PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Providing additional information about the benefits of statins in a leaflet for patients with coronary heart disease – a qualitative study of the impact on attitudes and beliefs
AUTHORS	Dickinson, R; Raynor, David; Knapp, Peter; MacDonald, Jan

VERSION 1 - REVIEW

REVIEWER	Alexander Turin Loyola University Medical Center Maywood, IL USA
REVIEW RETURNED	20-Apr-2016

GENERAL COMMENTS	Overview This is a qualitative study aimed at determining the effect of providing benefits information regarding simvastatin use in a pamphlet and assessing patient preferences relating to this information and their medication use. Patients were provided pamphlets with textual, NNT, and numerical frequency data and their opinions related to the pamphlets were reviewed to determine what patient preferences for information was and how it was interpreted. Title and Abstract 1. Please expand the abbreviation GP 2. It may strengthen your abstract to provide more concrete findings in the results section. There were “significant barriers” and “key themes” identified in the paper, but it is difficult to get a sense of what these were and how they relate to the conclusions Introduction 1. Paragraph 1, line 2: please correct the spelling of “licensed” 2. Paragraph 1: what kind of “information about medicines” is included in the PILs? It would help to understand this to form a better foundation for this paper. For instance, is it simply “this is a cholesterol medicine” or is it more in-depth about mechanism of action, or is it more statistical, or just a focus on adverse effects? 3. Paragraph 1: “adverse effects” is the preferable terms to “side effects” 4. Paragraph 2: again, it would help to know what kind of

information is provided in the PILs to get a sense for why they are so negative, if that is the case. Is it possible to include a sample PIL as a reference in the paper itself to illustrate this point?

5. Paragraph 3: the risk-benefit discussion with respect to starting anti-cholesterol medications was the key focus of the 2013 American College of Cardiology/American Heart Association guidelines on lipid management (Stone, et al.). This would be a valuable reference to review.
6. Paragraph 4: what are some of the reasons it is challenging to explain to patients the benefits of their treatments?
7. Paragraph 4: "a significant minority of whom will struggle with the numerical concepts" - this phrase is confusing and seems to contradict itself. Are you trying to say that a minority of patients struggle with numerical concepts but that this quantity of patients is significant? Or should this say "majority"?

Methods

1. Please be more explicit about the inclusion criteria. Were patients already prescribed or taking simvastatin at the time of enrollment? Were all patients taking simvastatin for secondary prevention rather than primary prevention? Was it limited to simvastatin use, as opposed to other statins?
2. What was the duration of the session? How long did participants have to review the PILs and how long were the interviews?
3. Page 6 – you note that simvastatin is used to treat an asymptomatic condition, which is not entirely accurate, particularly in patients with establish coronary artery disease. Perhaps a way to clarify this phrase would be to say that simvastatin itself does not alleviate symptoms.
4. Page 6 – the 3rd and 4th bullet points, while true statements, do not seem to address why simvastatin was chosen as opposed to another medication. Please clarify this.
5. Page 7 – what is Rebastatin?
6. Page 7 – NNT of 17 over 5 years seems low. In a population of patients with known coronary disease, based on the cholesterol treatment trialist's data (Lancet 2005), this number is higher.
7. Page 7 – Natural frequency section – a 28% risk of heart attack or stroke seems quite high in a generic secondary prevention population. Is this 28% over 5 years? Is this all based on the Heart Protection Study data?
8. Page 8 – what is NVIVO?
9. Page 8 – what coding categories did you use? Please elaborate on your coding system.
10. Any evaluation for medication adherence? Patients may say that they are willing to take a medicine or do whatever the doctor says, but then they go home and continue what they were doing previously.
11. Basing all data on a single study (Heart Protection Study) presents patients with incomplete or incorrect information.

Results

1. Please provide patient demographic information in greater detail. You should at least include comorbidities such as hypertension, diabetes, detail of coronary disease as well as detail on polypharmacy and number of medications prescribed per patient.
2. The value of Table 1 is not clear. Based on the data provided, it is not sufficient to demonstrate that the cohort sampled is representative of the entire practice.
3. Direct quotations are helpful to illustrate the key points in your main sections.
4. Page 11 – please rephrase "which often took some time to sink in" to avoid idiomatic expressions in scientific literature
5. Each section header illustrates several points which are aided by the direct quotations. However, various paragraphs note quantities to participants who felt a certain way (e.g. page 14, paragraph 2, "a small number of participants felt…" and this occurs throughout the results section. It is difficult to appreciate these opinionated sentiments without quantification – did 5/20 participants have difficulty with natural frequency numbers or was it closer to 19/20? It is difficult to interpret the significance of your results without these quantifiers

Discussion

1. Page 18, paragraph 3 – what is the role of citing sources 24-27 at the end of this paragraph? The two sentences here describe observations from your own study. Looking at those references, they seem to be studies discussing NNT and other statistics – it would be beneficial to describe some of their results in the context of yours at this point in the manuscript
2. Page 19, paragraph 2 – you discuss strategies that patients employ to help "deal" with the emotional response to figures and statistics but this was not mentioned prior when analyzing the results and should be in greater detail (i.e. what strategies? How did you discern these?)
3. Page 19, paragraph 3 – the main point of this paragraph is to state that patients will consider risks and benefits before taking a medication. Isn't this basic knowledge? You might add to this idea a little by noting that patient perceptions of risks and benefits may be askew, but this paragraph does not add much.
4. Page 19, paragraph 5 – the influence of the GP is extremely significant and was not addressed in the methods section at all. This would be a difficult variable to control for but especially if you agree with the point that the individual practitioner makes a big difference, then you should investigate this further. It is possible all of your data is simply based on the GP rather than any numerical values presented in the pamphlets – you can't know until you look further.
5. Page 20, paragraph 1 – this is a valid point about "medical inertia". Is there any data out there about this and

	medication adherence? 6. Strengths and weaknesses section – paragraph 2 – you are describing selection bias and should refer to it as such Conclusion 1. Page 21, paragraph 2 – did patients really overestimate benefit in this study? It seemed like, when evaluating comments related to NNT or numerical frequencies, patients underestimated benefit or even overestimated harm ("hoping to be one of 17 people who isn't harmed") 2. Page 21, paragraph 3 – this is the first time barriers and challenges of the PIL are discussed and feels a little out of scope of your study, or else it may serve better in the discussion section Final comments The introduction and initial principles to this study are sound. The practice of distribution of PIL with medications in order to provide information to patients is very appropriate, as is a study to investigate patient preferences and views in a generalized GP practice. The methods of this paper were fair given the inherent limitations to such a study, however they were limited in a few aspects, at least in reading this paper. First, all of the statistical data appears to be based on a single study; though large and involving simvastatin, there are countless other trials with both simvastatin and others that should be taken into account when presenting NNT and natural frequency data. Otherwise you run the risk of presenting inaccurate information. The methods section was also perilously lacking in detail with respect to analysis of the data. There is no description of the coding system or how information and conclusions were extracted from the interviews. As such, this makes interpreting the results challenging. The direct quotations from patients were extremely helpful in illustrating some of your conclusions, but again, without statistical or some qualitative analysis, it is difficult to generalize the results. For example, saying that some people did not understand NNT is a weak and generalized statement that can be argued is common knowledge, but saying that 120/176 patients had difficult with NNT is a much stronger argument. As a result of this lack of data availability and analysis, it is difficult to follow along with your discussion/conclusions with any level of confidence or coherence. There needs to be clear analysis presented, even if qualitative, such that the reader can understand how you came to your conclusions.

REVIEWER	David Diamond University of South Florida, USA
REVIEW RETURNED	13-Jun-2016

GENERAL COMMENTS	This research is flawed at every level of analysis. There is clear bias in this work to justify minimizing the specific research findings on statins to give patients the impression that statins are more beneficial than they actually are. The statement such as "patients might reject medicines because of disappointment with perceived benefits" is condescending and reveals that the goal of this work is to promote statins by providing misleading information about their benefits, rather than providing patients accurate information. Moreover, there was no attempt to quantify the findings in this research and yet in the Discussion the authors repeatedly refer to the magnitude of the effects. For example, the Discussion refers to "a small subset of patients", "the majority of patients:, the NNT was "frequently misinterpreted", participants "frequently overestimated", and yet, there was no basis for the repeated quantification of effects that were not measured. Finally, the authors used the Heart Protection Study as the basis of their research. If they were to set their goal as an accurate assessment of the findings of that study they should state that overall there was only about a 1-2% absolute risk reduction (benefit) to patients regarding coronary events or death, in comparison to the placebo group. This finding would provide the most accurate information regarding benefits that current and prospective patients should have regarding statin benefits.

REVIEWER	Enmanuel Chavarria, PhD., CHES H. Lee Moffitt Cancer Center and Research Institute; USA
REVIEW RETURNED	05-Jul-2016

GENERAL COMMENTS	This manuscript should be published as soon as possible. It is necessary to provide patients with logical information they can understand. Numeracy is a big problem both in the U.S. and the UK. I believe this article provides a solution for having patients understand numbers a bit clearer. Only suggestion is to provide a definition of simvastatin/statins in the introduction of the manuscript. Otherwise the reader has to look it up. Right now the authors are assuming the readers know the use of statins. Great job!!

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1 Reviewer Name: Alexander Turin
Institution and Country: Loyola University Medical Center, Maywood, IL USA Competing Interests: None declared

1. Please expand the abbreviation GP
General practitioner – completed [P.2]

2. It may strengthen your abstract to provide more concrete findings in the results section. There were “significant barriers” and “key themes” identified in the paper, but it is difficult to get a sense of what

these were and how they relate to the conclusions
Due to word limitations it is difficult to adequately described qualitative findings. However we have added some detail to the abstract as follows:
Significant barriers to the acceptance of numerical benefit information included difficulty in understanding the numbers. Patients over-estimated the benefits of statins and expressed surprise at the numerical information. [P.2]

3. Para 1, line 2: please correct the spelling of “licensed”
Completed [P.3]

4. Para 1: what kind of “information about medicines” is included in the PILs? It would help to understand this to form a better foundation for this paper. For instance, is it simply “this is a cholesterol medicine” or is it more in-depth about mechanism of action, or is it more statistical, or just a focus on adverse effects?
We agree more detail would be beneficial here and have added the following text [P.3]:
PILs provide information about medicines such as:
1. What X is and what it is used for
2. What you need to know before you take X
3. How to take X
4. Possible side effects
5. How to store X
6. Contents of the pack and other information
PILs are available on www.medicines.org.uk.

5. Para 1: “adverse effects” is the preferable terms to “side effects”
‘Side effects’ is the term generally used by patients and this is the term used in PILs. To clarify that we mean it to encompass adverse effects, we have amended the manuscript as follows [P.3]:
Information about side effects (adverse effects)
Para 2: again, it would help to know what kind of information is provided in the PILs to get a sense for why they are so negative, if that is the case. Is it possible to include a sample PIL as a reference in the paper itself to illustrate this point?
Covered in response 4 above.

6. Para 3: the risk-benefit discussion with respect to starting anti-cholesterol medications was the key focus of the 2013 American College of Cardiology/ American Heart Association guidelines on lipid management (Stone, et al.). This would be a valuable reference to review.
We agree that this is a valuable reference, but feel that our citation of the subsequent UK National Institute for Clinical Excellence (NICE) guidance appropriately covers the relevant evidence as applied to a UK population.

7. Para 4: what are some of the reasons it is challenging to explain to patients the benefits of their treatments?
We have added the following text to address this comment [P.4]:
This is because there are different statistical methods for communicating benefits, some of which can more persuasive than others. Furthermore it can be complex to communicate these data to patients, as a number of patients struggle with the numerical concepts used to communicate benefits.

8. Para 4: “a significant minority of whom will struggle with the numerical concepts” - this phrase is confusing and seems to contradict itself. Are you trying to say that a minority of patients struggle with numerical concepts but that this quantity of patients is significant? Or should this say “majority”?
Addressed in point 8 directly above.

9. Please be more explicit about the inclusion criteria. Were patients already prescribed or taking simvastatin at the time of enrollment? Were all patients taking simvastatin for secondary prevention rather than primary prevention? Was it limited to simvastatin use, as opposed to other statins?
At the end of the introduction we state that participants are actual users of simvastatin. For further clarity we have also added the following text under 'Participants and setting' [P.5]:
Already prescribed simvastatin for prior myocardial infarction (MI) or established coronary heart disease (CHD) (such as angina, unstable angina, previous Coronary Artery Bypass Graft (CABG) or angioplasty).[P.5]

10. What was the duration of the session? How long did participants have to review the PILs and how long were the interviews?
The following text has been added:
Interviews lasted approximately an hour and were conducted in the patient's own home by the researcher. [P.5]
Participants had as much time as they needed to review the PILs. [P.6]

11. Page 6 – you note that simvastatin is used to treat an asymptomatic condition, which is not entirely accurate, particularly in patients with establish coronary artery disease. Perhaps a way to clarify this phrase would be to say that simvastatin itself does not alleviate symptoms.
The text has been clarified as follows [P.6]:
Simvastatin itself does not alleviate symptoms. Consequently information provided about the chance of benefit may have particular significance for patients.[P.6]

12. Page 6 – the 3rd and 4th bullet points, while true statements, do not seem to address why simvastatin was chosen as opposed to another medication. Please clarify this.
Amended as follows – new text in colour [P.6].
• Our previous research has shown that medicines perceived as having quite a small chance of benefit can create upset amongst participants. We wished to explore different magnitudes of benefit.
• Although the individual benefits may still be perceived as small, the population benefits of statin prescribing are potentially considerable. Understanding how patients perceive individual benefits might have an impact on willingness to take a treatment and consequently on population benefits.

13. Page 7 – what is Rebastatin?
Clarification has been provided as follows [P.7]:-
The leaflets were designed to look like PILs typically available in the UK. Simvastatin was given the hypothetical name "Rebastatin" and each leaflet was marked with a highlighted section that stated 'This leaflet is for research purposes only'. The hypothetical name and highlighting were to ensure the leaflet was not mistaken for an actual PIL.

14. Page 7 – NNT of 17 over 5 years seems low. In a population of patients with known coronary disease, based on the cholesterol treatment trialist's data (Lancet 2005), this number is higher.
We endeavoured to present accurate data to the participants, but there is not one definitive NNT, as it depends on the source data used. We have amended the text as follows [P.6]:
"Data were taken from the Heart Protection Study, the largest published trial of simvastatin and which was funded by the UK Medical Research Council and the British Heart Foundation charity. We had identified a number of potential sources of data, including NICE guidelines - national evidence-based clinical guidelines in the UK. The NICE guidelines on statins for the prevention of cardiovascular events (20) are based on a meta-analysis of studies into a variety of statins. Hence this could not be used, as the data needed to be specific to simvastatin. We identified four studies specific to simvastatin in the NICE guidelines and chose the Heart Protection Study (HPS) because it provides effectiveness data for a secondary prevention or high-risk population. - With the aim that the statements were as relevant to the individual as possible (without the need for a risk calculator which

is not feasible in a PIL). The primary endpoints for which benefit data was presented, were the likelihood of having a heart attack or stroke (and the standard equation for calculating NNT was used)."
We have also added the following limitation to the study in the section strengths and limitations of the study [P.21].
"Another limitation of the study is the choice of data on the benefits of statins to a targeted sample. This study used the findings from the HPS study, however, it is acknowledged that other data may alter the magnitude of benefit. The producers of benefit information for patients need to ensure a transparent process for choosing and presenting benefit data."

15. Page 7 – Natural frequency section – a 28% risk of heart attack or stroke seems quite high in a generic secondary prevention population. Is this 28% over 5 years? Is this all based on the Heart Protection Study data?
See response to comment 15 directly above – all the data was derived from the HPS.

16. Page 8 – what is NVIVO?
Clarification provided [P.8]:
"A software package, NVIVO, was used to manage the data "

17. Page 8 – what coding categories did you use? Please elaborate on your coding system.
We have added additional detail on the process of data analysis as follows [P.7-8]:
Data were organised and analysed by Framework analysis, using the following processes:
[1] Familiarisation
After the interviews field notes were made and initial categories for coding considered. Emerging themes were considered and discussed with the research team.
[2] Identifying a thematic framework
One transcript was used to chart emerging codes which were developed into initial coding categories. These coding categories were checked against samples of the transcripts by 3 members of the research team (RD, JM and PK). The thematic framework was applied to each interview (see appendix 2).
[3] Indexing
The thematic framework was then applied to each interview and relevant data coded according to the framework. A software package, NVIVO, was used to manage the data (5).
[4] Charting
The indexed data were then sorted into charts. Each chart presented a main theme; every patient was represented by a row and each column was designated a sub-theme. This allowed for all pertinent quotes from patients on a particular sub-theme to be charted in a visually accessible way so that the researcher could view a summary of the data, yet view the different themes emerging by case and/or category.
[5] Mapping and Interpretation
The final stage saw a process of mapping and interpretation which was undertaken by both RD and JM during 2 full-day meetings. RD and JM undertook a 'post-it note' exercise where each category and sub-category in the charts were summarised and arranged in emerging themes. Each researcher took a category and organise the emerging themes into sub-themes until a coherent set of sub-themes had been developed for each category. Field notes and mind maps were developed to present the emergent themes and the most-important theme identified from the framework.

18. Any evaluation for medication adherence? Patients may say that they are willing to take a medicine or do whatever the doctor says, but then they go home and continue what they were doing previously.
This is already acknowledged as a limitation of the study on P.20 as follows:

"This study did not measure directly the impact of providing benefit information, it only explored self-reported behaviours. It is possible that while the participants might have reported that they would 'do what the doctor tells them' and remain adherent to their medicines, it is possible that the provision of benefit information might in practice change medicine-taking behaviour. More research examining the impact of this is needed." [P.19]

19. Basing all data on a single study (Heart Protection Study) presents patients with incomplete or incorrect information.
See above comment (15)

20. Please provide patient demographic information in greater detail. You should at least include comorbidities such as hypertension, diabetes, detail of coronary disease as well as detail on polypharmacy and number of medications prescribed per patient.
We collected data on age, gender, education and polypharmacy. We felt these were the most relevant criteria to the study. We did not collect data on co-morbidities.

21. The value of Table 1 is not clear. Based on the data provided, it is not sufficient to demonstrate that the cohort sampled is representative of the entire practice.
We agree the value of the table is not clear and have removed it.

22. Direct quotations are helpful to illustrate the key points in your main sections.
Thank you

23. Page 11 – please rephrase "which often took some time to sink in" to avoid idiomatic expressions in scientific literature
Amended as follows [P.11]:
….often took some time to be understood

24. Each section header illustrates several points which are aided by the direct quotations. However, various paragraphs note quantities to participants who felt a certain way (e.g. page 14, paragraph 2, "a small number of participants felt…" and this occurs throughout the results section. It is difficult to appreciate these opinionated sentiments without quantification – did 5/20 participants have difficulty with natural frequency numbers or was it closer to 19/20? It is difficult to interpret the significance of your results without these quantifiers
The aim of the study was to explore and present a range of different views and perspectives on the inclusion of benefit information in a PIL -rather than quantify these views. As with all such qualitative research using small sample sizes, it is not possible to generalise to the general population.
The use of 'quantifying' phrases is intended to be illustrative rather than suggest a proportion that is generalizable to the larger population. In order to address this misunderstanding we have removed references to quantity of participants and instead presented the range of perspectives offered (Richie and Spencer eds. 2003: Qualitative Research Practice: A Guide for Social Science Students and Researchers Paperback. Sage Publications, London).

25. Page 18, para 3 – what is the role of citing sources 24-27 at the end of this paragraph? The two sentences here describe observations from your own study. Looking at those references, they seem to be studies discussing NNT and other statistics – it would be beneficial to describe some of their results in the context of yours at this point in the manuscript
Added as clarification:
This is a finding that has been noted in other studies.

26. Page 19, para 2 – you discuss strategies that patients employ to help "deal" with the emotional response to figures and statistics but this was not mentioned prior when analyzing the results and

should be in greater detail (i.e. what strategies? How did you discern these?)
This has been edited for clarity [P.19]:
It was apparent that the participants were often shocked or disappointed with the benefit information and with the uncertainty associated with the effectiveness of the treatment. Previous experience with taking the medicine facilitated the appraisal of illness and treatment in the context of participants' current health state and appeared to play some role in mitigating this unease

Page 19, para 3 – the main point of this paragraph is to state that patients will consider risks and benefits before taking a medication. Isn't this basic knowledge? You might add to this idea a little by noting that patient perceptions of risks and benefits may be askew, but this paragraph does not add much.
We have amended this sentence as follows (new text in yellow) [P.19]:
This suggests that the users of medicines may not reject their treatments despite their concerns about perceived low benefits, and instead will weigh-up the likelihood of benefit and risk of harm of their treatments before altering their behaviour.

27. Page 19, para 5 – the influence of the GP is extremely significant and was not addressed in the methods section at all. This would be a difficult variable to control for but especially if you agree with the point that the individual practitioner makes a big difference, then you should investigate this further. It is possible all of your data is simply based on the GP rather than any numerical values presented in the pamphlets – you can't know until you look further.
The influence of the GP is clearly important. At this stage of the research we were focusing on the presentation of the benefit information. Further research should address this - we have added this text on P.19:
Further research is needed to explore the influence of the GP.

28. Page 20, para 1 – this is a valid point about "medical inertia". Is there any data out there about this and medication adherence?
This is an interesting point. However due to the limitations of the word count is not one we can explore in detail. As medical inertia was not the focus of the study we feel it sits outside the scope of our study.

29. Strengths and weaknesses section – paragraph 2 – you are describing selection bias and should refer to it as such
Text has been added for clarification on P.20
…consequently there may be a degree of selection bias within the sample.

30. Page 21, para 2 – did patients really overestimate benefit in this study? It seemed like, when evaluating comments related to NNT or numerical frequencies, patients underestimated benefit or even overestimated harm ("hoping to be one of 17 people who isn't harmed")
We have clarified this point by adding the following text [P.21]:
However, this study suggests that currently in the absence of the provision of numerical information about benefits many patients over-estimate the benefits of their statins.

31. Page 21, para 3 – this is the first time barriers and challenges of the PIL are discussed and feels a little out of scope of your study, or else it may serve better in the discussion section
We do mention some challenges associated with PILs and the regulatory measures recommended to address some of these challenges discussed in the introduction. We have also made reference to the proportion of patients who read the PIL in the Discussion and this is reiterated here.
The introduction and initial principles to this study are sound. The practice of distribution of PIL with medications in order to provide information to patients is very appropriate, as is a study to investigate patient preferences and views in a generalized GP practice. The methods of this paper were fair given

the inherent limitations to such a study, however they were limited in a few aspects, at least in reading this paper.
• First, all of the statistical data appears to be based on a single study; though large and involving simvastatin, there are countless other trials with both simvastatin and others that should be taken into account when presenting NNT and natural frequency data. Otherwise you run the risk of presenting inaccurate information.
See response 20 above.

• The methods section was also perilously lacking in detail with respect to analysis of the data. There is no description of the coding system or how information and conclusions were extracted from the interviews. As such, this makes interpreting the results challenging.
See response 18 above

• The direct quotations from patients were extremely helpful in illustrating some of your conclusions, but again, without statistical or some qualitative analysis, it is difficult to generalize the results. For example, saying that some people did not understand NNT is a weak and generalized statement that can be argued is common knowledge, but saying that 120/176 patients had difficult with NNT is a much stronger argument.
See response 25 above
• As a result of this lack of data availability and analysis, it is difficult to follow along with your discussion/conclusions with any level of confidence or coherence. There needs to be clear analysis presented, even if qualitative, such that the reader can understand how you came to your conclusions.
See response 18 above

Reviewer: 2 Reviewer Name: David Diamond
Institution and Country: University of South Florida, USA Competing Interests: none

32. This research is flawed at every level of analysis. There is clear bias in this work to justify minimizing the specific research findings on statins to give patients the impression that statins are more beneficial than they actually are. The statement such as "patients might reject medicines because of disappointment with perceived benefits" is condescending and reveals that the goal of this work is to promote statins by providing misleading information about their benefits, rather than providing patients accurate information.
We are dismayed by reference to bias in this work. The study was part of a wider PhD thesis co-supervised by 2 academics with published comments which consistently propose that people may over-estimate the benefits of statins – our impression is that the benefits of statins, from a patient perspective, are much less beneficial than they actually are.
The third supervisor is a senior member of the UK medicines regulatory agency (MHRA) which applies objective evidence to all decisions about medicines.
We have all re-read the manuscript, and cannot see how it could be construed as coming from a standpoint of giving patients the impression that statins are more beneficial than they actually are.

33. Moreover, there was no attempt to quantify the findings in this research and yet in the Discussion the authors repeatedly refer to the magnitude of the effects. For example, the Discussion refers to "a small subset of patients", "the majority of patients:, the NNT was "frequently misinterpreted", participants "frequently overestimated", and yet, there was no basis for the repeated quantification of effects that were not measured.
See response 25

34. Finally, the authors used the Heart Protection Study as the basis of their research. If they were to set their goal as an accurate assessment of the findings of that study they should state that overall

there was only about a 1-2% absolute risk reduction (benefit) to patients regarding coronary events or death, in comparison to the placebo group. This finding would provide the most accurate information regarding benefits that current and prospective patients should have regarding statin benefits.
See comment above (15)

Reviewer: 3 Reviewer Name: Enmanuel Chavarria, PhD., CHES
Institution and Country: H. Lee Moffitt Cancer Center and Research Institute; USA Competing Interests: None declared

35. This manuscript should be published as soon as possible. It is necessary to provide patients with logical information they can understand. Numeracy is a big problem both in the U.S. and the UK. I believe this article provides a solution for having patients understand numbers a bit clearer. Only suggestion is to provide a definition of simvastatin/statins in the introduction of the manuscript. Otherwise the reader has to look it up. Right now the authors are assuming the readers know the use of statins. Great job!!
We have elaborated on the use of statins in the introduction. See addition –

Statins, a class of lipid-lowering medications used in the treatment of cardiovascular disease.

Editorial Requests:

38. Please add a statement to the methods section confirming that you obtained written informed consent from participants.
The following statement has been added

All participants received a patient information leaflet with details of the research prior to providing written informed consent prior to participation. [P.9]
39. Along with your revised manuscript, please provide a completed copy of the COREQ checklist (http://www.equator-network.org/reporting-guidelines/coreq/).
Completed

VERSION 2 – REVIEW

REVIEWER	David Diamond USF, USA
REVIEW RETURNED	27-Aug-2016

GENERAL COMMENTS	This revised manuscript is flawed at multiple levels of analysis. First, it is not appropriate to respond to a reviewer's comments indirectly by claiming a higher authority has approved of it, i.e., it is "part of a wider PhD thesis co-supervised by 2 academics". Second, there is no quantification of the findings. There are no measures, no data, no statistics. The authors make statements that refer to the appearance of quantified observations, as in referring to how the majority of subjects responded to one question or another, but they have no measurements to confirm these statements. This is not an appropriate approach for publication in a medical journal. Third, there were inaccuracies in how the statin findings were presented to the subjects. For example, the NNT data were presented as a person will be prevented from having a "heart attack or stroke" in the manuscript, but the original HPS work included all events in that statistic, including "revascularisation", and the total number of all events in the HPS (absolute risk reduction) was

	reduced only by about 1.5% in the treated vs placebo groups. Similarly, the "natural frequency" text is inappropriate. The PIL should not state to a patient that 28 of 100 people like "you" will have a heart attack, as if it is a fact that the patient opening the medication can be told of the precise likelihood that he/she will have a heart attack. In the absence of knowledge of known risk factors for each patient this statement is inappropriate.

REVIEWER	Enmanuel Chavarria, PhD., CHES H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, United States
REVIEW RETURNED	02-Sep-2016

GENERAL COMMENTS	The authors have addressed prior comments. The manuscript will be a great addition to the literature on addressing health literacy and numeracy concerns for patients with difficulty understanding information on medication leaflets.

VERSION 2 – AUTHOR RESPONSE

Reviewer 2		
Second, there is no quantification of the findings. There are no measures, no data, no statistics. The authors make statements that refer to the appearance of quantified observations, as in referring to how the majority of subjects responded to one question or another, but they have no measurements to confirm these statements. This is not an appropriate approach for publication in a medical journal.	The study uses a qualitative approach, which is the appropriate approach to address the objectives of the research. Consequently we have not reported statistical data as this would not be representative or reliable when collected using a qualitative method.	Amendment to methods section P6
Third, there were inaccuracies in how the statin findings were presented to the subjects. For example, the NNT data were presented as a person will be prevented from having a "heart attack or stroke" in the manuscript, but the original HPS work included all events in that statistic, including "revascularisation" and the total number of all events in the HPS (absolute risk reduction) was reduced only by about 1.5% in the treated vs placebo groups.	We used the term 'heart attack or stroke' as these are the terms that lay people will understand, unlike 'revascularisation'. Our data presents an absolute risk reduction of about 5%, which in the context of the	

	magnitude of benefit, is a modest number. We do not believe this difference in benefit is significantly more persuasive for patients who wish to understand more about the benefits of their medicines. Nor do we feel this gives the impression that statins are more beneficial than they actually are.	
Similarly, the "natural frequency" text is inappropriate. The PIL should not state to a patient that 28 of 100 people like "you" will have a heart attack, as if it is a fact that the patient opening the medication can be told of the precise likelihood that he/she will have a heart attack. In the absence of knowledge of known risk factors for each patient this statement is inappropriate.	The term 'people like you' was used to highlight that the data was not specific to the general population, but instead to a population with coronary heart disease.	