**17**(5):405-24.

31. Smagarinsky Y, Burns C, Spinks C, et al. Development of a communication aid for explaining hypertrophic cardiomyopathy genetic test results. Pilot Feasibility Stud 2017;**3**:53.

32. Read CY, Perry DJ, Duffy ME. Design and psychometric evaluation of the Psychological Adaptation to Genetic Information Scale. J Nurs Scholarsh 2005;**37**(3):203-8.

33. Kasparian NA, Wakefield CE, Meiser B. Assessment of psychosocial outcomes in genetic counseling research: an overview of available measurement scales. Journal of genetic counseling 2007;**16**(6):693-712.

34. Erblich J, Brown K, Kim YM, et al. Development and validation of a breast cancer genetic counseling knowledge questionnaire. Patient Educ Couns 2005;**56**(2):182-91.

35. Shiloh S, Avdor O, Goodman RM. Satisfaction with genetic counseling: dimensions and measurement. American journal of medical genetics 1990;**37**(4):522-9.

36. McAllister M, Wood AM, Dunn G, et al. The Genetic Counseling Outcome Scale: a new patient-reported outcome measure for clinical genetics services. Clinical genetics 2011;**79**(5):413-24.

Table 1: Trial Registration Data	
Primary registry and trial identifying number	Australian New Zealand Clinical Trials Registry: ACTRN12617000706370
Date of registration in primary registry	17/05/2017
Secondary identifying numbers	NA
Source(s) of monetary or material support	National Heart Foundation of Australia
Primary sponsor	The University of Sydney
Secondary sponsor	NA
Contact for public queries	Dr Jodie Ingles j.ingles@centenary.org.au
Contact for scientific queries	Dr Jodie Ingles j.ingles@centenary.org.au
Public title	Use of an aid to improve communication of genetic risk information to families with hypertrophic cardiomyopathy (HCM)
Scientific title	Use of a custom designed aid to improve communication of genetic results in families with HCM
Countries of recruitment	Australia
Health condition (s) or problem (s) studied	HCM
Intervention	Use of a custom designed aid to communicate HCM genetic test results
Key inclusion and exclusion criteria	HCM probands with a genetic result ready for return Participants must be aged 18 years or older Sufficient written English skills as nominated by the participant
Study type	Prospective randomised controlled trial
Date of first enrolment	25/11/2016
Target sample size	45
Recruitment status	Recruiting
Primary outcome (s)	Ability and confidence of the proband to communicate genetic results to at-risk relatives
Key secondary outcomes	Secondary outcomes will assess genetic knowledge, satisfaction with services, outcomes from genetic counselling and psychological adaptation to genetic information

Table 2: Certainty sub-scale of the PAGIS scale
1. I understand how I came to have hypertrophic cardiomyopathy
2. I understand the health risks my relatives face because of hypertrophic cardiomyopathy
3. I feel certain that I understand the meaning of having hypertrophic cardiomyopathy
4. I understand the chances I have of passing hypertrophic cardiomyopathy along to my children
5. I feel that I can explain to other people what having hypertrophic cardiomyopathy means
6. I feel confused because I have been given different explanations of what having hypertrophic cardiomyopathy means

Abbreviations: PAGIS = Psychological Adaptation to Genetic Information Scale.

Table 3: Primary outcome measure converted to a primary outcome

Measures incorporated

1. Certainty sub scale from PAGIS (measuring confidence)
2. Adult first degree relatives informed of genetic risk (measuring ability)

Calculation examples

Example 1:

Certainty score from PAGIS sub scale = 18/36= 0.5

Relatives informed of risk = 3/6= 0.5

= (0.5 + 0.5 = 1) / 2= 0.5

= 50%

Therefore this participant falls into the 'poor communication' category of the primary outcome

Example 2:

Certainty score from PAGIS sub scale = 30/36= 0.83

Relatives informed of risk = 7/8= 0.88

(0.88+ 0.83) / 2= 0.86

= 86%
Therefore this participant falls into the 'fair communication' category of this primary outcome

Abbreviations: PAGIS = Psychological Adaptation to Genetic Information Scale.

FIGURE LEGENDS

FIGURE 1: Flow chart of overall study design

FIGURE 2: Example page from communication aid: Genetic testing step by step

FIGURE 3: Example page from communication aid: What is my genetic result?

FIGURE 4: Example page from communication aid: Family-screening guidelines

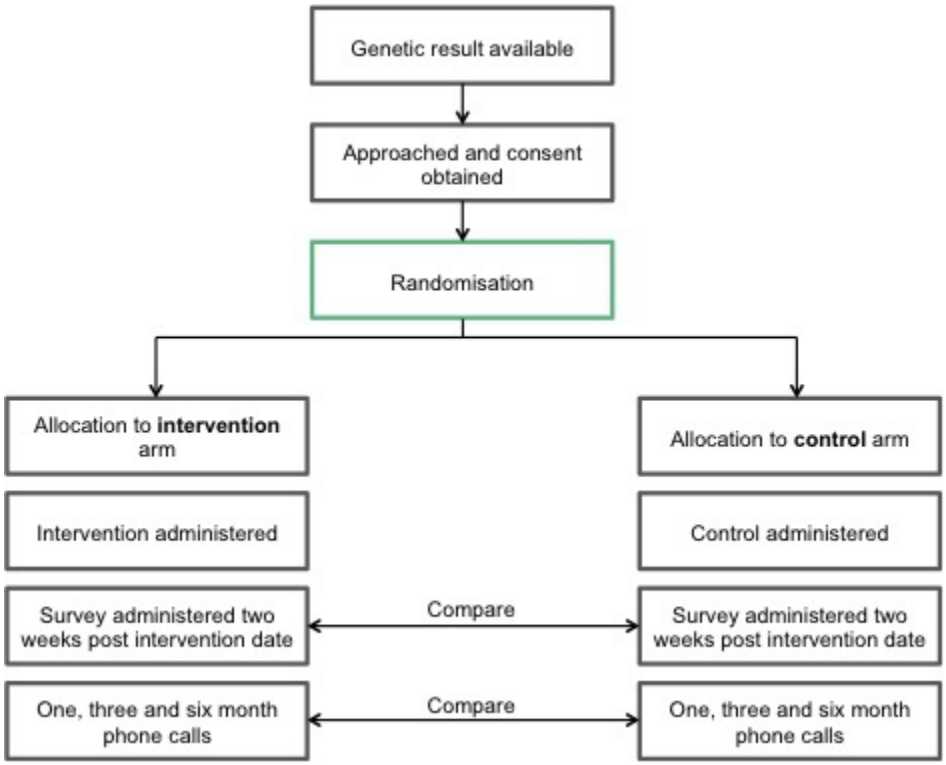

FIGURE 1: Flow chart of overall study design

165x133mm (72 x 72 DPI)

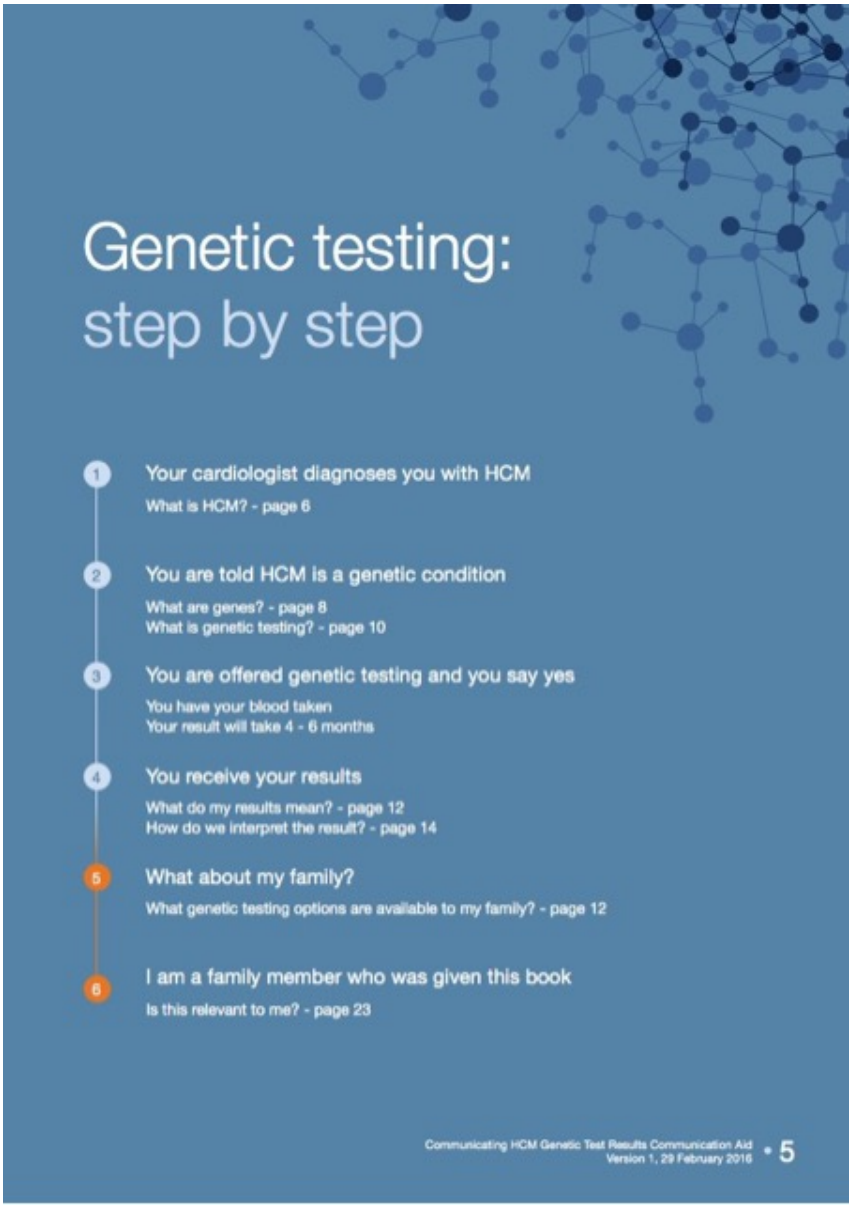

FIGURE 2: Example page from communication aid: Genetic testing step by step

159x225mm (72 x 72 DPI)

FIGURE 3

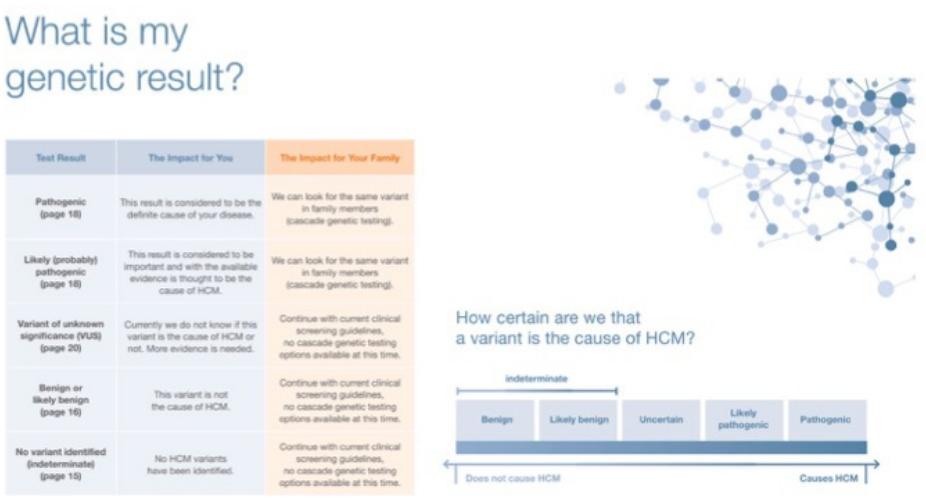

FIGURE 3: Example page from communication aid: What is my genetic result?

254x190mm (72 x 72 DPI)

FIGURE 4: Example page from communication aid: Family-screening guidelines

245x145mm (72 x 72 DPI)

Communicating Hypertrophic Cardiomyopathy (HCM) Genetic Test Results

INFORMATION FOR PARTICIPANTS

Introduction

You are invited to take part in a research study examining how we can best communicate genetic test results in hypertrophic cardiomyopathy (HCM). Genetic testing for genetic heart diseases like HCM has become increasingly complex and our method of explaining these results needs to evolve to meet these changing needs. Cardiac genetic counsellors coordinate the genetic testing process and they play a key role in ensuring the information you are receiving is clear and meaningful for you and your family. The objective of this study is to compare the effectiveness of an intervention aimed at improving the way we communicate genetic test result information with our current usual care. If you consent to the study, you will be randomly assigned to either the new communication intervention or to usual care.

Individuals with hypertrophic cardiomyopathy are eligible to participate in this study if they are the first in their family to have genetic testing. People aged 16 years or older are eligible to participate; however children younger than this are excluded.

The study is being conducted by Dr Jodie Ingles, Prof Christopher Semsarian, Ms Laura Yeates and Ms Charlotte Burns from the Molecular Cardiology Research Program, Centenary Institute and Royal Prince Alfred Hospital Sydney.

Study Procedures

If you agree to participate in this study, you will be asked to complete the participant consent form. You will then be randomly allocated to one of two groups, to receive your genetic test result. Two weeks after your genetic test result appointment, you will be asked to complete a survey *(either paper or online)*, asking about your understanding of genetic testing for HCM. This survey will take between 10-20 minutes to complete.

In addition, the researchers would like to phone you at one, three and six month intervals to follow up with you after you receive your genetic result. These phone calls will take approximately 10 minutes and will be conducted at a time that suits you.

Researchers will have access to your medical record to obtain information relevant to this study. Information about you may also be sought from the *Australian Genetic Heart Disease Registry*, if you have enrolled (www.heartregistry.org.au).
Confidentiality of the survey responses will be paramount. Your name will be replaced with a unique code and only Dr Jodie Ingles will have access to the true identity of respondents.

No additional genetic testing will be carried out as part of this study.

Information collected about you will be securely stored.

Benefits

While we intend that this research study furthers medical knowledge and may improve management of genetic heart diseases in the future, it may not be of direct benefit to you.

Voluntary Participation

Participation in this study is entirely voluntary. You do not have to take part in it. If you do take part, you can withdraw at any time without having to give a reason. Whatever your decision, please be assured that it will not affect your medical treatment or your relationship with the staff who are caring for you.

Confidentiality

All of the information collected from you for the study will be treated confidentially, and only the researchers named above will have access to it. The study results may be presented at a conference or in a scientific publication, but individual participants will not be identifiable in such a presentation.

Any forms completed online, including the participant consent form and survey will be extremely secure to maintain participant privacy.

Further Information

When you have read this information, one of the investigators is available to discuss it with you further and answer any questions you may have. If you would like to know more at any stage, please feel free to contact:

Dr Jodie Ingles
Molecular Cardiology Research Program
Centenary Institute
Locked Bag No 6, Newtown NSW 2042
Ph. 02 9565 6293
Email. j.ingles@centenary.org.au Web. www.heartregistry.org.au

This information sheet is for you to keep.

Ethics Approval and Complaints

This study has been approved by the Ethics Review Committee (RPAH Zone) of the Sydney Local Health District. Any person with concerns or complaints about the conduct of this study should contact the Executive Officer on 02 9515 6766 and quote protocol number X16-0030.

Communicating Hypertrophic Cardiomyopathy (HCM) Genetic Test Results

PARTICIPANT CONSENT FORM

I, ... *[name]*

of

.....*[address]*

.....*[email]*

have read and understood the Information for Participants on the abovenamed research study

and have discussed the study with .....

I have been made aware of the procedures involved in the study.

I understand that my participation in this study will allow the researchers to have access to my medical record, including information held by the Australian Genetic Heart Disease Registry (if I am enrolled), and I agree to this.

I freely choose to participate in this study and understand that I can withdraw at any time.

I also understand that the research study is strictly confidential.

I hereby agree to participate in this research study.

NAME: .....

SIGNATURE: .....

DATE: .....

NAME OF WITNESS: .....

SIGNATURE OF WITNESS: .....

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	**1**
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	**2, Table 1**
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	**9, Table 1**
Protocol version	#3	Date and version identifier	**1**
Funding	#4	Sources and types of financial, material, and other support	**18**
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	**1, 18**
Roles and	#5b	Name and contact information for the trial	**NA- No trial sponsor.**

responsibilities: sponsor contact information		sponsor	
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	**NA- no role other than funding for key researchers.**
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	**NA**
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	**4**
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	11
Objectives	#7	Specific objectives or hypotheses	**7,8**
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	**9**
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	**9**

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	**9**
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	**11**
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	**NA**
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	**NA- intervention was one clinic appointment**
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	**NA**
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	**12,13,14**
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	**8, Figure 1**

Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	**10**
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	**9**
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	**9,10**
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	**9,10**
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	**9,10**
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	**15**
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	**NA- researcher will be blinded to treatment arm for analysis only, however researchers will not be blinded during intervention**

			because of nature of intervention.
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	**12,13,14, Table 2, Figure 2, Figure 3, Figure 4**
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	**15**
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	**15**
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	**16**
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	**16**
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical	**NA- not relevant to study design.**

		methods to handle missing data (eg, multiple imputation)	
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	**NA- not relevant, no data monitoring committee.**
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	**NA- no interim analysis.**
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	**NA**
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	**NA**
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	**15**
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	**NA- No protocol modifications will be made.**
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or	**9**

		authorised surrogates, and how (see Item 32)	
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	**NA**
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	**16**
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	**1**
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	**16/17**
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	**NA**
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	**16/17**
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	**18**
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	**17**
Informed consent	#32	Model consent form and other related	**Supplementary material**

materials		documentation given to participants and authorised surrogates	
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	**NA**

EVALUATING A CUSTOM DESIGNED AID TO IMPROVE COMMUNICATION OF GENETIC RESULTS IN FAMILIES WITH HYPERTROPHIC CARDIOMYOPATHY: STUDY PROTOCOL FOR A RANDOMISED CONTROLLED TRIAL

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EVALUATING A CUSTOM DESIGNED AID TO IMPROVE COMMUNICATION OF GENETIC RESULTS IN FAMILIES WITH HYPERTROPHIC CARDIOMYOPATHY: STUDY PROTOCOL FOR A RANDOMISED CONTROLLED TRIAL

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Total word count: 3097 (not including abstract or references)

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NO DISCLOSURES

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ABSTRACT

Introduction: Genetic testing for hypertrophic cardiomyopathy (HCM) in the era of genomics brings unique challenges for genetic counselling. The number of genes routinely included in an HCM gene panel has increased markedly, many with minimal if any robust evidence of gene-disease association. Subsequently there is a greater chance of uncertain genetic findings. The responsibility of communicating this information with at-risk relatives lies with the index case (proband). We have developed a communication aid to assist with the delivery of genetic results to the proband. We have previously shown the aid is feasible and acceptable, and have now developed a study protocol for a randomised controlled trial of a genetic counsellor-led intervention incorporating the communication aid.

Methods and Analysis: This is a prospective randomised controlled trial. We will investigate the impact of a genetic counsellor-led intervention to return proband gene results using a custom designed communication aid. We aim to improve knowledge and empowerment. The primary outcome of this trial is the ability and confidence of the proband to communicate genetic results to at-risk relatives. Secondary outcomes will assess genetic knowledge, satisfaction with services, outcomes from genetic counselling and psychological adaptation to genetic information.

Ethics and Dissemination: This study has been approved by and is in strict accordance with the Sydney Local Health District Ethics Review Committee (X16-0030; 22/01/2016; version 1). Results from this trial will be prepared as a manuscript and submitted to peer-reviewed journals for publication as well as submission for presentation at national and international meetings.

Registration Details: This trial is registered with the Australian New Zealand Clinical Trials Registry: ACTRN12617000706370

STRENGHTS AND LIMITATIONS

- This study will assess the effectiveness of a communication aid to improve the ability and confidence of patients with hypertrophic cardiomyopathy (HCM) to communicate genetic test results with their at-risk relatives.
- The results of this trial will inform genetic counselling practice for HCM genetic testing, as well as be broadly applicable for other inherited heart diseases.
- Limitations include the generalisability of our findings, which are true for a specialised multidisciplinary clinic where the intervention was performed but may not be representative of the broader HCM population undergoing genetic testing.
- As genomic technologies continue to evolve, uncertainty and complexity of genetic findings will likely increase over time.

INTRODUCTION

Background and rationale

Genetic testing in the era of genomics brings unique challenges for the genetic counselling of families. Hypertrophic cardiomyopathy (HCM) is a clinically heterogeneous inherited heart disease characterised by unexplained left ventricular hypertrophy in the absence of a loading condition such as hypertension.[1] With a prevalence of 1 in 200-500, it is one of the most common inherited heart diseases and clinical manifestations can range from asymptomatic through to heart failure or sudden cardiac death.[2] In the setting of HCM, genetic testing of the index case (proband) can provide invaluable information by allowing at-risk relatives the opportunity to undergo cascade genetic testing to look for the presence or absence of the family-specific variants.[3] The first step is often the most challenging, requiring identification of a variant for which there is sufficient evidence of causation.

Genetic counselling is a critical aspect of the process, not just for genetic testing, but also for understanding inheritance risks, characterisation of the family history and information and emotional support.[4] Within a clinical setting, pre- and post-test genetic counselling should include discussion of inheritance risks and clinical screening guidelines for at-risk relatives.[5] This allows asymptomatic at-risk relatives to make proactive, informed decisions regarding their risk, including family planning decisions.

How a patient understands and communicates this genetic information to their at-risk relatives is critical to ensuring patients' get the most value out of genetic testing. This task of communication relies on the proband within the family. Current Australian practice and privacy laws dictate that in most cases the health care provider does not make contact with relatives to disclose risk information. Therefore, it follows that in order to communicate genetic results or risk information the proband must have adequate understanding of the

information they have received from their healthcare provider. Several studies indicate this may be problematic, and some individuals may not retain or understand the information presented to them.[6]

Existing knowledge

Currently literature estimates between 20-40% of relatives remain unaware of relevant genetic information and do not act on information even when they have reportedly been informed of their risk.[7-9] Many factors have been identified which influence family communication about genetic risk, including complicated family dynamics, guilt, anxiety and gender, however are difficult to target as areas for improvement within the context of one or two genetic counselling sessions.[7 8 10 11] There are stages within the genetic counselling process, where communication of genetic results and uptake of appropriate screening may be influenced.

Our group and others have shown some of the barriers that can negatively impact on family communication. In a qualitative study of HCM patients undergoing comprehensive genetic testing, many patients reported uncertain results to be conveyed less amongst families.[12] Further, these results are often misunderstood. For example, amongst this cohort, probands with uncertain results perceived these results as falsely reassuring or conversely suggests their disease is 'worse' or 'different'. This led to a misunderstanding that their result was not heritable and therefore communication with relatives did not occur.[12] Supporting these findings, the general genetics literature highlights that risk perception and understanding of results though varied, can be poor, inaccurate and incomplete.[13 14]

There is evidence for the effectiveness of a genetic counsellor in addressing some of the communication and knowledge barriers.[15-17] One key area for intervention is during the post-test genetic counselling session. Genetic and risk information can be difficult to understand and explain clearly and as a consequence, the patient may not gain sufficient knowledge and lack confidence to convey these key messages to at-risk relatives.[12] Further, it is recognised that patients deliberate on the appropriate time to communicate genetic information and make decisions regarding which relatives the information is pertinent to, regardless of the recommendation of professionals.[7 18 19] Few resources exist which aim to facilitate effective communication to at-risk relatives. We therefore hypothesise that improving knowledge of an HCM genetic diagnosis will have a positive impact on communication to at-risk relatives, as well as genetic knowledge, satisfaction with services, outcomes from genetic counselling and psychological adaptation to genetic information.

Utility of a communication aid

When asked about family communication, most patients report families should communicate risk amongst themselves with varying levels of support from their healthcare providers.[14 17 20] In addition, there is evidence for the effectiveness of genetic counselling to assist with this process.[15 16 20] Hodgson et al. published a randomised controlled trial assessing the impact of a genetic counselling phone intervention on communication of genetic information within families.[21] They found no significant difference between the intervention and control group when measuring contact with genetic services, though in sub-analyses of the high-risk children group, the primary outcome was significantly improved. Importantly, the primary outcome measure was contact with a genetic service, which can be difficult to ascertain and may not be the most accurate measure of effectiveness or a direct reflection of communication efforts.

Resources such as decision and communication aids, or family letters, may provide additional support to this process, though more data is needed regarding efficacy.[15 19 21 22] Decision or communication aids are tools specifically designed to support patients with decision making and unmet information needs. There is evidence for the effectiveness of an aid with regard to improved knowledge and accuracy of risk perceptions.[23-25] Further, most health information is written which may not be the most effective health communication method. Communication and decision aids provide a format to include visual elements that may improve comprehension, recall and comfort with the information, particularly when health literacy may be an issue.

Need for a trial

Overall, the literature highlights that probands require additional support to understand and communicate genetic results. The rationale for this study is the critical gap in supporting patients' comprehension and consequent communication of genetic risk to at-risk relatives. Though genetic counsellors are specifically trained in delivering genetic information, information needs of patients are not always met and communication amongst at-risk relatives can be suboptimal. As genetic test results become increasingly complex, an evidence-based approach to supporting patients with genetic knowledge and risk communication should be explored.

STUDY AIMS AND OUTCOMES

The aim of this randomised controlled trial is to determine if a genetic counsellor-led intervention using a communication aid for the delivery of HCM genetic test results improves the ability and confidence of the proband to communicate genetic results to at-risk relatives compared with current clinical practice.

1. The primary outcome is the ability and confidence of the proband to communicate genetic results to at-risk relatives, measured at 2 weeks post-intervention.

2. Secondary outcomes will assess genetic knowledge, satisfaction with services, patient reported outcome of genetic counselling and psychological adaptation to genetic information, measured at 2 weeks post-intervention.

3. As a longer-term outcome, we will systematically assess and document family communication as reported by the proband measured by phone calls at one, three and six monthly intervals. The researcher conducting these phone calls will not be blinded to the treatment arm of the participant. During these phone calls a series of questions regarding family communication and uptake of family screening will be asked of the proband. These phone calls will be conducted and analysed after collection of the primary and secondary outcomes data. This is to prevent interference with results because the phone calls themselves may serve as a family communication intervention. A phone script to be used as a guide for these phone calls is available in the supplementary material.

METHODS AND ANALYSIS

Trial design

This is a prospective randomised controlled trial. The protocol is reported in accordance with the SPIRIT statement, which provides recommendations for a minimum set of scientific, ethical and administrative elements that should be addressed within a clinical trial protocol.[26] All items from the World Health Organization Trial Registration Data Set are listed in Table 1. Consecutive HCM patients will be invited to participate when they are notified on the phone that their genetic result is ready to be returned. Once written consent is obtained they will be randomised to receive their genetic result via the intervention or control arm of the study (Figure 1).

Study setting

This trial will be carried out within a specialised multidisciplinary HCM clinic. This incorporates the expertise of specialist cardiologists and cardiac genetic counsellors.[27] Patients with HCM attending these clinics at Royal Prince Alfred Hospital will be invited to attend.

Eligibility criteria

HCM probands with a genetic result ready for return are eligible. HCM probands are defined as the first person in the family to undergo genetic testing for HCM. Probands include those with and without a family history of disease provided genetic testing has been ordered. Participants must be aged 16 years or older, with sufficient written English skills as nominated by the participant. Genetic testing is performed as part of a research study, or commercial laboratory as previously published.[28] [29] All identified variants are classified in the same manner, as per current clinical standards and guidelines.[30] Recruitment commenced in November 2017 and is expected to end in November 2018.

Participants will be invited to participate in the study during their routine pre clinic phone call conducted as normal clinical process. Informed consent will be obtained by the cardiac genetic counsellor present at the participants clinic consultation (supplementary material).

Randomisation

A randomised list was prepared using the Excel (Microsoft Office) "Random" function and study participants who consent to the study are allocated the next number on the random list. This number is linked to either control or intervention. A researcher not involved in the study performs the randomisation.

Sample size and power calculations

Prior to commencement of the study, power calculations were performed using the results from our published feasibility study.[31] The primary outcome of this trial is the ability and confidence of the proband to communicate genetic results to at-risk relatives. Data from the feasibility study indicated 75% of participants communicated genetic results to at-risk relatives. Assuming the control group communicates in 50% of cases, at a significance level of 5% and 80% statistical power, a sample size of n=21 is required per group.

Development of the custom communication aid

We have developed a communication aid to assist with the delivery of genetic results to the proband and support family communication. A pilot study demonstrating feasibility and acceptability of this aid has been previously reported.[31] In brief, development of the aid involved review of the literature alongside multidisciplinary meetings. Development was a multistep process and on the basis of meeting outcomes, literature review and empirical evidence from the multidisciplinary team. The aid addresses:

1. Genetic test basic background information

2. Possible outcomes of genetic testing
3. Overview of the process involved in classification of a genetic variant
4. Implications for at-risk relatives including family screening recommendations

Control arm

Those within the control arm of the study will receive their result via normal clinical practice. There are currently no evidence-based guidelines for return of comprehensive genetic test results within the multidisciplinary clinic setting. Normal clinical practice typically involves return of a genetic result either by the cardiologist or genetic counsellor. Return of the result is usually performed following clinical cardiology review, which is often the primary purpose of the consult. In the majority of cases a genetic counsellor is present.

Intervention arm

Those randomised to the intervention arm will be allocated a separate appointment time after clinical review with their cardiologist, where they will see the cardiac genetic counsellor who will return their genetic result using the communication aid.

The communication aid covers the process of genetic testing and risk from diagnosis of HCM through to the implications of a genetic result for at-risk relatives (Figure 2). There is a section in the aid under 'Results', which goes through the meaning of each category of genetic result. These include an indeterminate result (no variant identified), a variant of uncertain significance and a likely pathogenic/pathogenic result (Figure 3). The genetic counsellor returning the genetic result will mark the appropriate category of result, which applies to the patient in front of them. The genetic counsellor will return the genetic result, and then go through the communication aid, referencing the individual result and specific recommendations for the rest of the family. There will be an opportunity to ask questions,

and the genetic counsellor will write the specific recommendations for each family member in the box provided at the end of the communication aid (Figure 4).

Patient and Public Involvement

Development of this research question and outcome measures were informed by clinical experience of the authors in a specialised clinic setting, as well as published research identifying gaps in communication with relatives. Specifically, there are known challenges associated with understanding and subsequent communication of genetic information to relatives. We have shown poor understanding, recall, and communication of genetic results amongst HCM probands.[7 12] Prior to implementation and development of this trial, a pilot study involving patients was conducted, incorporating patient preference and needs allowing development of both the communication aid and the study protocol.[31] Results will be disseminated to patients in the form of a research participant newsletter on completion of the study. In addition, those randomised to the control arm will receive a copy of the communication aid. Patients provided written consent to participate in the study, with an understanding of the requirements of the study. These were not considered by the patients or study team to be burdensome for the patients participating in the study.

DATA COLLECTION AND OUTCOMES

Both the primary and secondary outcomes will be measured at a single time point (2-weeks post intervention) using a survey comprised of a number of previously published and validated scales. A number of demographic questions will also be asked within the survey. The survey will be available online via qualtrics (https://www.qualtrics.com/) with a direct link sent to participants. For those who prefer a hard copy it will be posted with a return envelope. The survey will be sent two weeks after return of genetic results. Evidence regarding the most appropriate time between genetic result disclosure and family

communication is lacking. However, given the risk of arrhythmia and sudden death within the inherited heart disease context, two weeks post result disclosure was considered by the study team to be an appropriate time point to send the survey.[25] Return of the survey is followed up on a fortnightly basis.

Primary outcome

The primary outcome of this trial is the ability and confidence of the proband to communicate genetic results to at-risk relatives. This will be measured at a single time point, administered two weeks after return of genetic results. Ability and confidence will be assessed by two measures and then combined into a binary outcome. The certainty sub-scale of the Psychological Adaptation to Genetic Information (PAGIS) scale will measure confidence with genetic knowledge.[32] This sub-scale measures the patients' perception and confidence in their genetic knowledge and the items from this sub-scale are listed in Table 2. Subsequent ability to pass this information on will be measured by the number of at-risk relatives informed of genetic results by the proband. We will average the scores from both measures to determine a final score. The calculations used to determine this cut-off are illustrated in Table 3.

In summary, we will calculate the total PAGIS certainty sub-scale score (denominator of 36). This will be added to the total number of relatives informed over the total number of relatives at risk. This number will then be converted to a percentage. The final score will be converted to a binary outcome of fair versus poor ability and confidence to communicate genetic results to at-risk relatives. A cut-off of ≥75% will be used to indicate fair communication, based on data indicating 20-40% of relatives are not informed of their genetic risk. This outcome has been specifically designed for this study.

Factors that influence communication of genetic results to at-risk relatives are multidimensional. For this reason, we chose this combination approach to more broadly reflect the communication process. Many studies rely on single and linear measures of communication such as contact by relatives with genetics departments or self reported communication with at-risk relatives only. To overcome this, we aimed to incorporate a multidimensional approach that included the probands confidence regarding their knowledge of genetics alongside the action linked to this knowledge, being the communication to relatives. This will aim to determine consistency between the probands confidence with genetic information against their self-reported percentage of immediate family members informed

The certainty sub-scale of the Psychological Adaptation to Genetic Information Scale (PAGIS) will be used to measure confidence with genetic knowledge as described above.[32] Guided by grounded theory in patient perspectives of genetic counselling and the Roy Adaptation to Genetic Information Model, the 26-item PAGIS scale allows for evaluation of the efficacy of genetic counselling.[32 33] The scale aims to incorporate the multidimensional adaptation to genetic information and comprises of five domains which include; a) non-intrusiveness, b) support c) self-worth, d) certainty and e) self-efficacy.[32] Evidence for the utility of this scale has been published and illustrates its potential use for assessing genetic counselling interventions.[32]

Secondary outcomes

The survey comprises three additional scales to assess primary and secondary outcomes, a number of questions regarding communication with relatives, as well as a number of demographic questions.

Genetic knowledge will be assessed using an amended version of the Breast Cancer Genetic Counseling Knowledge Questionnaire (BGKQ).[33 34] This scale was originally developed to assess knowledge of information typically included in genetic counselling for breast cancer. The original scale was a 27 item questionnaire including statements regarding genetics such as '*50% (half) of your genetic information was passed down from your mother*' and participants were asked if the statement was true or false. Items in the original scale were empirically derived from detailed content analysis of breast cancer genetic counselling sessions. The original scale demonstrated a high content validity with cronbachs α = 0.92, with demonstrated ability to discriminate between patients before and after genetic counselling sessions.[34] We have amended questions to reflect the HCM context and 10 items were included.

Satisfaction with services received will be assessed using the widely used Satisfaction with Genetic Counseling Scale (SGCS).[35] The original questionnaire was designed to assess three dimensions of patient satisfaction: instrumental, affective and procedural.[33 35] This survey will use an amended version of the 12 item short form of the survey.

The genetic counselling outcome scale (GCOS-24) will be used to assess patient reported outcomes of genetic counselling.[36] The questionnaire was designed to be used pre and post genetic counselling, though we have used it in the post counselling setting. The authors of this scale used the construct of empowerment to summarise the patient derived benefits from genetic counselling.

Data management

All data from the survey will be entered into Microsoft Excel. Patient identifiers will be removed with study codes allocated. The primary researcher will be blinded to treatment

arm of the patient for analysis of the primary and secondary outcome data. A second senior researcher and supervisor will oversee data storage and analysis. Data will be stored in accordance with the Sydney Local Health District Ethics Review Committee and Centenary Institute.

Data analysis plan

Data will be analysed using Prism (version 7.0) and SPSS (Version 23.0). We will compare the primary outcome as a binary measure between the intervention and control group. We will use chi-square analyses using $p<0.05$ for statistical significance. For assessment of secondary outcomes we will be guided by published scoring systems for the validated scales to score genetics knowledge, satisfaction with services and genetic counselling outcomes. Mean scores for each scale will be compared between the intervention and control group and comparisons between the control and intervention group will be analysed using unpaired t-tests for continuous data and chi-square analysis for categorical data. Sub-group analysis will also be performed; specifically we will compare outcomes in the study groups stratified by the gene result (i.e. causative, uncertain or indeterminate results) and compare familial and non-familial HCM probands, which has been previously shown to influence family communication practices.[37]

As a longer-term outcome, we will systematically assess and document family communication as reported by the proband measured by phone calls at one, three and six monthly intervals. These phone calls will also measure uptake of family screening as reported by the proband. This will be assessed separately to the primary and secondary outcomes. We will compare outcomes between the study groups stratified by the gene result (i.e. causative, uncertain or indeterminate results). In addition, we will compare

outcomes between study groups stratified by those with and without a family history of HCM.

ETHICS AND DISSEMINATION

Ethics

All aspects of the study will be performed according to institutional human research ethics committee approval. This study has been approved by and is in strict accordance with the Sydney Local Health District Ethics Review Committee (X16-0030).

Dissemination

Results from this trial will be prepared as a manuscript and submitted to peer-reviewed journals for publication. In addition, it will form part of the first authors' PhD thesis. Results from the study will be submitted to international and national scientific sessions with the aim of being presented. We will make a copy of the aid available to a wider genetic audience for use in their clinical practice and study data will be available from the authors. This will include development of an electronic form of the aid.

ACKNOWLEDGEMENTS AND FUNDING

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AUTHOR STATEMENT

All authors contributed to the manuscript, specifically:

(1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work (CB, LY, CS, JI); AND

(2) Drafting the work or revising it critically for important intellectual content (CB, LY, CS, JI); AND

(3) Final approval of the version to be published (CB, LY, CS, JI); AND

(4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved (CB, LY, CS, JI).

COMPETING INTERESTS

All authors declare they have no disclosures regarding competing interests.

REFERENCES

1. Maron BJ, Maron MS, Semsarian C. Genetics of hypertrophic cardiomyopathy after 20 years: clinical perspectives. *Journal of the American College of Cardiology* 2012;60(8):705-15. doi: 10.1016/j.jacc.2012.02.068

2. Semsarian C, Ingles J, Maron MS, et al. New perspectives on the prevalence of hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2015;65(12):1249-54. doi: 10.1016/j.jacc.2015.01.019

3. Ingles J, Burns C, Barratt A, et al. Application of Genetic Testing in Hypertrophic Cardiomyopathy for Preclinical Disease Detection. *Circ Cardiovasc Genet* 2015;8(6):852-9. doi: 10.1161/CIRCGENETICS.115.001093

4. National Society of Genetic Counselors' Definition Task F, Resta R, Biesecker BB, et al. A new definition of Genetic Counseling: National Society of Genetic Counselors' Task Force report. *Journal of genetic counseling* 2006;15(2):77-83. doi: 10.1007/s10897-005-9014-3

5. Semsarian C, Ingles J. A clinical approach to genetic testing for non-specialists. *Bmj* 2017;358:j4101. doi: 10.1136/bmj.j4101

6. Burns C, James C, Ingles J. Communication of genetic information to families with inherited rhythm disorders. *Heart rhythm* 2018;15(5):780-86. doi: 10.1016/j.hrthm.2017.11.024

7. Burns C, McGaughran J, Davis A, et al. Factors influencing uptake of familial long QT syndrome genetic testing. *Am J Med Genet A* 2016;170A(2):418-25. doi: 10.1002/ajmg.a.37455

8. Christiaans I, Birnie E, Bonsel GJ, et al. Uptake of genetic counselling and predictive DNA testing in hypertrophic cardiomyopathy. *Eur J Hum Genet* 2008;16(10):1201-7. doi: ejhg200892 [pii]
10.1038/ejhg.2008.92 [published Online First: 2008/05/15]

9. Gaff CL, Clarke AJ, Atkinson P, et al. Process and outcome in communication of genetic information within families: a systematic review. *European journal of human genetics : EJHG* 2007;15(10):999-1011. doi: 10.1038/sj.ejhg.5201883

10. Claes E, Evers-Kiebooms G, Boogaerts A, et al. Communication with close and distant relatives in the context of genetic testing for hereditary breast and ovarian cancer in cancer patients. *American journal of medical genetics Part A* 2003;116A(1):11-9. doi: 10.1002/ajmg.a.10868

11. Barsevick AM, Montgomery SV, Ruth K, et al. Intention to communicate BRCA1/BRCA2 genetic test results to the family. *Journal of family psychology : JFP : journal of the Division of Family Psychology of the American Psychological Association* 2008;22(2):303-12. doi: 10.1037/0893-3200.22.2.303

12. Burns C, Yeates L, Spinks C, et al. Attitudes, knowledge and consequences of uncertain genetic findings in hypertrophic cardiomyopathy. *Eur J Hum Genet* 2017;25(7):809-15. doi: 10.1038/ejhg.2017.66

13. Patenaude AF, Tung N, Ryan PD, et al. Young adult daughters of BRCA1/2 positive mothers: what do they know about hereditary cancer and how much do they worry? *Psycho-oncology* 2013;22(9):2024-31. doi: 10.1002/pon.3257

14. Young AL, Butow PN, Vetsch J, et al. Family Communication, Risk Perception and Cancer Knowledge of Young Adults from BRCA1/2 Families: a Systematic Review. *Journal of genetic counseling* 2017;26(6):1179-96. doi: 10.1007/s10897-017-0125-4

15. Forrest LE, Burke J, Bacic S, et al. Increased genetic counseling support improves communication of genetic information in families. *Genetics in medicine : official journal of the American College of Medical Genetics* 2008;10(3):167-72. doi: 10.1097/GIM.0b013e318164540b

16. Fiallos K, Applegate C, Mathews DJ, et al. Choices for return of primary and secondary genomic research results of 790 members of families with Mendelian disease. *European journal of human genetics : EJHG* 2017;25(5):530-37. doi: 10.1038/ejhg.2017.21

17. Forrest K, Simpson SA, Wilson BJ, et al. To tell or not to tell: barriers and facilitators in family communication about genetic risk. *Clinical genetics* 2003;64(4):317-26.

18. Montgomery SV, Barsevick AM, Egleston BL, et al. Preparing individuals to communicate genetic test results to their relatives: report of a randomized control trial. *Fam Cancer* 2013;12(3):537-46. doi: 10.1007/s10689-013-9609-z

19. Seymour KC, Addington-Hall J, Lucassen AM, et al. What Facilitates or Impedes Family Communication Following Genetic Testing for Cancer Risk? A Systematic Review and Meta-Synthesis of Primary Qualitative Research. *Journal of genetic counseling* 2010;19(4):330-42. doi: 10.1007/s10897-010-9296-y

20. Healey E, Taylor N, Greening S, et al. Quantifying family dissemination and identifying barriers to communication of risk information in Australian BRCA families. *Genetics in medicine : official journal of the American College of Medical Genetics* 2017;19(12):1323-31. doi: 10.1038/gim.2017.52

21. Hodgson J, Metcalfe S, Gaff C, et al. Outcomes of a randomised controlled trial of a complex genetic counselling intervention to improve family communication. *European journal of human genetics : EJHG* 2016;24(3):356-60. doi: 10.1038/ejhg.2015.122

22. Suthers GK, Armstrong J, McCormack J, et al. Letting the family know: balancing ethics and effectiveness when notifying relatives about genetic testing for a familial disorder. *Journal of medical genetics* 2006;43(8):665-70. doi: 10.1136/jmg.2005.039172

23. Stacey D, Legare F, Lewis K, et al. Decision aids for people facing health treatment or screening decisions. *Cochrane Db Syst Rev* 2017(4) doi: Artn Cd001431 10.1002/14651858.Cd001431.Pub5

24. Wakefield CE, Meiser B, Homewood J, et al. Development and pilot testing of two decision aids for individuals considering genetic testing for cancer risk. *Journal of genetic counseling* 2007;16(3):325-39. doi: 10.1007/s10897-006-9068-x

25. Vavolizza RD, Kalia I, Aaron KE, et al. Disclosing Genetic Information to Family Members About Inherited Cardiac Arrhythmias: An Obligation or a Choice? *Journal of genetic counseling* 2015;24(4):608-15. doi: 10.1007/s10897-014-9783-7

26. Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Annals of internal medicine* 2013;158(3):200-7. doi: 10.7326/0003-4819-158-3-201302050-00583

27. Ingles J, Lind JM, Phongsavan P, et al. Psychosocial impact of specialized cardiac genetic clinics for hypertrophic cardiomyopathy. *Genet Med* 2008;10(2):117-20. doi: 10.1097/GIM.0b013e3181612cc7
00125817-200802000-00007 [pii] [published Online First: 2008/02/19]

28. Bagnall RD, Weintraub RG, Ingles J, et al. A Prospective Study of Sudden Cardiac Death among Children and Young Adults. *New Engl J Med* 2016;374(25):2441-52. doi: 10.1056/NEJMoa1510687

29. Burns C, Bagnall RD, Lam L, et al. Multiple Gene Variants in Hypertrophic Cardiomyopathy in the Era of Next-Generation Sequencing. *Circ Cardiovasc Genet* 2017;10(4) doi: 10.1161/CIRCGENETICS.116.001666

30. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genetics in Medicine* 2015;17(5):405-24. doi: 10.1038/gim.2015.30

31. Smagarinsky Y, Burns C, Spinks C, et al. Development of a communication aid for explaining hypertrophic cardiomyopathy genetic test results. *Pilot Feasibility Stud* 2017;3:53. doi: 10.1186/s40814-017-0205-0

32. Read CY, Perry DJ, Duffy ME. Design and psychometric evaluation of the Psychological Adaptation to Genetic Information Scale. *J Nurs Scholarsh* 2005;37(3):203-8.

33. Kasparian NA, Wakefield CE, Meiser B. Assessment of psychosocial outcomes in genetic counseling research: an overview of available measurement scales. *Journal of genetic counseling* 2007;16(6):693-712. doi: 10.1007/s10897-007-9111-6 [published Online First: 2007/08/19]

34. Erblich J, Brown K, Kim YM, et al. Development and validation of a breast cancer genetic counseling knowledge questionnaire. *Patient Educ Couns* 2005;56(2):182-91. doi: 10.1016/j.pec.2004.02.007

35. Shiloh S, Avdor O, Goodman RM. Satisfaction with genetic counseling: dimensions and measurement. *American journal of medical genetics* 1990;37(4):522-9. doi: 10.1002/ajmg.1320370419 [published Online First: 1990/12/01]

36. McAllister M, Wood AM, Dunn G, et al. The Genetic Counseling Outcome Scale: a new patient-reported outcome measure for clinical genetics services. *Clinical genetics* 2011;79(5):413-24. doi: 10.1111/j.1399-0004.2011.01636.x [published Online First: 2011/01/25]

37. Ko C, Arscott P, Concannon M, et al. Genetic testing impacts the utility of prospective familial screening in hypertrophic cardiomyopathy through identification of a nonfamilial subgroup. *Genet Med* 2017 doi: 10.1038/gim.2017.79

Table 1: Trial Registration Data	
Primary registry and trial identifying number	Australian New Zealand Clinical Trials Registry: ACTRN12617000706370
Date of registration in primary registry	17/05/2017
Secondary identifying numbers	NA
Source(s) of monetary or material support	National Heart Foundation of Australia
Primary sponsor	The University of Sydney
Secondary sponsor	NA
Contact for public queries	Dr Jodie Ingles j.ingles@centenary.org.au
Contact for scientific queries	Dr Jodie Ingles j.ingles@centenary.org.au
Public title	Use of an aid to improve communication of genetic risk information to families with hypertrophic cardiomyopathy (HCM)
Scientific title	Use of a custom designed aid to improve communication of genetic results in families with HCM
Countries of recruitment	Australia
Health condition (s) or problem (s) studied	HCM
Intervention	Use of a custom designed aid to communicate HCM genetic test results
Key inclusion and exclusion criteria	HCM probands with a genetic result ready for return Participants must be aged 18 years or older Sufficient written English skills as nominated by the participant
Study type	Prospective randomised controlled trial
Date of first enrolment	25/11/2016
Target sample size	45
Recruitment status	Recruiting
Primary outcome (s)	Ability and confidence of the proband to communicate genetic results to at-risk relatives
Key secondary outcomes	Secondary outcomes will assess genetic knowledge, satisfaction with services, outcomes from genetic counselling and psychological adaptation to genetic information

Table 2: Certainty sub-scale of the PAGIS scale
1. I understand how I came to have hypertrophic cardiomyopathy
2. I understand the health risks my relatives face because of hypertrophic cardiomyopathy
3. I feel certain that I understand the meaning of having hypertrophic cardiomyopathy
4. I understand the chances I have of passing hypertrophic cardiomyopathy along to my children
5. I feel that I can explain to other people what having hypertrophic cardiomyopathy means
6. I feel confused because I have been given different explanations of what having hypertrophic cardiomyopathy means

Abbreviations: PAGIS = Psychological Adaptation to Genetic Information Scale.

Table 3: Primary outcome measure converted to a primary outcome

Measures incorporated

1. Certainty sub scale from PAGIS (measuring confidence)
2. Adult first degree relatives informed of genetic risk (measuring ability)

Calculation examples

Example 1:

Certainty score from PAGIS sub scale = 18/36= 0.5

Relatives informed of risk = 3/6= 0.5

= (0.5 + 0.5 = 1) / 2= 0.5

= 50%

Therefore this participant falls into the 'poor communication' category of the primary outcome

Example 2:

Certainty score from PAGIS sub scale = 30/36= 0.83

Relatives informed of risk = 7/8= 0.88

(0.88+ 0.83) / 2= 0.86

= 86%
Therefore this participant falls into the 'fair communication' category of this primary outcome

Abbreviations: PAGIS = Psychological Adaptation to Genetic Information Scale.

FIGURE LEGENDS

FIGURE 1: Flow chart of overall study design

FIGURE 2: Example page from communication aid: Genetic testing step by step

FIGURE 3: Example page from communication aid: What is my genetic result?

FIGURE 4: Example page from communication aid: Family-screening guidelines

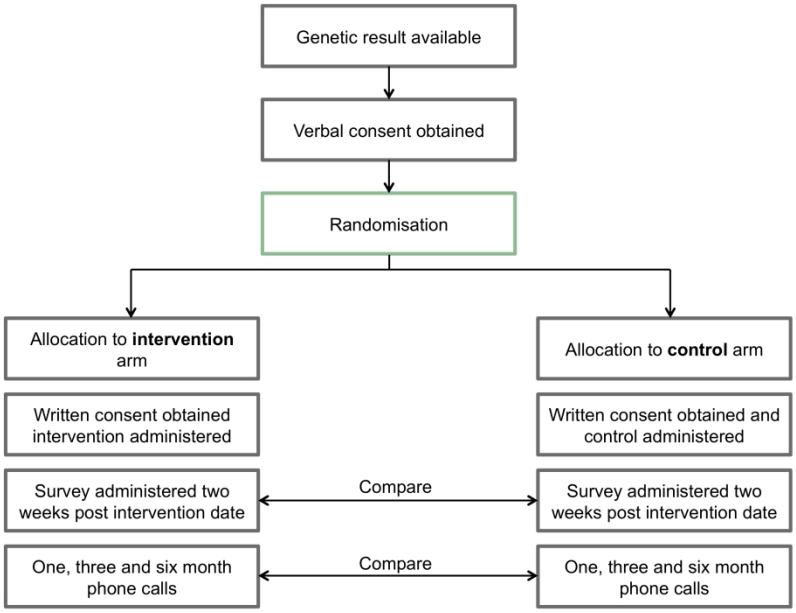

Figure 1

297x209mm (300 x 300 DPI)

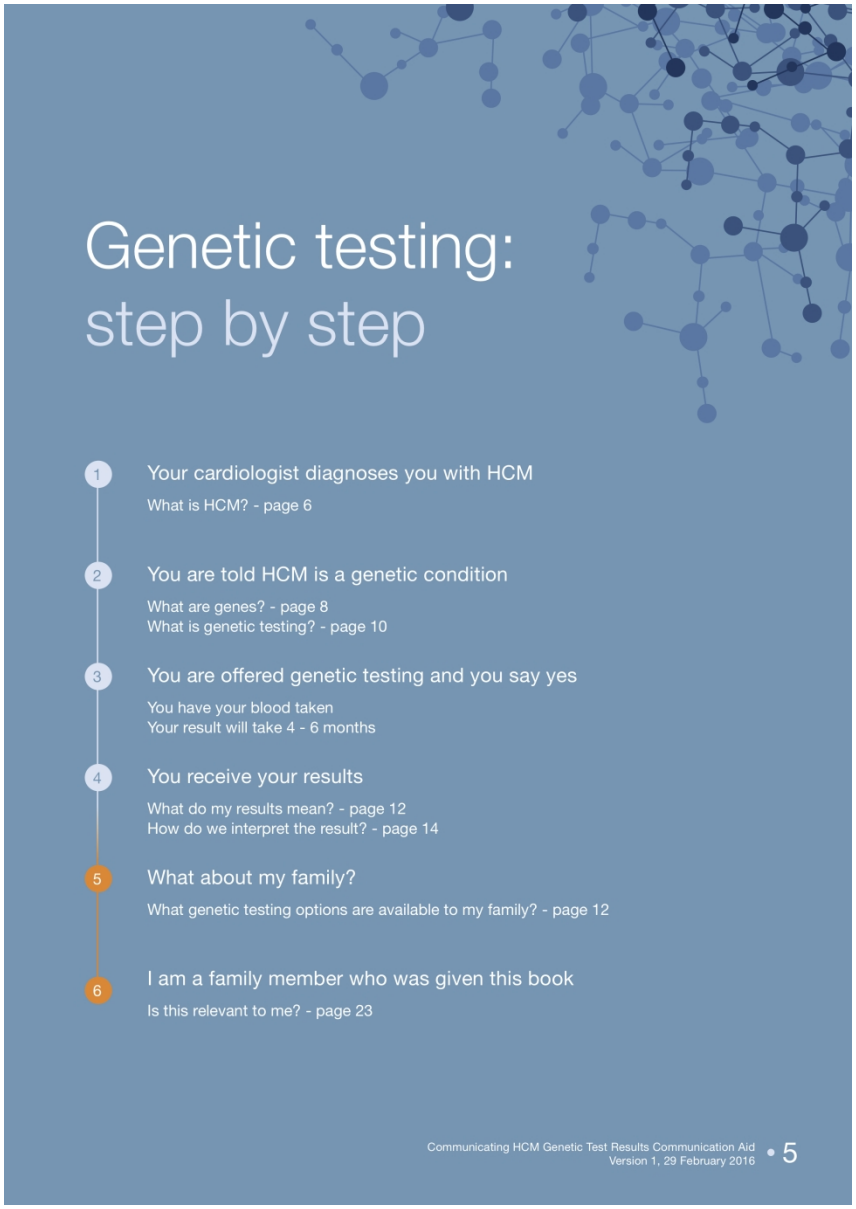

Figure 2

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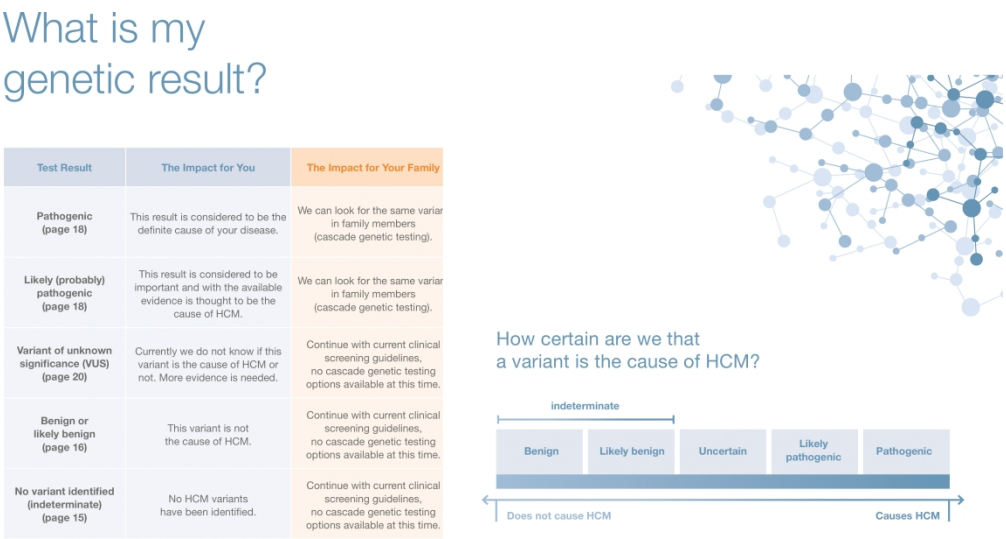

Figure 3

374x197mm (300 x 300 DPI)

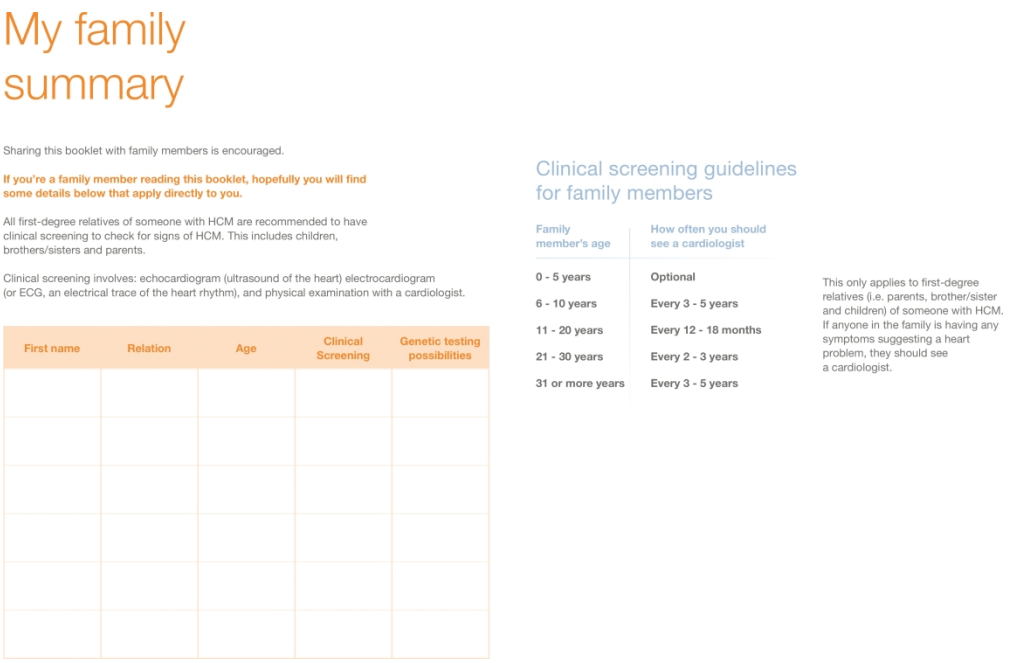

Figure 4

349x225mm (300 x 300 DPI)

Communicating Hypertrophic Cardiomyopathy (HCM) Genetic Test Results

INFORMATION FOR PARTICIPANTS

Introduction

You are invited to take part in a research study examining how we can best communicate genetic test results in hypertrophic cardiomyopathy (HCM). Genetic testing for genetic heart diseases like HCM has become increasingly complex and our method of explaining these results needs to evolve to meet these changing needs. Cardiac genetic counsellors coordinate the genetic testing process and they play a key role in ensuring the information you are receiving is clear and meaningful for you and your family. The objective of this study is to compare the effectiveness of an intervention aimed at improving the way we communicate genetic test result information with our current usual care. If you consent to the study, you will be randomly assigned to either the new communication intervention or to usual care.

Individuals with hypertrophic cardiomyopathy are eligible to participate in this study if they are the first in their family to have genetic testing. People aged 16 years or older are eligible to participate; however children younger than this are excluded.

The study is being conducted by Dr Jodie Ingles, Prof Christopher Semsarian, Ms Laura Yeates and Ms Charlotte Burns from the Molecular Cardiology Research Program, Centenary Institute and Royal Prince Alfred Hospital Sydney.

Study Procedures

If you agree to participate in this study, you will be asked to complete the participant consent form. You will then be randomly allocated to one of two groups, to receive your genetic test result. Two weeks after your genetic test result appointment, you will be asked to complete a survey *(either paper or online)*, asking about your understanding of genetic testing for HCM. This survey will take between 10-20 minutes to complete.

In addition, the researchers would like to phone you at one, three and six month intervals to follow up with you after you receive your genetic result. These phone calls will take approximately 10 minutes and will be conducted at a time that suits you.

Researchers will have access to your medical record to obtain information relevant to this study. Information about you may also be sought from the *Australian Genetic Heart Disease Registry*, if you have enrolled (www.heartregistry.org.au).
Confidentiality of the survey responses will be paramount. Your name will be replaced with a unique code and only Dr Jodie Ingles will have access to the true identity of respondents.

No additional genetic testing will be carried out as part of this study.

Information collected about you will be securely stored.

Benefits

While we intend that this research study furthers medical knowledge and may improve management of genetic heart diseases in the future, it may not be of direct benefit to you.

Voluntary Participation

Participation in this study is entirely voluntary. You do not have to take part in it. If you do take part, you can withdraw at any time without having to give a reason. Whatever your decision, please be assured that it will not affect your medical treatment or your relationship with the staff who are caring for you.

Confidentiality

All of the information collected from you for the study will be treated confidentially, and only the researchers named above will have access to it. The study results may be presented at a conference or in a scientific publication, but individual participants will not be identifiable in such a presentation.

Any forms completed online, including the participant consent form and survey will be extremely secure to maintain participant privacy.

Further Information

When you have read this information, one of the investigators is available to discuss it with you further and answer any questions you may have. If you would like to know more at any stage, please feel free to contact:

Dr Jodie Ingles
Molecular Cardiology Research Program
Centenary Institute
Locked Bag No 6, Newtown NSW 2042
Ph. 02 9565 6293
Email. j.ingles@centenary.org.au Web. www.heartregistry.org.au

This information sheet is for you to keep.

Ethics Approval and Complaints

This study has been approved by the Ethics Review Committee (RPAH Zone) of the Sydney Local Health District. Any person with concerns or complaints about the conduct of this study should contact the Executive Officer on 02 9515 6766 and quote protocol number X16-0030.

Communicating Hypertrophic Cardiomyopathy (HCM) Genetic Test Results

PARTICIPANT CONSENT FORM

I, ... *[name]*

of

.....*[address]*

.....*[email]*

have read and understood the Information for Participants on the abovenamed research study

and have discussed the study with .....

I have been made aware of the procedures involved in the study.

I understand that my participation in this study will allow the researchers to have access to my medical record, including information held by the Australian Genetic Heart Disease Registry (if I am enrolled), and I agree to this.

I freely choose to participate in this study and understand that I can withdraw at any time.

I also understand that the research study is strictly confidential.

I hereby agree to participate in this research study.

NAME: .....

SIGNATURE: .....

DATE: .....

NAME OF WITNESS: .....

SIGNATURE OF WITNESS: .....

Hello, this is (Insert Name) from the Centenary Institute, may I please speak to (Participant name)?

I am phoning (as we discussed back in (insert month of genetic result return) to follow up with you after you received your genetic result as part of our research into communicating genetic results. This is your (one month, three month, six month) follow up phone call. I was hoping to get some additional information from you regarding your gene result. Do you have 10 minutes or so to do this now- or I can arrange a more appropriate time?

SECTION 1: 3-generation pedigree documented – Have this documented prior to phone call. Confirm during phone call.

SECTION 2

Who in the family have you told about the following: (List names/details): Your diagnosis of HCM?

About your genetic result?

Who in the family has had an echo/ecg/Cardiology review- Outcome? (Assess against guidelines)?

Who in the family has had genetic testing- Outcome?

Who in the family is awaiting an appointment- with whom?

SECTION 3:

Total number of first degree relatives informed of diagnosis =

Total number of first degree relatives informed of genetic test outcome=

Total number of first degree relatives who have had cardiology review=

Total number of first degree relatives who have had genetic review=

Total number of first degree relatives awaiting review=

Total number of first degree relatives with a positive clinical screen=

Total number of relatives with a negative clinical screen =

Total number of first degree relatives with a positive genetic result =

Total number of first degree relatives with a negative genetic result=

Total number of other relatives informed =

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	**1**
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	**2, Table 1**
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	**9, Table 1**
Protocol version	#3	Date and version identifier	**1**
Funding	#4	Sources and types of financial, material, and other support	**18**
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	**1, 18**
Roles and	#5b	Name and contact information for the trial	**NA- No trial sponsor.**

responsibilities: sponsor contact information		sponsor	
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	**NA- no role other than funding for key researchers.**
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	**NA**
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	**4**
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	11
Objectives	#7	Specific objectives or hypotheses	**7,8**
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	**9**
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	**9**

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	**9**
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	**11**
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	**NA**
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	**NA- intervention was one clinic appointment**
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	**NA**
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	**12,13,14**
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	**8, Figure 1**

Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	**10**
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	**9**
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	**9,10**
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	**9,10**
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	**9,10**
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	**15**
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	**NA- researcher will be blinded to treatment arm for analysis only, however researchers will not be blinded during intervention**

			because of nature of intervention.
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	**12,13,14, Table 2, Figure 2, Figure 3, Figure 4**
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	**15**
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	**15**
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	**16**
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	**16**
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical	**NA- not relevant to study design.**

		methods to handle missing data (eg, multiple imputation)	
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	**NA- not relevant, no data monitoring committee.**
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	**NA- no interim analysis.**
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	**NA**
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	**NA**
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	**15**
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	**NA- No protocol modifications will be made.**
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or	**9**

		authorised surrogates, and how (see Item 32)	
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	**NA**
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	**16**
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	**1**
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	**16/17**
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	**NA**
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	**16/17**
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	**18**
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	**17**
Informed consent	#32	Model consent form and other related	**Supplementary material**

materials		documentation given to participants and authorised surrogates	
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	**NA**

EVALUATING A CUSTOM DESIGNED AID TO IMPROVE COMMUNICATION OF GENETIC RESULTS IN FAMILIES WITH HYPERTROPHIC CARDIOMYOPATHY: STUDY PROTOCOL FOR A RANDOMISED CONTROLLED TRIAL

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EVALUATING A CUSTOM DESIGNED AID TO IMPROVE COMMUNICATION OF GENETIC RESULTS IN FAMILIES WITH HYPERTROPHIC CARDIOMYOPATHY: STUDY PROTOCOL FOR A RANDOMISED CONTROLLED TRIAL

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NO DISCLOSURES

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ABSTRACT

Introduction: Genetic testing for hypertrophic cardiomyopathy (HCM) in the era of genomics brings unique challenges for genetic counselling. The number of genes routinely included in an HCM gene panel has increased markedly, many with minimal if any robust evidence of gene-disease association. Subsequently there is a greater chance of uncertain genetic findings. The responsibility of communicating this information with at-risk relatives lies with the index case (proband). We have developed a communication aid to assist with the delivery of genetic results to the proband. We have previously shown the aid is feasible and acceptable, and have now developed a study protocol for a randomised controlled trial of a genetic counsellor-led intervention incorporating the communication aid.

Methods and Analysis: This is a prospective randomised controlled trial. We will investigate the impact of a genetic counsellor-led intervention to return proband genetic results using a custom designed communication aid. We aim to improve knowledge and empowerment. The primary outcome of this trial is the ability and confidence of the proband to communicate genetic results to at-risk relatives. Secondary outcomes will assess genetic knowledge, satisfaction with services, outcomes from genetic counselling and psychological adaptation to genetic information.

Ethics and Dissemination: This study has been approved by and is in strict accordance with the Sydney Local Health District Ethics Review Committee (X16-0030; 22/01/2016; version 1). Results from this trial will be prepared as a manuscript and submitted to peer-reviewed journals for publication as well as submission for presentation at national and international meetings.

Registration Details: This trial is registered with the Australian New Zealand Clinical Trials Registry: ACTRN12617000706370

STRENGHTS AND LIMITATIONS

- This study will assess the effectiveness of a communication aid to improve the ability and confidence of patients with hypertrophic cardiomyopathy (HCM) to communicate genetic test results with their at-risk relatives.
- The results of this trial will inform genetic counselling practice for HCM genetic testing, as well as be broadly applicable for other inherited heart diseases.
- Limitations include the generalisability of our findings, which are true for a specialised multidisciplinary clinic where the intervention was performed but may not be representative of the broader HCM population undergoing genetic testing.
- As genomic technologies continue to evolve, uncertainty and complexity of genetic findings will likely increase over time.

INTRODUCTION

Background and rationale

Genetic testing in the era of genomics brings unique challenges for the genetic counselling of families. Hypertrophic cardiomyopathy (HCM) is a clinically heterogeneous inherited heart disease characterised by unexplained left ventricular hypertrophy in the absence of a loading condition such as hypertension.[1] With a prevalence of 1 in 200-500, it is one of the most common inherited heart diseases and clinical manifestations can range from asymptomatic through to heart failure or sudden cardiac death.[2] In the setting of HCM, genetic testing of the index case (proband) can provide invaluable information by allowing at-risk relatives the opportunity to undergo cascade genetic testing to look for the presence or absence of the family-specific variants.[3] The first step is often the most challenging, requiring identification of a variant for which there is sufficient evidence of causation.

Genetic counselling is a critical aspect of the process, not just for genetic testing, but also for understanding inheritance risks, characterisation of the family history and information and emotional support.[4] Within a clinical setting, pre- and post-test genetic counselling should include discussion of inheritance risks and clinical screening guidelines for at-risk relatives.[5] This allows asymptomatic at-risk relatives to make proactive, informed decisions regarding their risk, including family planning decisions.

How a patient understands and communicates this genetic information to their at-risk relatives is critical to ensuring patients' get the most value out of genetic testing. This task of communication relies on the proband within the family. Current Australian practice and privacy laws dictate that in most cases the health care provider does not make contact with relatives to disclose risk information. Therefore, it follows that in order to communicate genetic results or risk information the proband must have adequate understanding of the

information they have received from their healthcare provider. Several studies indicate this may be problematic, and some individuals may not retain or understand the information presented to them.[6]

Existing knowledge

Currently literature estimates between 20-40% of relatives remain unaware of relevant genetic information and do not act on information even when they have reportedly been informed of their risk.[7-9] Many factors have been identified which influence family communication about genetic risk, including complicated family dynamics, guilt, anxiety and gender, however these factors are difficult to target as areas for improvement within the context of one or two genetic counselling sessions.[7 8 10 11] There are stages within the genetic counselling process, where communication of genetic results and uptake of appropriate screening may be influenced.

Our group and others have shown some of the barriers that can negatively impact on family communication. In a qualitative study of HCM patients undergoing comprehensive genetic testing, many patients reported uncertain results to be conveyed less amongst families.[12] Further, these results are often misunderstood. For example, amongst this cohort, probands with uncertain results perceived these results as falsely reassuring or conversely suggests their disease is 'worse' or 'different'. This led to a misunderstanding that their result was not heritable and therefore communication with relatives did not occur.[12] Supporting these findings, the general genetics literature highlights that risk perception and understanding of results though varied, can be poor, inaccurate and incomplete.[13 14]

There is evidence for the effectiveness of a genetic counsellor in addressing some of the communication and knowledge barriers.[15-17] One key area for intervention is during the post-test genetic counselling session. Genetic and risk information can be difficult to understand and explain clearly and as a consequence, the patient may not gain sufficient knowledge and lack confidence to convey these key messages to at-risk relatives.[12] Further, it is recognised that patients deliberate on the appropriate time to communicate genetic information and make decisions regarding which relatives the information is pertinent to, regardless of the recommendation of professionals.[7 18 19] Few resources exist which aim to facilitate effective communication to at-risk relatives. We therefore hypothesise that improving knowledge of an HCM genetic diagnosis will have a positive impact on communication to at-risk relatives, as well as genetic knowledge, satisfaction with services, outcomes from genetic counselling and psychological adaptation to genetic information.

Utility of a communication aid

When asked about family communication, most patients report families should communicate risk amongst themselves with varying levels of support from their healthcare providers.[14 17 20] In addition, there is evidence for the effectiveness of genetic counselling to assist with this process.[15 16 20] Hodgson et al. published a randomised controlled trial assessing the impact of a genetic counselling phone intervention on communication of genetic information within families.[21] They found no significant difference between the intervention and control group when measuring contact with genetic services, though in sub-analyses of the high-risk children group, the primary outcome was significantly improved. Importantly, the primary outcome measure was contact with a genetic service, which can be difficult to ascertain and may not be the most accurate measure of effectiveness or a direct reflection of communication efforts.

Resources such as decision and communication aids, or family letters, may provide additional support to this process, though more data is needed regarding efficacy.[15 19 21 22] Decision or communication aids are tools specifically designed to support patients with decision making and unmet information needs. There is evidence for the effectiveness of an aid with regard to improved knowledge and accuracy of risk perceptions.[23-25] Further, most health information is provided in a written format, which may not be the most effective health communication method. Communication and decision aids provide a format to include visual elements that may improve comprehension, recall and comfort with the information, particularly when health literacy may be an issue.

Need for a trial

Overall, the literature highlights that probands require additional support to understand and communicate genetic results. The rationale for this study is the critical gap in supporting patients' comprehension and consequent communication of genetic risk to at-risk relatives. Though genetic counsellors are specifically trained in delivering genetic information, information needs of patients are not always met and communication amongst at-risk relatives can be suboptimal. As genetic test results become increasingly complex, an evidence-based approach to supporting patients with genetic knowledge and risk communication should be explored.

STUDY AIMS AND OUTCOMES

The aim of this randomised controlled trial is to determine if a genetic counsellor-led intervention using a communication aid for the delivery of HCM genetic test results improves the ability and confidence of the proband to communicate genetic results to at-risk relatives compared with current clinical practice.

1. The primary outcome is the ability and confidence of the proband to communicate genetic results to at-risk relatives, measured at 2 weeks post-intervention.

2. Secondary outcomes will assess genetic knowledge, satisfaction with services, patient reported outcome of genetic counselling and psychological adaptation to genetic information, measured at 2 weeks post-intervention.

3. As a longer-term outcome, we will systematically assess and document family communication as reported by the proband measured by phone calls at one, three and six monthly intervals. The researcher conducting these phone calls will not be blinded to the treatment arm of the participant. During these phone calls a series of questions regarding family communication and uptake of family screening will be asked of the proband. These phone calls will be conducted and analysed after collection of the primary and secondary outcomes data. This is to prevent interference with results because the phone calls themselves may serve as a family communication intervention. A phone script to be used as a guide for these phone calls is available in the supplementary material.

METHODS AND ANALYSIS

Trial design

This is a prospective randomised controlled trial. The protocol is reported in accordance with the SPIRIT statement, which provides recommendations for a minimum set of scientific, ethical and administrative elements that should be addressed within a clinical trial protocol.[26] All items from the World Health Organization Trial Registration Data Set are listed in Table 1. Consecutive HCM patients will be invited to participate when they are notified on the phone that their genetic result is ready to be returned. Once written consent is obtained they will be randomised to receive their genetic result via the intervention or control arm of the study (Figure 1).

Study setting

This trial will be carried out within a specialised multidisciplinary HCM clinic. This incorporates the expertise of specialist cardiologists and cardiac genetic counsellors.[27] Patients with HCM attending these clinics at Royal Prince Alfred Hospital will be invited to attend.

Eligibility criteria

HCM probands with a genetic result ready for return are eligible. HCM probands are defined as the first person in the family to undergo genetic testing for HCM. Probands include those with and without a family history of disease provided genetic testing has been ordered. Participants must be aged 16 years or older, with sufficient written English skills as nominated by the participant. Genetic testing is performed as part of a research study, or commercial laboratory as previously published.[28] [29] All identified variants are classified in the same manner, as per current clinical standards and guidelines.[30] Recruitment commenced in November 2017 and is expected to end in November 2018.

Participants will be invited to participate in the study during their routine pre clinic phone call conducted as normal clinical process. Informed consent will be obtained by the cardiac genetic counsellor present at the participants clinic consultation (supplementary material).

Randomisation

A randomised list was prepared using the Excel (Microsoft Office) "Random" function and study participants who consent to the study are allocated the next number on the random list. This number is linked to either control or intervention. A researcher not involved in the study performs the randomisation.

Sample size and power calculations

Prior to commencement of the study, power calculations were performed using the results from our published feasibility study.[31] The primary outcome of this trial is the ability and confidence of the proband to communicate genetic results to at-risk relatives. Data from the feasibility study indicated 75% of participants communicated genetic results to at-risk relatives. Assuming the control group communicates in 50% of cases, at a significance level of 5% and 80% statistical power, a sample size of n=21 is required per group.

Development of the custom communication aid

We have developed a communication aid to assist with the delivery of genetic results to the proband and support family communication. A pilot study demonstrating feasibility and acceptability of this aid has been previously reported.[31] In brief, development of the aid involved review of the literature alongside multidisciplinary meetings. Development was a multistep process and on the basis of meeting outcomes, literature review and empirical evidence from the multidisciplinary team. The aid addresses:

1. Genetic test basic background information

2. Possible outcomes of genetic testing
3. Overview of the process involved in classification of a genetic variant
4. Implications for at-risk relatives including family screening recommendations

Control arm

Those within the control arm of the study will receive their result via normal clinical practice. There are currently no evidence-based guidelines for return of comprehensive genetic test results within the multidisciplinary clinic setting. Normal clinical practice typically involves return of a genetic result either by the cardiologist or genetic counsellor. Return of the result is usually performed following clinical cardiology review, which is often the primary purpose of the consult. In the majority of cases a genetic counsellor is present.

Intervention arm

Those randomised to the intervention arm will be allocated a separate appointment time after clinical review with their cardiologist, where they will see the cardiac genetic counsellor who will return their genetic result using the communication aid.

The communication aid covers the process of genetic testing and risk from diagnosis of HCM through to the implications of a genetic result for at-risk relatives (Figure 2). There is a section in the aid under 'Results', which goes through the meaning of each category of genetic result. These include an indeterminate result (no variant identified), a variant of uncertain significance and a likely pathogenic/pathogenic result (Figure 3). The genetic counsellor returning the genetic result will mark the appropriate category of result, which applies to the patient in front of them. The genetic counsellor will return the genetic result, and then go through the communication aid, referencing the individual result and specific recommendations for the rest of the family. There will be an opportunity to ask questions,

and the genetic counsellor will write the specific recommendations for each family member in the box provided at the end of the communication aid (Figure 4).

Patient and Public Involvement

Development of this research question and outcome measures were informed by clinical experience of the authors in a specialised clinic setting, as well as published research identifying gaps in communication with relatives. Specifically, there are known challenges associated with understanding and subsequent communication of genetic information to relatives. We have shown poor understanding, recall, and communication of genetic results amongst HCM probands.[7 12] Prior to implementation and development of this trial, a pilot study involving patients was conducted, incorporating patient preference and needs allowing development of both the communication aid and the study protocol.[31] Results will be disseminated to patients in the form of a research participant newsletter on completion of the study. In addition, those randomised to the control arm will receive a copy of the communication aid. Patients provided written consent to participate in the study, with an understanding of the requirements of the study. These were not considered by the patients or study team to be burdensome for the patients participating in the study.

DATA COLLECTION AND OUTCOMES

Both the primary and secondary outcomes will be measured at a single time point (2-weeks post intervention) using a survey comprised of a number of previously published and validated scales. A number of demographic questions will also be asked within the survey. The survey will be available online via qualtrics (https://www.qualtrics.com/) with a direct link sent to participants. For those who prefer a hard copy it will be posted with a return envelope. The survey will be sent two weeks after return of genetic results. Evidence regarding the most appropriate time between genetic result disclosure and family

communication is lacking. However, given the risk of arrhythmia and sudden death within the inherited heart disease context, two weeks post result disclosure was considered by the study team to be an appropriate time point to send the survey.[25] Return of the survey is followed up on a fortnightly basis.

Primary outcome

The primary outcome of this trial is the ability and confidence of the proband to communicate genetic results to at-risk relatives. This will be measured at a single time point, administered two weeks after return of genetic results. Ability and confidence will be assessed by two measures and then combined into a binary outcome. The certainty sub-scale of the Psychological Adaptation to Genetic Information (PAGIS) scale will measure confidence with genetic knowledge.[32] This sub-scale measures the patients' perception and confidence in their genetic knowledge and the items from this sub-scale are listed in Table 2. Subsequent ability to pass this information on will be measured by the number of at-risk relatives informed of genetic results by the proband. We will average the scores from both measures to determine a final score. The calculations used to determine this cut-off are illustrated in Table 3.

In summary, we will calculate the total PAGIS certainty sub-scale score (denominator of 36). This will be added to the total number of relatives informed over the total number of relatives at risk. This number will then be converted to a percentage. The final score will be converted to a binary outcome of fair versus poor ability and confidence to communicate genetic results to at-risk relatives. A cut-off of ≥75% will be used to indicate fair communication, based on data indicating 20-40% of relatives are not informed of their genetic risk. This outcome has been specifically designed for this study.

Factors that influence communication of genetic results to at-risk relatives are multidimensional. For this reason, we chose this combination approach to more broadly reflect the communication process. Many studies rely on single and linear measures of communication such as contact by relatives with genetics departments or self reported communication with at-risk relatives only. To overcome this, we aimed to incorporate a multidimensional approach that included the probands confidence regarding their knowledge of genetics alongside the action linked to this knowledge, being the communication to relatives. This will aim to determine consistency between the probands confidence with genetic information against their self-reported percentage of immediate family members informed

The certainty sub-scale of the Psychological Adaptation to Genetic Information Scale (PAGIS) will be used to measure confidence with genetic knowledge as described above.[32] Guided by grounded theory in patient perspectives of genetic counselling and the Roy Adaptation to Genetic Information Model, the 26-item PAGIS scale allows for evaluation of the efficacy of genetic counselling.[32 33] The scale aims to incorporate the multidimensional adaptation to genetic information and comprises of five domains which include; a) non-intrusiveness, b) support c) self-worth, d) certainty and e) self-efficacy.[32] Evidence for the utility of this scale has been published and illustrates its potential use for assessing genetic counselling interventions.[32]

Secondary outcomes

The survey comprises three additional scales to assess primary and secondary outcomes, a number of questions regarding communication with relatives, as well as a number of demographic questions.

Genetic knowledge will be assessed using an amended version of the Breast Cancer Genetic Counseling Knowledge Questionnaire (BGKQ).[33 34] This scale was originally developed to assess knowledge of information typically included in genetic counselling for breast cancer. The original scale was a 27 item questionnaire including statements regarding genetics such as '*50% (half) of your genetic information was passed down from your mother*' and participants were asked if the statement was true or false. Items in the original scale were empirically derived from detailed content analysis of breast cancer genetic counselling sessions. The original scale demonstrated a high content validity with cronbachs α = 0.92, with demonstrated ability to discriminate between patients before and after genetic counselling sessions.[34] We have amended questions to reflect the HCM context and 10 items were included.

Satisfaction with services received will be assessed using the widely used Satisfaction with Genetic Counseling Scale (SGCS).[35] The original questionnaire was designed to assess three dimensions of patient satisfaction: instrumental, affective and procedural.[33 35] This survey will use an amended version of the 12 item short form of the survey.

The genetic counselling outcome scale (GCOS-24) will be used to assess patient reported outcomes of genetic counselling.[36] The questionnaire was designed to be used pre and post genetic counselling, though we have used it in the post counselling setting. The authors of this scale used the construct of empowerment to summarise the patient derived benefits from genetic counselling.

Data management

All data from the survey will be entered into Microsoft Excel. Patient identifiers will be removed with study codes allocated. The primary researcher will be blinded to treatment

arm of the patient for analysis of the primary and secondary outcome data. A second senior researcher and supervisor will oversee data storage and analysis. Data will be stored in accordance with the Sydney Local Health District Ethics Review Committee and Centenary Institute.

Data analysis plan

Data will be analysed using Prism (version 7.0) and SPSS (Version 23.0). We will compare the primary outcome as a binary measure between the intervention and control group. We will use chi-square analyses using $p<0.05$ for statistical significance. For assessment of secondary outcomes we will be guided by published scoring systems for the validated scales to score genetics knowledge, satisfaction with services and genetic counselling outcomes. Mean scores for each scale will be compared between the intervention and control group and comparisons between the control and intervention group will be analysed using unpaired t-tests for continuous data and chi-square analysis for categorical data. Sub-group analysis will also be performed; specifically we will compare outcomes in the study groups stratified by the genetic result (i.e. causative, uncertain or indeterminate results) and compare familial and non-familial HCM probands, which has been previously shown to influence family communication practices.[37]

As a longer-term outcome, we will systematically assess and document family communication as reported by the proband measured by phone calls at one, three and six monthly intervals. These phone calls will also measure uptake of family screening as reported by the proband. This will be assessed separately to the primary and secondary outcomes. We will compare outcomes between the study groups stratified by the genetic result (i.e. causative, uncertain or indeterminate results). In addition, we will compare

outcomes between study groups stratified by those with and without a family history of HCM.

ETHICS AND DISSEMINATION

Ethics

All aspects of the study will be performed according to institutional human research ethics committee approval. This study has been approved by and is in strict accordance with the Sydney Local Health District Ethics Review Committee (X16-0030).

Dissemination

Results from this trial will be prepared as a manuscript and submitted to peer-reviewed journals for publication. In addition, it will form part of the first authors' PhD thesis. Results from the study will be submitted to international and national scientific sessions with the aim of being presented. We will make a copy of the aid available to a wider genetic audience for use in their clinical practice and study data will be available from the authors. This will include development of an electronic form of the aid.

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AUTHOR STATEMENT

All authors contributed to the manuscript, specifically:

(1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work (CB, LY, CS, JI); AND

(2) Drafting the work or revising it critically for important intellectual content (CB, LY, CS, JI); AND

(3) Final approval of the version to be published (CB, LY, CS, JI); AND

(4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved (CB, LY, CS, JI).

COMPETING INTERESTS

All authors declare they have no disclosures regarding competing interests.

REFERENCES

1. Maron BJ, Maron MS, Semsarian C. Genetics of hypertrophic cardiomyopathy after 20 years: clinical perspectives. *Journal of the American College of Cardiology* 2012;60(8):705-15. doi: 10.1016/j.jacc.2012.02.068

2. Semsarian C, Ingles J, Maron MS, et al. New perspectives on the prevalence of hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2015;65(12):1249-54. doi: 10.1016/j.jacc.2015.01.019

3. Ingles J, Burns C, Barratt A, et al. Application of Genetic Testing in Hypertrophic Cardiomyopathy for Preclinical Disease Detection. *Circ Cardiovasc Genet* 2015;8(6):852-9. doi: 10.1161/CIRCGENETICS.115.001093

4. National Society of Genetic Counselors' Definition Task F, Resta R, Biesecker BB, et al. A new definition of Genetic Counseling: National Society of Genetic Counselors' Task Force report. *Journal of genetic counseling* 2006;15(2):77-83. doi: 10.1007/s10897-005-9014-3

5. Semsarian C, Ingles J. A clinical approach to genetic testing for non-specialists. *Bmj* 2017;358:j4101. doi: 10.1136/bmj.j4101

6. Burns C, James C, Ingles J. Communication of genetic information to families with inherited rhythm disorders. *Heart rhythm* 2018;15(5):780-86. doi: 10.1016/j.hrthm.2017.11.024

7. Burns C, McGaughran J, Davis A, et al. Factors influencing uptake of familial long QT syndrome genetic testing. *Am J Med Genet A* 2016;170A(2):418-25. doi: 10.1002/ajmg.a.37455

8. Christiaans I, Birnie E, Bonsel GJ, et al. Uptake of genetic counselling and predictive DNA testing in hypertrophic cardiomyopathy. *Eur J Hum Genet* 2008;16(10):1201-7. doi: ejhg200892 [pii]
10.1038/ejhg.2008.92 [published Online First: 2008/05/15]

9. Gaff CL, Clarke AJ, Atkinson P, et al. Process and outcome in communication of genetic information within families: a systematic review. *European journal of human genetics : EJHG* 2007;15(10):999-1011. doi: 10.1038/sj.ejhg.5201883

10. Claes E, Evers-Kiebooms G, Boogaerts A, et al. Communication with close and distant relatives in the context of genetic testing for hereditary breast and ovarian cancer in cancer patients. *American journal of medical genetics Part A* 2003;116A(1):11-9. doi: 10.1002/ajmg.a.10868

11. Barsevick AM, Montgomery SV, Ruth K, et al. Intention to communicate BRCA1/BRCA2 genetic test results to the family. *Journal of family psychology : JFP : journal of the Division of Family Psychology of the American Psychological Association* 2008;22(2):303-12. doi: 10.1037/0893-3200.22.2.303

12. Burns C, Yeates L, Spinks C, et al. Attitudes, knowledge and consequences of uncertain genetic findings in hypertrophic cardiomyopathy. *Eur J Hum Genet* 2017;25(7):809-15. doi: 10.1038/ejhg.2017.66

13. Patenaude AF, Tung N, Ryan PD, et al. Young adult daughters of BRCA1/2 positive mothers: what do they know about hereditary cancer and how much do they worry? *Psycho-oncology* 2013;22(9):2024-31. doi: 10.1002/pon.3257

14. Young AL, Butow PN, Vetsch J, et al. Family Communication, Risk Perception and Cancer Knowledge of Young Adults from BRCA1/2 Families: a Systematic Review. *Journal of genetic counseling* 2017;26(6):1179-96. doi: 10.1007/s10897-017-0125-4

15. Forrest LE, Burke J, Bacic S, et al. Increased genetic counseling support improves communication of genetic information in families. *Genetics in medicine : official journal of the American College of Medical Genetics* 2008;10(3):167-72. doi: 10.1097/GIM.0b013e318164540b

16. Fiallos K, Applegate C, Mathews DJ, et al. Choices for return of primary and secondary genomic research results of 790 members of families with Mendelian disease. *European journal of human genetics : EJHG* 2017;25(5):530-37. doi: 10.1038/ejhg.2017.21

17. Forrest K, Simpson SA, Wilson BJ, et al. To tell or not to tell: barriers and facilitators in family communication about genetic risk. *Clinical genetics* 2003;64(4):317-26.

18. Montgomery SV, Barsevick AM, Egleston BL, et al. Preparing individuals to communicate genetic test results to their relatives: report of a randomized control trial. *Fam Cancer* 2013;12(3):537-46. doi: 10.1007/s10689-013-9609-z

19. Seymour KC, Addington-Hall J, Lucassen AM, et al. What Facilitates or Impedes Family Communication Following Genetic Testing for Cancer Risk? A Systematic Review and Meta-Synthesis of Primary Qualitative Research. *Journal of genetic counseling* 2010;19(4):330-42. doi: 10.1007/s10897-010-9296-y

20. Healey E, Taylor N, Greening S, et al. Quantifying family dissemination and identifying barriers to communication of risk information in Australian BRCA families. *Genetics in medicine : official journal of the American College of Medical Genetics* 2017;19(12):1323-31. doi: 10.1038/gim.2017.52

21. Hodgson J, Metcalfe S, Gaff C, et al. Outcomes of a randomised controlled trial of a complex genetic counselling intervention to improve family communication. *European journal of human genetics : EJHG* 2016;24(3):356-60. doi: 10.1038/ejhg.2015.122

22. Suthers GK, Armstrong J, McCormack J, et al. Letting the family know: balancing ethics and effectiveness when notifying relatives about genetic testing for a familial disorder. *Journal of medical genetics* 2006;43(8):665-70. doi: 10.1136/jmg.2005.039172

23. Stacey D, Legare F, Lewis K, et al. Decision aids for people facing health treatment or screening decisions. *Cochrane Db Syst Rev* 2017(4) doi: Artn Cd001431 10.1002/14651858.Cd001431.Pub5

24. Wakefield CE, Meiser B, Homewood J, et al. Development and pilot testing of two decision aids for individuals considering genetic testing for cancer risk. *Journal of genetic counseling* 2007;16(3):325-39. doi: 10.1007/s10897-006-9068-x

25. Vavolizza RD, Kalia I, Aaron KE, et al. Disclosing Genetic Information to Family Members About Inherited Cardiac Arrhythmias: An Obligation or a Choice? *Journal of genetic counseling* 2015;24(4):608-15. doi: 10.1007/s10897-014-9783-7

26. Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Annals of internal medicine* 2013;158(3):200-7. doi: 10.7326/0003-4819-158-3-201302050-00583

27. Ingles J, Lind JM, Phongsavan P, et al. Psychosocial impact of specialized cardiac genetic clinics for hypertrophic cardiomyopathy. *Genet Med* 2008;10(2):117-20. doi: 10.1097/GIM.0b013e3181612cc7
00125817-200802000-00007 [pii] [published Online First: 2008/02/19]

28. Bagnall RD, Weintraub RG, Ingles J, et al. A Prospective Study of Sudden Cardiac Death among Children and Young Adults. *New Engl J Med* 2016;374(25):2441-52. doi: 10.1056/NEJMoa1510687

29. Burns C, Bagnall RD, Lam L, et al. Multiple Gene Variants in Hypertrophic Cardiomyopathy in the Era of Next-Generation Sequencing. *Circ Cardiovasc Genet* 2017;10(4) doi: 10.1161/CIRCGENETICS.116.001666

30. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genetics in Medicine* 2015;17(5):405-24. doi: 10.1038/gim.2015.30

31. Smagarinsky Y, Burns C, Spinks C, et al. Development of a communication aid for explaining hypertrophic cardiomyopathy genetic test results. *Pilot Feasibility Stud* 2017;3:53. doi: 10.1186/s40814-017-0205-0

32. Read CY, Perry DJ, Duffy ME. Design and psychometric evaluation of the Psychological Adaptation to Genetic Information Scale. *J Nurs Scholarsh* 2005;37(3):203-8.

33. Kasparian NA, Wakefield CE, Meiser B. Assessment of psychosocial outcomes in genetic counseling research: an overview of available measurement scales. *Journal of genetic counseling* 2007;16(6):693-712. doi: 10.1007/s10897-007-9111-6 [published Online First: 2007/08/19]

34. Erblich J, Brown K, Kim YM, et al. Development and validation of a breast cancer genetic counseling knowledge questionnaire. *Patient Educ Couns* 2005;56(2):182-91. doi: 10.1016/j.pec.2004.02.007

35. Shiloh S, Avdor O, Goodman RM. Satisfaction with genetic counseling: dimensions and measurement. *American journal of medical genetics* 1990;37(4):522-9. doi: 10.1002/ajmg.1320370419 [published Online First: 1990/12/01]

36. McAllister M, Wood AM, Dunn G, et al. The Genetic Counseling Outcome Scale: a new patient-reported outcome measure for clinical genetics services. *Clinical genetics* 2011;79(5):413-24. doi: 10.1111/j.1399-0004.2011.01636.x [published Online First: 2011/01/25]

37. Ko C, Arscott P, Concannon M, et al. Genetic testing impacts the utility of prospective familial screening in hypertrophic cardiomyopathy through identification of a nonfamilial subgroup. *Genet Med* 2017 doi: 10.1038/gim.2017.79

Table 1: Trial Registration Data	
Primary registry and trial identifying number	Australian New Zealand Clinical Trials Registry: ACTRN12617000706370
Date of registration in primary registry	17/05/2017
Secondary identifying numbers	NA
Source(s) of monetary or material support	National Heart Foundation of Australia
Primary sponsor	The University of Sydney
Secondary sponsor	NA
Contact for public queries	Dr Jodie Ingles j.ingles@centenary.org.au
Contact for scientific queries	Dr Jodie Ingles j.ingles@centenary.org.au
Public title	Use of an aid to improve communication of genetic risk information to families with hypertrophic cardiomyopathy (HCM)
Scientific title	Use of a custom designed aid to improve communication of genetic results in families with HCM
Countries of recruitment	Australia
Health condition (s) or problem (s) studied	HCM
Intervention	Use of a custom designed aid to communicate HCM genetic test results
Key inclusion and exclusion criteria	HCM probands with a genetic result ready for return Participants must be aged 18 years or older Sufficient written English skills as nominated by the participant
Study type	Prospective randomised controlled trial
Date of first enrolment	25/11/2016
Target sample size	45
Recruitment status	Recruiting
Primary outcome (s)	Ability and confidence of the proband to communicate genetic results to at-risk relatives
Key secondary outcomes	Secondary outcomes will assess genetic knowledge, satisfaction with services, outcomes from genetic counselling and psychological adaptation to genetic information

Table 2: Certainty sub-scale of the PAGIS scale
1. I understand how I came to have hypertrophic cardiomyopathy
2. I understand the health risks my relatives face because of hypertrophic cardiomyopathy
3. I feel certain that I understand the meaning of having hypertrophic cardiomyopathy
4. I understand the chances I have of passing hypertrophic cardiomyopathy along to my children
5. I feel that I can explain to other people what having hypertrophic cardiomyopathy means
6. I feel confused because I have been given different explanations of what having hypertrophic cardiomyopathy means

Abbreviations: PAGIS = Psychological Adaptation to Genetic Information Scale.

Table 3: Primary outcome measure converted to a primary outcome

Measures incorporated

1. Certainty sub scale from PAGIS (measuring confidence)
2. Adult first degree relatives informed of genetic risk (measuring ability)

Calculation examples

Example 1:

Certainty score from PAGIS sub scale = 18/36= 0.5

Relatives informed of risk = 3/6= 0.5

= (0.5 + 0.5 = 1) / 2= 0.5

= 50%

Therefore this participant falls into the 'poor communication' category of the primary outcome

Example 2:

Certainty score from PAGIS sub scale = 30/36= 0.83

Relatives informed of risk = 7/8= 0.88

(0.88+ 0.83) / 2= 0.86

= 86%
Therefore this participant falls into the 'fair communication' category of this primary outcome

Abbreviations: PAGIS = Psychological Adaptation to Genetic Information Scale.

FIGURE LEGENDS

FIGURE 1: Flow chart of overall study design

FIGURE 2: Example page from communication aid: Genetic testing step by step

FIGURE 3: Example page from communication aid: What is my genetic result?

FIGURE 4: Example page from communication aid: Family-screening guidelines

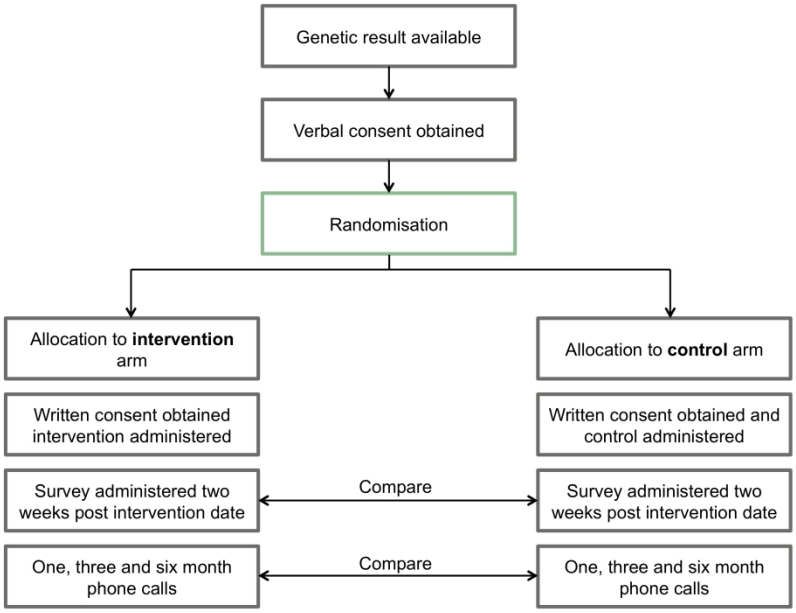

Figure 1

297x209mm (300 x 300 DPI)

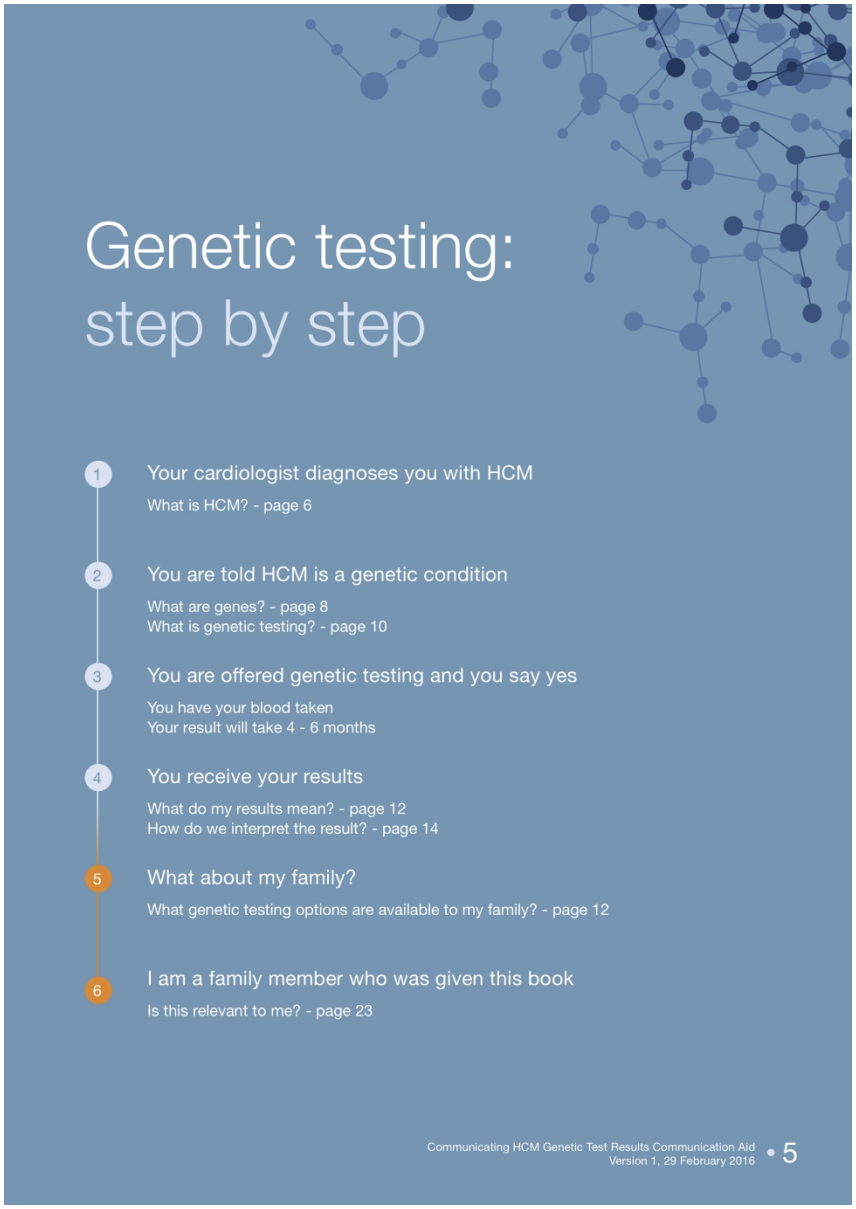

Figure 2

209x296mm (300 x 300 DPI)

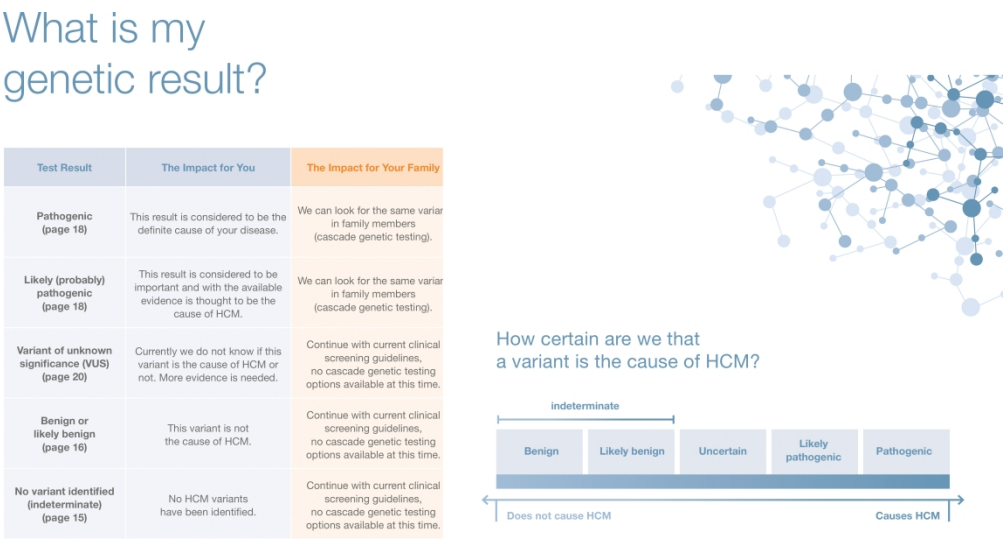

Figure 3

374x197mm (300 x 300 DPI)

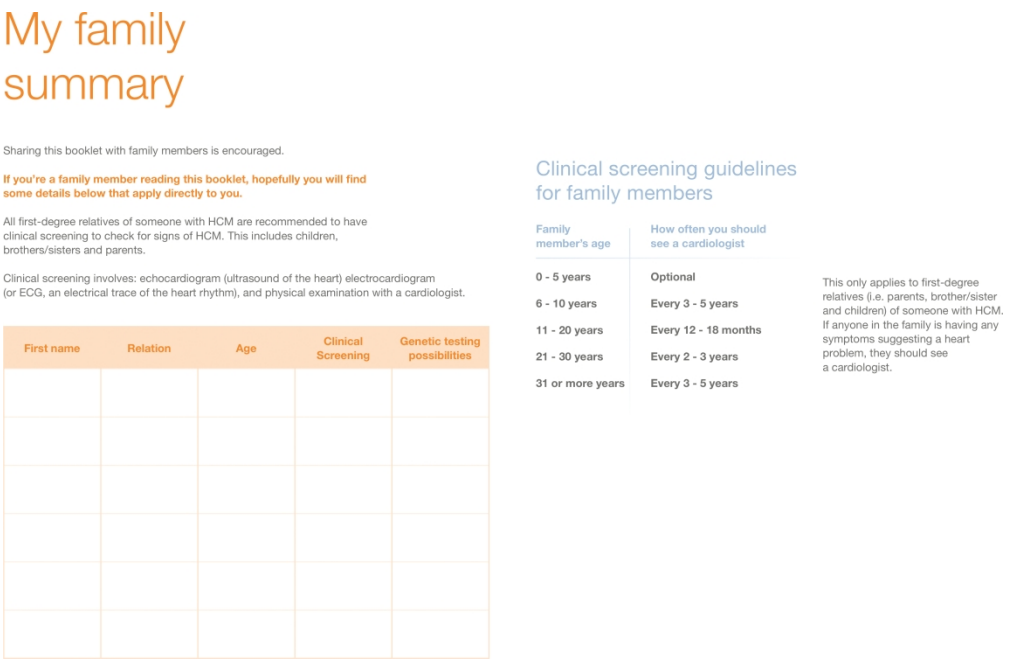

Figure 4

349x225mm (300 x 300 DPI)

Communicating Hypertrophic Cardiomyopathy (HCM) Genetic Test Results

INFORMATION FOR PARTICIPANTS

Introduction

You are invited to take part in a research study examining how we can best communicate genetic test results in hypertrophic cardiomyopathy (HCM). Genetic testing for genetic heart diseases like HCM has become increasingly complex and our method of explaining these results needs to evolve to meet these changing needs. Cardiac genetic counsellors coordinate the genetic testing process and they play a key role in ensuring the information you are receiving is clear and meaningful for you and your family. The objective of this study is to compare the effectiveness of an intervention aimed at improving the way we communicate genetic test result information with our current usual care. If you consent to the study, you will be randomly assigned to either the new communication intervention or to usual care.

Individuals with hypertrophic cardiomyopathy are eligible to participate in this study if they are the first in their family to have genetic testing. People aged 16 years or older are eligible to participate; however children younger than this are excluded.

The study is being conducted by Dr Jodie Ingles, Prof Christopher Semsarian, Ms Laura Yeates and Ms Charlotte Burns from the Molecular Cardiology Research Program, Centenary Institute and Royal Prince Alfred Hospital Sydney.

Study Procedures

If you agree to participate in this study, you will be asked to complete the participant consent form. You will then be randomly allocated to one of two groups, to receive your genetic test result. Two weeks after your genetic test result appointment, you will be asked to complete a survey *(either paper or online)*, asking about your understanding of genetic testing for HCM. This survey will take between 10-20 minutes to complete.

In addition, the researchers would like to phone you at one, three and six month intervals to follow up with you after you receive your genetic result. These phone calls will take approximately 10 minutes and will be conducted at a time that suits you.

Researchers will have access to your medical record to obtain information relevant to this study. Information about you may also be sought from the *Australian Genetic Heart Disease Registry*, if you have enrolled (www.heartregistry.org.au).
Confidentiality of the survey responses will be paramount. Your name will be replaced with a unique code and only Dr Jodie Ingles will have access to the true identity of respondents.

No additional genetic testing will be carried out as part of this study.

Information collected about you will be securely stored.

Benefits

While we intend that this research study furthers medical knowledge and may improve management of genetic heart diseases in the future, it may not be of direct benefit to you.

Voluntary Participation

Participation in this study is entirely voluntary. You do not have to take part in it. If you do take part, you can withdraw at any time without having to give a reason. Whatever your decision, please be assured that it will not affect your medical treatment or your relationship with the staff who are caring for you.

Confidentiality

All of the information collected from you for the study will be treated confidentially, and only the researchers named above will have access to it. The study results may be presented at a conference or in a scientific publication, but individual participants will not be identifiable in such a presentation.

Any forms completed online, including the participant consent form and survey will be extremely secure to maintain participant privacy.

Further Information

When you have read this information, one of the investigators is available to discuss it with you further and answer any questions you may have. If you would like to know more at any stage, please feel free to contact:

Dr Jodie Ingles
Molecular Cardiology Research Program
Centenary Institute
Locked Bag No 6, Newtown NSW 2042
Ph. 02 9565 6293
Email. j.ingles@centenary.org.au Web. www.heartregistry.org.au

This information sheet is for you to keep.

Ethics Approval and Complaints

This study has been approved by the Ethics Review Committee (RPAH Zone) of the Sydney Local Health District. Any person with concerns or complaints about the conduct of this study should contact the Executive Officer on 02 9515 6766 and quote protocol number X16-0030.

Communicating Hypertrophic Cardiomyopathy (HCM) Genetic Test Results

PARTICIPANT CONSENT FORM

I, ... *[name]*

of

.....*[address]*

.....*[email]*

have read and understood the Information for Participants on the abovenamed research study

and have discussed the study with .....

I have been made aware of the procedures involved in the study.

I understand that my participation in this study will allow the researchers to have access to my medical record, including information held by the Australian Genetic Heart Disease Registry (if I am enrolled), and I agree to this.

I freely choose to participate in this study and understand that I can withdraw at any time.

I also understand that the research study is strictly confidential.

I hereby agree to participate in this research study.

NAME: .....

SIGNATURE: .....

DATE: .....

NAME OF WITNESS: .....

SIGNATURE OF WITNESS: .....

Hello, this is (Insert Name) from the Centenary Institute, may I please speak to (Participant name)?

I am phoning (as we discussed back in (insert month of genetic result return) to follow up with you after you received your genetic result as part of our research into communicating genetic results. This is your (one month, three month, six month) follow up phone call. I was hoping to get some additional information from you regarding your gene result. Do you have 10 minutes or so to do this now- or I can arrange a more appropriate time?

SECTION 1: 3-generation pedigree documented – Have this documented prior to phone call. Confirm during phone call.

SECTION 2

Who in the family have you told about the following: (List names/details): Your diagnosis of HCM?

About your genetic result?

Who in the family has had an echo/ecg/Cardiology review- Outcome? (Assess against guidelines)?

Who in the family has had genetic testing- Outcome?

Who in the family is awaiting an appointment- with whom?

SECTION 3:

Total number of first degree relatives informed of diagnosis =

Total number of first degree relatives informed of genetic test outcome=

Total number of first degree relatives who have had cardiology review=

Total number of first degree relatives who have had genetic review=

Total number of first degree relatives awaiting review=

Total number of first degree relatives with a positive clinical screen=

Total number of relatives with a negative clinical screen =

Total number of first degree relatives with a positive genetic result =

Total number of first degree relatives with a negative genetic result=

Total number of other relatives informed =

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	**1**
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	**2, Table 1**
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	**9, Table 1**
Protocol version	#3	Date and version identifier	**1**
Funding	#4	Sources and types of financial, material, and other support	**18**
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	**1, 18**
Roles and	#5b	Name and contact information for the trial	**NA- No trial sponsor.**

responsibilities: sponsor contact information		sponsor	
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	**NA- no role other than funding for key researchers.**
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	**NA**
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	**4**
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	11
Objectives	#7	Specific objectives or hypotheses	**7,8**
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	**9**
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	**9**

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	**9**
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	**11**
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	**NA**
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	**NA- intervention was one clinic appointment**
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	**NA**
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	**12,13,14**
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	**8, Figure 1**

Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	**10**
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	**9**
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	**9,10**
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	**9,10**
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	**9,10**
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	**15**
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	**NA- researcher will be blinded to treatment arm for analysis only, however researchers will not be blinded during intervention**

			because of nature of intervention.
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	**12,13,14, Table 2, Figure 2, Figure 3, Figure 4**
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	**15**
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	**15**
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	**16**
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	**16**
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical	**NA- not relevant to study design.**

		methods to handle missing data (eg, multiple imputation)	
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	**NA- not relevant, no data monitoring committee.**
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	**NA- no interim analysis.**
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	**NA**
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	**NA**
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	**15**
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	**NA- No protocol modifications will be made.**
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or	**9**

		authorised surrogates, and how (see Item 32)	
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	**NA**
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	**16**
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	**1**
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	**16/17**
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	**NA**
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	**16/17**
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	**18**
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	**17**
Informed consent	#32	Model consent form and other related	**Supplementary material**

materials		documentation given to participants and authorised surrogates	
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	**NA**