Author's response to reviews

Title: Patient accounts of diagnostic testing for familial hypercholesterolemia: comparing responses to genetic and non-genetic testing methods

Authors:

Gareth J Hollands (gareth.hollands@kcl.ac.uk)
David Armstrong (david.armstrong@kcl.ac.uk)
Angela Macfarlane (angela.macfarlane@wpct.nhs.uk)
Martin A Crook (m.crook@nhs.net)
Theresa M Marteau (theresa.marteau@kcl.ac.uk)

Version: 2 Date: 27 June 2012

Author's response to reviews: see over
Dear Prof Marteau,

Your manuscript has now been peer reviewed and the comments are accessible in PDF format from the link below. Do let us know if you have any problems opening the file.

Referee 1: http://www.biomedcentral.com/imedia/1610824273709013_comment.pdf
Referee 2: http://www.biomedcentral.com/imedia/1325138398715735_comment.pdf

We would be grateful if you could address the comments in a revised manuscript and provide a cover letter giving a point-by-point response to the concerns.

Please also ensure that your revised manuscript conforms to the journal style (http://www.biomedcentral.com/info/ifora/medicine_journals). It is important that your files are correctly formatted. Please also ensure that your manuscript meets the RATS requirement for qualitative research (http://www.biomedcentral.com/ifora/rats).

We look forward to receiving your revised manuscript by 26 May 2012. If you imagine that it will take longer to prepare please give us some estimate of when we can expect it.

You should upload your cover letter and revised manuscript through http://www.biomedcentral.com/manuscript/login/man.asp?txt_nav=man&txt_man_id=6186128726649600. You will find more detailed instructions at the base of this email.

Please don't hesitate to contact me if you have any problems or questions regarding your manuscript.

With best wishes,

Tim Sands PhD
Executive Editor
BMC-series Journals
BioMed Central
Floor 6, 236 Gray's Inn Road
London, WC1X 8HL

Tel: +44 (0) 20 3192 2013
e-mail: editorial@biomedcentral.com
Web: http://www.biomedcentral.com/
Dear Dr. Sands,

Thank you for allowing us the opportunity to respond to the helpful feedback of the reviewers. Below, we have responded to each of their comments in turn.

Kind regards,

Theresa Marteau, on behalf of all authors

Reviewer's report 1

Title: Patient accounts of diagnostic testing for familial hypercholesterolemia: comparing responses to genetic and non-genetic testing methods

Version: 1 Date: 6 April 2012

Reviewer: gerald watts

Reviewer's report:
An important study based on qualitative methods suggesting that genetic and phenotypic testing for FH does not have a discernible adverse impact on patients' lives. Endpoints confirm continuity of perspectives, reduction in uncertainty, lack of prominence of FH relative to other conditions and only minor social impact. So all is well with testing for FH by which ever method, but how generalizable are the results, given the small sample size and selected group?

RESPONSE: Empirical (rather than conceptual) generalisation from qualitative studies is difficult, as we have acknowledged in the Discussion. Nevertheless, we have tried to validate our findings in the context of other studies, in particular reviews of the problems in this area.

Design appropriate, but method of selection of volunteers unclear. ? randomly selected from parent population?

RESPONSE: We agree with the reviewer that this was not clearly explained in the previous manuscript. We recruited consecutive patients to ‘fill’ the four cells of the factorial sampling frame as is now explained in the Methods section (second paragraph).

Clinical characteristics of patients not specified. Table required. Were these all people without CHD or low risk FH. Not all FH mutations are the same in UK; non-pathogenic mutations may not cause concern, whereas major deletion with very high cholesterol can. Details required.

RESPONSE: We have now added a participant characteristics table (Table 1). Outside of the information contained in this table and that apparent from the eligibility criteria (aged 18 years+; first or second degree relative of proband with FH; undergoing
diagnostic testing for FH (having received no prior diagnosis), we did not systematically gather detailed information on participants’ clinical characteristics. Participants were only asked whether they had received cholesterol tests in the past and what test result they expected, but clearly more information for interpretation would have been valuable and as such is a limitation of the study.

Results would be easier to follow in Summary Table, rather than sentences with annotations that remind one of The Tractatus.

**RESPONSE:** We doubt if the paper has the same significance as Wittgenstein’s masterpiece, but hope it is not as dense. We regard the presentation here as unexceptional for reporting qualitative studies.

Page 5 para 2 line 3: 100-fold relative risk of fatal CHD in FH is a gross exaggeration emanating from initial analyses from Simon Broome Registry. HRs are now accepted to be lower, ranging from 10 to 15.

**RESPONSE:** Thanks for this. We have revised this section and taken out the original reference.

The language is in part somewhat Baroque and arcane: are words like 'ineluctable', 'provenance' and 'salience' really necessary. The simpler word would do better and have greater impact with non-specialist readers in this reviewer’s opinion

**RESPONSE:** We have now revised the paper throughout in line with the suggestion, aiming to make the article clearer and more readable.

**Level of interest:** An article of importance in its field
**Quality of written English:** Needs some language corrections before being published
**Statistical review:** No, the manuscript does not need to be seen by a statistician.
1. The methods section needs to spell out the diagnostic process – what clinical interactions led up to this? What did receiving results of the diagnostic test consist of? How were results delivered? What does providing a ‘formal FH diagnosis’ entail? This particularly needs clarification for non-DNA diagnosis – especially in the light of your earlier paper (Will et al, 2010). This will help readers to make sense of what interviewees might know at T1 and T2 interviews. Also, what was the clinical history of the participants? eg How many already knew they had high cholesterol? How many were already being treated for high cholesterol? This is very important contextual information, given the levels of acceptance reported in the findings. Without an indication of prior clinical experience, it’s difficult to interpret the lack of apparent impact of the diagnosis of FH, which is the main conclusion of the paper.

RESPONSE: We have attempted to address this in the revised Methods section whilst acknowledging that we have limited information on individual clinical histories and pathways leading to the specialist clinic. This would have been valuable information and it represents a limitation of the study. We mean by formal diagnosis simply a clinically administered diagnosis from a specialist i.e. not an interim or provisional diagnosis but the most definitive assessment that is available and this is explained following its use in the text. Whilst we do not report detailed information on clinical characteristics, we have intended to make it clearer in the Methods section what the typical route through services is and the fact that participants are likely to have a sense of their likely diagnosis at the time of referral to specialist services. This is consistent with the finding that participants can predict their diagnosis.

2. In my view, the analysis could be expanded/clarified in parts. The data segments need more context throughout in order for the reader to make sense of the data. This might mean including the questions that people were responding to, or expanding the cited segment eg p8 ‘well I would know that anyway, so it wouldn’t surprise me’ – know what? P11 ‘they’re peace of mind you know’ – what does ‘they’ refer to here? Etc.

RESPONSE: We have followed the reviewer’s suggestion and included the questions that people were responding to in several places where we think the context may be unclear.

Further points for clarification: page 8 - explain ‘normalisation and continuity’ and ‘realistic expectations’-realistic in what sense? page 8 - ‘very few patients expressed much surprise at the outcome of their diagnostic assessment’ – this statement doesn’t make sense here as all the data cited comes from T1, so they hadn’t had the results yet?

RESPONSE: The passages following the ‘Continuity and normalisation’ heading have been revised to clarify these statements. We have added some text to indicate that this and other quotes here refer to responses prior to receiving the results, consistent with responses following the results which we go on to outline.

Page 11 - discussion of reduction of uncertainty, the last quote doesn’t seem to belong here as it is from T1- doesn’t fit with the analytic account of the data. Page 14 - the point relating to the quote from the person with psoriasis is not clear to me – suggest expand on significance of this data.

RESPONSE: Regarding the first point, on reflection we agree and have removed this quote as it deals with the subject of reduction of uncertainty but does not illustrate that
this was experienced following the test result. Regarding the second point, we have expanded the quote and explanatory text to attempt to make this clearer.

3. Other specific comments: P4 last line ‘genetic diagnosis’ – meaning here not immediately clear. P7 hospital sites are numbered 01-10 – is this a typo? Earlier, methods section stated that there were 11 participating hospitals.

RESPONSE: We have now altered this text as we agree it was confusing. That was a typo and has now been corrected. Thanks for pointing this out.

Discretionary revisions
1. P5 FH is probably better described as a genetic or inherited condition rather than a genetic mutation?

RESPONSE: We have now changed this in line with the suggestion.

2. P5 might include a brief discussion of questions about the relationship between genotype and phenotype – see for example Damgaard et al (2005) Atherosclerosis 80, 155-160.

RESPONSE: We have now included brief mention of the relationship between genotype and phenotype but feel that anything more detailed would not be relevant for a study examining patients’ response to diagnostic information.

3. P6-7 first para of methods section is confusing – suggest rewrite to clarify

RESPONSE: We have rewritten this section in the course of addressing other comments from the reviewers. We hope that it is now clearer.

4. P11 in relation to reduction of uncertainty – were DNA diagnostic results ever equivocal in this study ie high cholesterol, but mutation negative; low cholesterol but mutation positive? Was the non-DNA diagnosis ever equivocal? If so, how did participants speak about this?

RESPONSE: We are not aware of any instances of this. From the sample characteristics that we have now added, it is interesting to observe that most participants had had cholesterol tests in the past and this contributed to being able to predict accurately their likely test outcome (no participants with a positive test result expected to get a negative result and vice versa). As such, there was little real surprise shown upon receiving the results, although the reduction in uncertainty was still valued.

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: I declare that I have no competing interests