PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	EVALUATING A CUSTOM DESIGNED AID TO IMPROVE COMMUNICATION OF GENETIC RESULTS IN FAMILIES WITH HYPERTROPHIC CARDIOMYOPATHY: STUDY PROTOCOL FOR A RANDOMISED CONTROLLED TRIAL
AUTHORS	Burns, Charlotte; Yeates, Laura; Semsarian, Christopher; Ingles, Jodie

VERSION 1 – REVIEW

REVIEWER	Adam Helms University of Michigan, United States
REVIEW RETURNED	27-Oct-2018

GENERAL COMMENTS	The authors present a randomized study design to investigate the impact of a novel aid for communication of genetic testing results to hypertrophic cardiomyopathy (HCM) patients. The investigators have identified an important area of study with great need of improvement. The primary purpose of the study is to improve HCM patients' understanding of their genetic testing results, so that they will be subsequently more likely to communicate specific recommendations for screening to their at-risk relatives. The study has been carefully planned and organized. The follow-up and statistical analysis plans are appropriate. They have met the SPIRIT guidelines applicable to this study and the statistical analysis plan is appropriate. Overall, this will be a high impact study in the field of HCM genetics, with likely applicability to other genetic conditions as well. I have a few questions/suggestions as the authors finalize their plans. 1. Will the study include all HCM patients who have genetic testing performed? I think it would be ideal if the type of HCM to be studied is clarified. Both the investigators and our own group have demonstrated that ~half of HCM cases at referral centers represent in an apparently non-familial group – relatives of this group would have less to gain from screening. My opinion is that it would be better to focus on familial HCM (either by using a cut-off on the Toronto score for study entry, or by limiting to HCM with either positive genetic test, VUS, or positive family history. 2. The genetic test result will inevitably influence the screening follow-up in family members, even if the investigators do not intend this. Our previous survey study of familial vs. non-familial HCM showed that adherence to screening recommendations was significantly higher in the familial/+genetic test group, even though our recommendations at the time were not different for the apparently non-familial group. Therefore, the authors may consider randomization by group so that the intervention group has an

	equal number of positive genetic tests / VUS / negative genetic test. If the investigators choose to include the apparently non-familial group, then I think it would be important to randomize an equal number of those patients to each study group – particularly with the relatively low number of study participants planned, random variation in allocation could significantly confound the results (i.e. if by random chance, more non-familial get randomized into one of the study groups). Additionally, we currently give different recommendations based on the likelihood of familial HCM. If the investigators are also influenced in the strength of their recommendations based on the type of HCM, that should also be considered in the study entry criteria. 3. The investigators use confidence in understanding the genetic testing result / screening recommendations as primary end point that is a surrogate endpoint for the major clinically relevant endpoint, which is the actual follow through by relatives to have screening for HCM. The latter is assessed as a long-term (non-primary) outcome. I think this is reasonable from a practical standpoint, but does raise some limitations: a. There could significant inter-individual variability in perceptions of self-confidence (unrelated to the study) that would possibly confound the statistical power and may not be fully appreciated in the assumptions used for the power calculation. A larger study group than 21 per group would be better to account for this. b. There could be other reasons, aside from confidence, that results are not transmitted to relatives and these would not be reflected in the confidence rating. The investigators bring up these issues in the introduction – specifically, interpersonal relationships and opinions held by the family members would also affect actual follow-through on screening recommendations. Ideally, the intervention is employed in a way that addresses these considerations as well (see #4). 4. From my perspective, the longer-term endpoint (actual family member follow-through on screening) is the most important. From our prior survey-based study, only ~1/3 of relatives actually followed through on screening (with a difference based on genetic test result as above) despite thorough genetic counseling and phone follow-up in almost all patients. Increasing the follow-through rate is clearly very important. a. I would suggest, if practically feasible, the authors to consider powering the study also for the longer-term outcome. b. Randomization by group (as above) may be important for this outcome. c. Another suggestion is to consider a paper and electronic forms of the communication aid specifically for dissemination among family members. We have taken to the practice of giving either multiple copies of a letter, or a letter by email, to each patient that is intended for them to give to the family members. The letter contains specific instructions to family members for screening – in this way, the patient can directly pass the letter to family members (without our direct involvement), which hopefully increases the accuracy of information getting to the relatives (we have no studies planned to assess this practice). The communication aid could be used similarly – so it may not only help understanding by the patient, but also directly by family members. d. Although it may not be within the scope of this study, another idea for increasing follow-through by family members would be a short video, available by hyperlink through the communication aid, that could be directly viewable by family members. The video could reinforce the importance of screening in asymptomatic family

	members of HCM patients with a strong likelihood of autosomal dominant inheritance. 5. The first follow-up phone call for the long-term outcome is 1 month out from the clinic visit. This may not be enough time for family members to have followed through on screening and as the authors note, may actually influence subsequent screening practices, confounding differences between the study and control groups. I would suggest considering omitting the 1-month phone follow-up, but keeping the 3 and 6-month phone calls. 6. In Figure 3, shouldn't the indeterminate bar be over the "Uncertain" category?

REVIEWER	Susan Christian University of Alberta, Canada
REVIEW RETURNED	30-Oct-2018

GENERAL COMMENTS	This is a nicely designed randomized control study evaluating the effectiveness of a communication tool to assist with risk communications for families diagnosed with HCM. This study will provide valuable outcome data to the field of cardiac genetics. Comments: • Page 8 line 12/13- Further, it is recognised "that" patients… • What does the post counselling phone calls look like? Is there a script? Communication aid: • Is this always a paper aid or is an electronic version available to the patient. Many patients share information with relatives electronically via email especially if they don't live close by. This could impact the likelihood that they share the aid itself. Are you asking if they shared the aid or just the risk information? Data collection and outcomes Primary Outcomes: "Subsequent ability to pass this information on will be measured by the number of at-risk relatives informed of genetic results by the proband." • Based on Table 2 you are calculating a percentage by using the total at risk family members as denominator. This should be described in the text here. • Please describe the cut off you are using to distinguish between a poor communicator and a fair communicator? Also, how you came to that cut-off. Additional Comments: • There is a discrepancy in the eligibility criteria between the text and the invitation to take part in the study. Eligibility Criteria: Participants must be aged 18 years or older…" Invitation to participate: "People aged 16 years or older are eligible to participate; however children younger than this are excluded."

VERSION 1 – AUTHOR RESPONSE

Response to the reviewers:

We thank the reviewers for their comments. We have responded below and in the revised manuscript.

Response to Reviewer # 1:

The authors present a randomized study design to investigate the impact of a novel aid for communication of genetic testing results to hypertrophic cardiomyopathy (HCM) patients. The investigators have identified an important area of study with great need of improvement. The primary purpose of the study is to improve HCM patients' understanding of their genetic testing results, so that they will be subsequently more likely to communicate specific recommendations for screening to their at-risk relatives. The study has been carefully planned and organized. The follow-up and statistical analysis plans are appropriate. They have met the SPIRIT guidelines applicable to this study and the statistical analysis plan is appropriate. Overall, this will be a high impact study in the field of HCM genetics, with likely applicability to other genetic conditions as well.

I have a few questions/suggestions as the authors finalize their plans.

1. Will the study include all HCM patients who have genetic testing performed? I think it would be ideal if the type of HCM to be studied is clarified. Both the investigators and our own group have demonstrated that ~half of HCM cases at referral centers represent in an apparently non-familial group – relatives of this group would have less to gain from screening. My opinion is that it would be better to focus on familial HCM (either by using a cut-off on the Toronto score for study entry, or by limiting to HCM with either positive genetic test, VUS, or positive family history.

Yes, the study includes all HCM patients attending our clinic who have had genetic testing performed with a genetic result ready to be returned. We have clarified this in the methods (Page 9). Unfortunately when the trial was designed we had not considered whether non-familial status would impact on communication, however we will keep this in mind when interpreting our results.

2. The genetic test result will inevitably influence the screening follow-up in family members, even if the investigators do not intend this. Our previous survey study of familial vs. non-familial HCM showed that adherence to screening recommendations was significantly higher in the familial/+genetic test group, even though our recommendations at the time were not different for the apparently non-familial group. Therefore, the authors may consider randomization by group so that the intervention group has an equal number of positive genetic tests / VUS / negative genetic test. If the investigators choose to include the apparently non-familial group, then I think it would be important to randomize an equal number of those patients to each study group – particularly with the relatively low number of study participants planned, random variation in allocation could significantly confound the results (i.e. if by random chance, more non-familial get randomized into one of the study groups). Additionally, we currently give different recommendations based on the likelihood of familial HCM. If the investigators are also influenced in the strength of their recommendations based on the type of HCM, that should also be considered in the study entry criteria.

We do agree this would potentially be a useful way to perform the study, however recruitment is in fact nearing completion. Currently all of our HCM patients receive the same advice regarding clinical screening of family, however as per the Ko et al. GIM paper (as referred to) we have amended the analysis section to state sub-group analyses will be performed comparing familial and non-familial HCM probands (Page 16).

3. The investigators use confidence in understanding the genetic testing result / screening recommendations as primary end point that is a surrogate endpoint for the major clinically relevant endpoint, which is the actual follow through by relatives to have screening for HCM. The latter is assessed as a long-term (non-primary) outcome. I think this is reasonable from a practical standpoint, but does raise some limitations:

a. There could significant inter-individual variability in perceptions of self-confidence (unrelated to the study) that would possibly confound the statistical power and may not be fully appreciated in the assumptions used for the power calculation. A larger study group than 21 per group would be better to account for this.

We agree, determining the endpoint for this study was difficult and due to potential heterogeneity of responses our sample may end up underpowered. We have almost completed recruitment and currently have n= 50 participants (n= 23 in the control and n= 27 in the intervention). We also have a number of secondary end-points, which will hopefully yield important data, and we feel these are adequately powered.

b. There could be other reasons, aside from confidence, that results are not transmitted to relatives and these would not be reflected in the confidence rating. The investigators bring up these issues in the introduction – specifically, interpersonal relationships and opinions held by the family members would also affect actual follow-through on screening recommendations. Ideally, the intervention is employed in a way that addresses these considerations as well (see #4).

We agree, family communication and understanding about genetics and risk is complicated and multi-dimensional. We have included a number of secondary outcome measures to incorporate some of these issues. The aid and intervention have been developed and used to focus on providing the genetic information to improve understanding, confidence and ability to communicate. We do hope to build on this tool, and offering methods to actively support communication that help overcome factors such as poor family relationships may be a logical next step.

4. From my perspective, the longer-term endpoint (actual family member follow-through on screening) is the most important. From our prior survey-based study, only ~1/3 of relatives actually followed through on screening (with a difference based on genetic test result as above) despite thorough genetic counseling and phone follow-up in almost all patients. Increasing the follow-through rate is clearly very important.
a. I would suggest, if practically feasible, the authors to consider powering the study also for the longer-term outcome.

While this is an important area, we did consider that confidence to communicate would be the primary goal rather than actual family member behaviours. If we make the assumption the communication aid group have good screening (40% is a conservative “good” estimate based on the Ko et al. GIM paper of sarcomere positive relatives) compared to lower screening rate of 10-20% in the control group, then we would be adequately powered using the current sample size.

b. Randomization by group (as above) may be important for this outcome.

This is a good suggestion and we have amended the protocol on Page 17 to include this sub-analysis in our data analysis plan.

c. Another suggestion is to consider a paper and electronic forms of the communication aid specifically for dissemination among family members. We have taken to the practice of giving either multiple copies of a letter, or a letter by email, to each patient that is intended for them to give to the family members. The letter contains specific instructions to family members for screening – in this way, the patient can directly pass the letter to family members (without our direct involvement), which hopefully increases the accuracy of information getting to the relatives (we have no studies planned to assess this practice). The communication aid could be used similarly – so it may not only help understanding by the patient, but also directly by family members.

Although it may not be within the scope of this study, another idea for increasing follow-through by family members would be a short video, available by hyperlink through the communication aid, that could be directly viewable by family members. The video could reinforce the importance of screening in asymptomatic family members of HCM patients with a strong likelihood of autosomal dominant inheritance.

We agree and as mentioned we will definitely be considering other ways we can build on the communication aid, including electronic versions, building in some decision support for family members considering cascade genetic testing and providing even greater support to overcome some of those communication obstacles such as poor family relationships.

We have amended the protocol to include mention of developing an electronic version of the aid on Page 17 under the heading 'Dissemination'.

5. The first follow-up phone call for the long-term outcome is 1 month out from the clinic visit. This may not be enough time for family members to have followed through on screening and as the authors note, may actually influence subsequent screening practices, confounding differences between the study and control groups. I would suggest considering omitting the 1-month phone follow-up, but keeping the 3 and 6-month phone calls.

We do agree that longer term outcomes would be better collected beyond 1 month, and are collecting this data. We were concerned about including these measures as "outcomes" given the periodic calls may themselves act as reminders to communicate with relatives. We feel 1 month calls will give us a good indication of the intention to communicate. We have tried to better clarify this on Page 16/17.

6. In Figure 3, shouldn't the indeterminate bar be over the "Uncertain" category?

We have considered uncertain results differently as they often alter the discussion with the proband and in some cases may warrant further investigation (such as co-segregation testing in affected relatives, experimental work such as RNA studies etc). When going through the aid with patients who have received an uncertain result, the genetic counsellor elaborates on this and the page for VUS results delves into these issues in greater detail.

Response to Reviewer # 2:

This is a nicely designed randomized control study evaluating the effectiveness of a communication tool to assist with risk communications for families diagnosed with HCM. This study will provide valuable outcome data to the field of cardiac genetics.

- Page 8 line 12/13- Further, it is recognised "that" patients…

Thank you, we have amended this in the manuscript.

- What does the post counselling phone calls look like? Is there a script?

We have amended the manuscript on page 8 to incorporate the phone call script into the supplementary material.

Communication aid:

- Is this always a paper aid or is an electronic version available to the patient. Many patients share information with relatives electronically via email especially if they don't live close by. This

could impact the likelihood that they share the aid itself. Are you asking if they shared the aid or just the risk information?

Thank you, we agree. This is an important consideration. As per reviewer 1's comment we have included a sentence on Page 17 to state that further development of communication will likely include making it electronic or web-based. We are asking about communication of the risk information and have clarified this on Page 8.

Data collection and outcomes
Primary Outcomes:
"Subsequent ability to pass this information on will be measured by the number of at-risk relatives informed of genetic results by the proband."

- Based on Table 2 you are calculating a percentage by using the total at risk family members as denominator. This should be described in the text here.

Thank you, this is an important omission from the protocol. We have amended the manuscript on page 13 to correct this.

- Please describe the cut off you are using to distinguish between a poor communicator and a fair communicator? Also, how you came to that cut-off.

As above, we have amended this on Page 13/14.

Additional Comments:
- There is a discrepancy in the eligibility criteria between the text and the invitation to take part in the study.

Eligibility Criteria: Participants must be aged 18 years or older…"
Invitation to participate: "People aged 16 years or older are eligible to participate; however children younger than this are excluded."

Thank you for pointing this out. We have amended the manuscript inclusion criteria and it is now correct (Page 9).

VERSION 2 – REVIEW

REVIEWER	Adam Helms University of Michigan, United States of America
REVIEW RETURNED	04-Dec-2018

GENERAL COMMENTS	The authors have responded or revised for all comments and I do not have any further suggestions -- will look forward to seeing results of the study.

REVIEWER	Susan Christian University of Alberta
REVIEW RETURNED	29-Nov-2018

GENERAL COMMENTS	All my previous edits have been addressed. I only have a few minor edits:

	1. I think the authors should be consistent with using gene result or genetic result. Genetic result seems to be used more often therefore the following edits are suggested (page 44 line 27 - change gene to genetic, page 53 line 20 should be genetic result not genetic test result, page 58 line 41 change gene to genetic, page 58 line 60 change gene to genetic) 2. Page 47, line 23- suggest adding "these factors " are difficult to target as areas for improvement. 3. page 49, line 13- suggest adding health information is "provided in written format"

VERSION 2 – AUTHOR RESPONSE

Response to the reviewers:

We thank the reviewers for their comments. We have responded to reviewer 2's remaining minor comments and changes are shown in the manuscript.

Response to Reviewer # 2:

Reviewer Name: Susan Christian

Institution and Country: University of Alberta

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

All my previous edits have been addressed. I only have a few minor edits:

1. I think the authors should be consistent with using gene result or genetic result. Genetic result seems to be used more often therefore the following edits are suggested (page 44 line 27 - change gene to genetic, page 53 line 20 should be genetic result not genetic test result, page 58 line 41 change gene to genetic, page 58 line 60 change gene to genetic)

This has been changed to genetic result throughout the manuscript.

2. Page 47, line 23- suggest adding "these factors " are difficult to target as areas for improvement.

Agree, this has been changed.

3. page 49, line 13- suggest adding health information is "provided in written format"

This has been changed.