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Responding to Reviewers' Comments

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Background

Many researchers think of peer-review with a certain amount of dread. However, peer-review is extremely important. It not only validates the research and confirms its significance, but can often lead to important improvements in the paper. The process is imperfect, and it can be painful, but it ultimately improves research. As researchers, we should use peer-review to our advantage.

This section describes the peer review process, and the possible paths that it can take. The next section describes principles that you can use when you first draft your paper, to avoid receiving negative comments from peer reviewers later in the process. The third section details how to respond to those comments, when you receive them. This is followed by a section containing some handy hints, and finally there is a brief section describing how to handle the peer review process when it just isn't working. At Appendix A there is a real, worked example of parts of the response to a reviewer's comments that was made by one of the authors, Prof Emily Banks. It demonstrates some of the principles and approaches described in this module.

The process

You've prepared your manuscript lovingly and submitted it to the journal of your choice. Ultimately, responsibility for decisions falls on the editor, who is meant to be impartial. The editor is involved in three stages of the process and is the key to getting your work published. The first step in the review process is editorial consideration, which is a fairly light review of the paper without going into any of the details. The abstract and covering letter are particularly important at this stage, as they will be the focus of the editor's attention. At this point, there are two possible outcomes:

- Reject without peer review
- Send for peer review

If your paper is rejected at this point, it generally does not reflect on the quality of the research, since there has been limited review of the detail. It usually means that it is not suitable for that particular journal. If this is the case, you can submit it to another journal. It is a good idea to have a list of possible journals to which you could submit your paper, in priority order. That way, if your paper is rejected without peer review, you can immediately send it to the next journal on your list.

If your paper passes the first milestone, it is sent to one or more reviewers. The critical thing to remember is that peer reviewers are just that: our peers. They are just like us and come in all shapes and sizes, metaphorically. Some are helpful, some are hurtful, some have their own agenda, but most are reasonable, thoughtful specialists in their field, who are giving their time freely to the cause of improving academic research.

The reviewers read your paper and make their comments, which they send back to the editor. The editor will then decide on one of four possible courses of action:

- Reject the paper after peer review
- Require major revisions (either with or without further review)
- Require minor revisions
- Accept without revisions

Reject the paper after peer review

If the paper is rejected following peer review, the reasoning behind this decision should be given. If it is a case of incompatibility with the journal, then you should send the paper to the next journal on your list of possible publications. If serious methodological flaws have been pointed out, then you should make appropriate changes and re-consider the overall structure of the paper before submitting to another journal.

Require major revisions

If major revisions are required, you can choose two actions: (1) withdraw the paper and submit it to another journal, whilst taking on board the reviewers' comments; or, (2) make changes to the paper and re-submit it. The editor will decide whether there should be a further review by the original reviewers. The rest of this module is concerned with how to address those changes, including how to politely refuse to change some aspects.

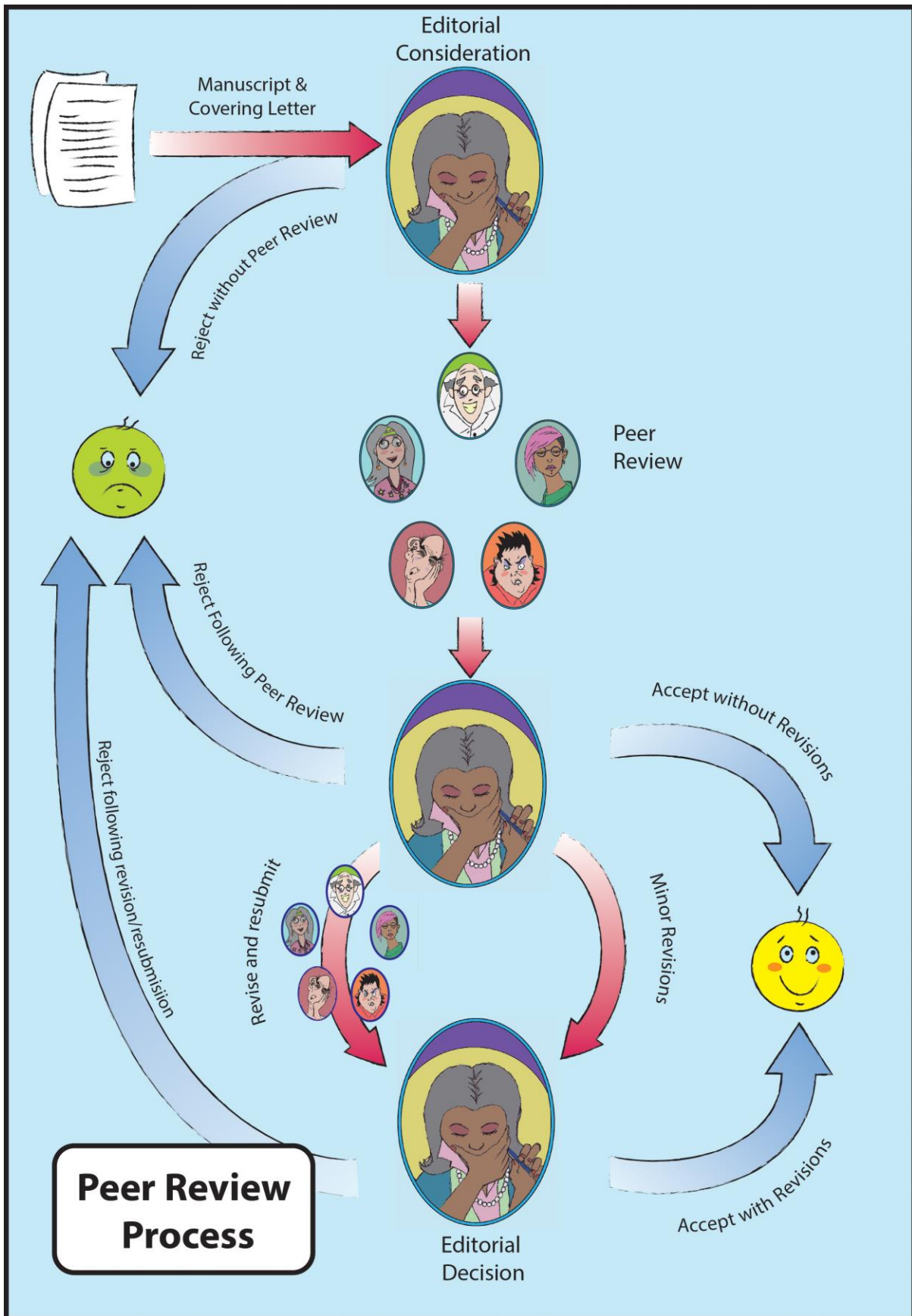
Require minor revisions

The third post-review outcome is that only minor revisions are required, such as referencing, terminology or diagrams. After you have made the changes, the paper then goes straight to the editor for a final decision, without being returned to the reviewers.

Accept without revisions

The best possible outcome of the initial review process is that the paper is accepted without revision. In that case, you should celebrate appropriately, as this is fairly rare!

Diagrammatically, the process of peer review can be visualised like this.



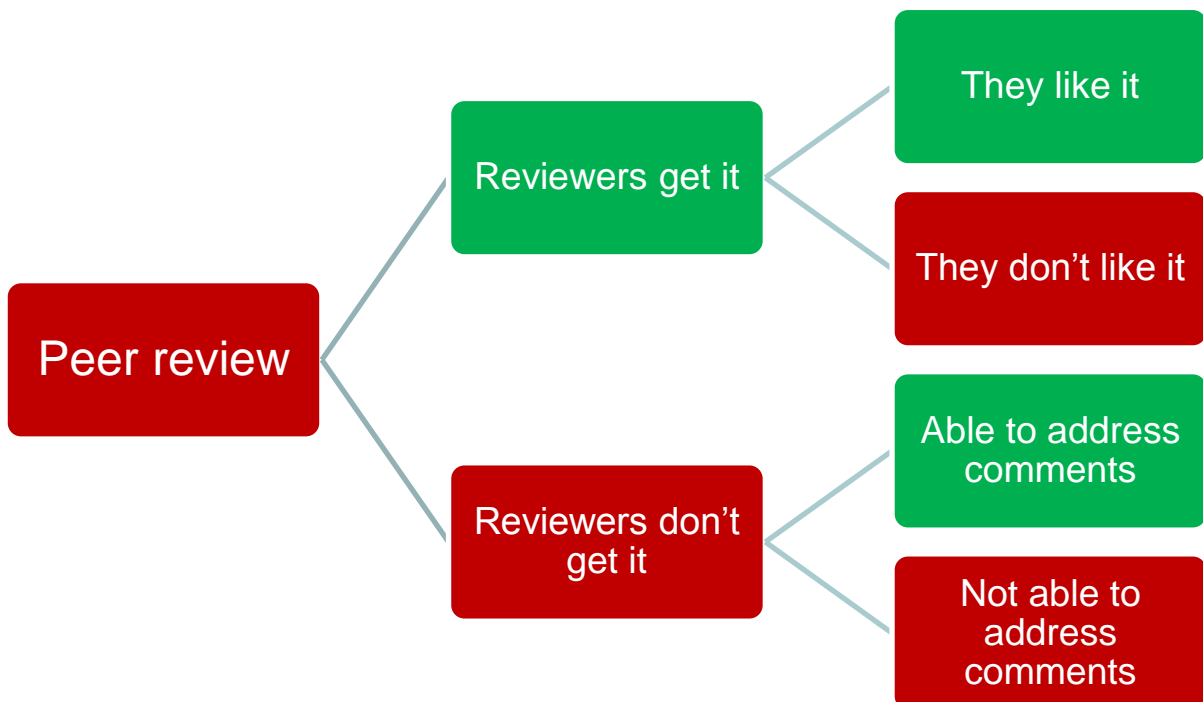
Essential issues

The quality of peer review is variable. Put simply, the reviewers can respond to your paper in a variety of ways. Firstly, they either “get” your paper, or they don’t. By “get” your paper, we mean that they understand the central scientific contribution that your paper makes.

If they “get” your paper, an individual reviewer can like it, or not like it. If they like it, they are recognising that the central scientific contribution is sufficiently strong to justify publication, although they may acknowledge some issues, large or small. If they “get” it but don’t like it, a reviewer might feel that the contribution is insufficient to justify publication, or feel that the weaknesses outweigh the strengths. They may have a genuine disagreement about some aspect of the research, or even just have a different perspective from you. In and of itself, having a different perspective is not a valid reason to reject a paper; this occurs more often amongst younger and less experienced reviewers.

If a reviewer doesn’t “get” your paper, it may be because the reviewer doesn’t have sufficient expertise in the subject matter. Alternatively, it might be because the paper is not written well enough, and you may need to re-consider how you have explained your central scientific contribution. If a reviewer doesn’t “get” it, it may still be possible to address their comments. This will be discussed in more detail in the rest of this module. On the other hand, if they don’t “get” your paper and their comments cannot be addressed, you may need to re-submit the paper to another journal.

The essential issues of peer review can be expressed diagrammatically like this:



Worst Comments

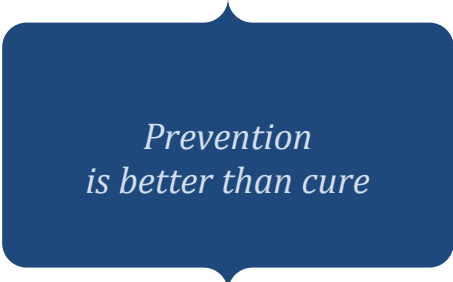
If you're feeling hurt about a comment received from a reviewer, bear in mind the following selection of the worst comments on papers received by members of the National Centre for Epidemiology and Population Health. You'll note that, in every case, the paper was eventually published in a reputable journal, including the journal to which it was originally submitted.

- "(Publishing) it is an abuse of publishing in my view, as it is of no interest to anyone." (*ultimately published BMC Public Health*)
- "Advocating anything based on limited data in this study is folly."
- "This manuscript should be rewritten, preferably in English." (*ultimately published IJE*)
- "The final conclusion made by the researchers in the second paragraph of the conclusion is staggering." (*ultimately published BMC Public Health*)
- "It's as if you've bought a Ferrari and only used it to drive around the corner for a pint of milk" (*PhD thesis*)
- "The only reasonable conclusion to come to is that what the authors have done is simply incorrect." (*ultimately published in the journal submitted to*)
- "...leave the convoluted math on the cutting room floor." (*ultimately published Emerging Infectious Diseases*)
- "This is waffle...Your final paragraph is completely mealy mouthed." (*published Journal of Health Services Research and Policy*)
- "The data from different sources is a profound limiting factor (acknowledged). This makes coordination of the data almost impossible and certainly incomprehensible." (*published Diab Metab Research Rev*)

Remember that it's not the rule to receive this type of comment, and it can feel patently unfair when it does happen. When your turn comes to undertake peer review, you should avoid being discourteous and phrase your concerns politely.

Principles for drafting a paper

The old adage that “prevention is better than cure” applies not just to public health, but to preparing papers for peer review. It is far better to spend extra time getting a paper right before the cold gaze of the reviewer falls upon it, than it is to fix issues later. This section describes some basic writing principles which may help to prevent you from receiving comments like the ones on the previous page.



*Prevention
is better than cure*

State scientific contribution clearly

The central scientific contribution of your paper must be made crystal clear. It also needs to be in perspective; be careful not to overstate the importance of your research. Your statement of central scientific contribution should be covered in more detail than the limitations described in the Discussion section of your paper.

Pre-empt concerns

If you can predict the concerns of potential reviewers, you can address them before you submit the paper, and save the reviewer having to make an unfavourable comment. Take a critical eye to your paper and think about what an outsider might have concerns with, and address these in the Discussion section of the paper.

For example, you might imagine that a reviewer could question the representativeness of your sample. Explain why your sample really is representative, if that's the case, or if it's not, explain how you have accounted for this in analysing your results and how the results can be used. In the Handy Hints section of this module, we discuss common issues that you can pre-empt before the reviewer ever lays eyes on your paper.

Conduct internal peer review

Writing a paper within a group is a type of internal peer review. Even if you are preparing the paper in a group, and feel that it has been internally peer-reviewed throughout its ephemeral life, it is worth having a non-involved peer examine the paper. Sometimes they can spot an omission that is “obvious” to the co-authors, but needs to be spelt out to anyone who has not been involved in the research.

Target correctly

Choose your target journal wisely and be prepared to move onto the next journal on your list of potential publishers. Ensure that you include long shots, such as very high impact journals.

Be aware that there are cultural issues, even in scientific disciplines, and that these might affect your choice of journal. For example, the US is generally committed to randomised trials as the most effective way of measuring differences within a population, whereas the UK and Europe, in general, are more open to the benefits of observational studies.

Remember that the reviewers are your peers

Peer-reviewers are us. They are good and bad, clever and not-so-clever. They are definitely not omniscient, so you cannot assume that they know the fullness of your work, or that they've read all that you've published. You must ensure that crucial points are spelt out, but that their intelligence is not insulted. Remember, they are like you, but they are not you.

Optimise the quality of the manuscript

The manuscript should be an exquisite work of beauty. You don't want to distract the reviewer with unnecessary, and unimportant, concerns. The reviewer should be solely focussed on the beauty of your research, not the fact that the fonts are inconsistent, or the tables are mis-labelled. It is well worth spending time ensuring that the manuscript is formatted perfectly, and rigorously adheres to the journal's formatting requirements.

Appreciate the editorial role

The editor's job is to put high-quality papers in the journal. The editor may not have specific expertise in the precise subject of your paper, but will be an expert in the overall field of the journal's discipline. The editor is a judge, who examines the reviewers' comments, along with your response, and then makes a decision in the best interests of the journal.

Be part of the solution

You can help improve the peer-review process by doing balanced peer reviews yourself. Being a thoughtful and objective peer reviewer will help, not only to improve your academic discipline overall, but will assist you in preparing your own papers for future review.

Cultivate resilience

It can be tough receiving negative comments on a paper that you have worked so hard on and believe is of high quality. You will need resilience to get you through the peer review process. Remember that it is very rare for papers to be accepted without any changes, so expect that there will be requests for changes. You should be mentally prepared for rejection when you submit the paper. Some ways to cultivate resilience include:

- Talk about the comments with your peers, friends and family. Just being listened to makes a difference to our feelings.
- Share your feelings about the comments, not just the technical side. It's OK to be disappointed and de-motivated for a short time, and sharing feelings can help to dispel them.
- Use humour as a way of putting it all in perspective.
- Watch the *Third Reviewer* video at <https://www.youtube.com/watch?v=-VRBWLpYCPY> 😊

Approach to responding to reviewers' comments

Consider that responding to reviewers' comments is an opportunity to improve your manuscript, rather than defending a personal attack upon you. To do this, you need to use a clear, somewhat Machiavellian approach. When responding to reviewers' comments the best approach, as Machiavelli noted, is either to be nice to them by agreeing or to completely extinguish their arguments with your data and logic. This section considers ways of approaching your response to reviewers' comments.

Read comments carefully

When you first read the comments of a reviewer, don't get lost directing anger at the reviewers and questioning their academic credentials. Read the comments carefully and summarise them in a few words.

Consider the implications

When deciding whether to make any given change, consider the implications. How will it affect the overall thrust of the paper and its central scientific contribution? If a change is made in one part of the paper, will that necessitate a change in another? How much work is involved in making the change?

Make changes you agree with

You should roll over and make changes whenever that is possible and does not have negative implications for the paper, or actually improves it. Agreeing to some changes will indicate to the editor that you are serious about improving the paper and have thought through the comments carefully. If you refuse to make any changes, the editor may think that you have not considered the comments properly.

Judiciously choose the changes that you will oppose

If there are some comments that you oppose and that you will refuse to accept, think carefully about how you will argue your case. Focus on the data and the facts, rather than on how unpleasant the change might be. Choose to do battle over issues that you can win.

Handle disagreement tactfully

When there is an instance where you and the reviewer simply disagree, the disagreement needs to be addressed and not ignored.

- Note that there is a disagreement
- Note that opinion is divided and make it clear that you understand the reviewer's concerns



“...men ought either to be well treated or crushed, because they can avenge themselves of lighter injuries, of more serious ones they cannot; therefore the injury that is to be done to a man ought to be of such a kind that one does not stand in fear of revenge.”

Niccolò Machiavelli
Il Principe, c1505

- Concede what you can, including noting in the manuscript that opinion is divided
- Defer to the editor

There is a worked example of handling disagreement in Appendix A.

Be courteous and appreciative, not adversarial

Make it clear that you appreciate the time that the reviewer has spent thoughtfully reviewing your paper. Don't treat the reviewer as an enemy to be defeated, but as a confederate in the cause of advancing scientific understanding.

Primarily address the editor

When you respond to a reviewer's comments, it will always go back to the editor, and may go back to the reviewers themselves, so bear these people in mind when formulating your response. You should refer to the reviewer in the third person, but keep in mind that they may read your response, so be polite but confident in your statements. Also, consider the reader of the paper when it is finally published in the journal, and appeal to their needs, when necessary. For example, a request to re-phrase something could be opposed on the grounds that it would potentially confuse the reader.

Remember that these skills are generalisable

Responding to the comments of other people about your work is a useful skill and has a place outside the peer-review process. For example, being able to formulate arguments about the value or techniques of your research will be very useful for writing grant applications. In some sense, reviewers of papers are similar to reviewers of grant applications, and mastering this process will stand you in good stead in the grant application process.

Useful phrases

Here are some useful phrases that can be modified to suit your paper, and contain the right mix of politeness but firmness.

- "While this is an important point and would be a potentially useful contribution, we consider it beyond the scope of the paper."
- "We are concerned that including xx may be confusing to the reader and detract from the overall focus of the paper. However, we are happy to take editorial advice on the matter."
- "...would not be of service to the reader."
- "We had considered this, in the light of xx [reference] but were concerned that it would ..."
- "We are unsure what the reviewer means by this but ... and would be happy to take editorial advice on the matter."

Handy hints

Here are some handy hints about how to phrase your response to reviewers' comments.

Emphasise the points that you have accommodated

You will have decided to concede some points and to change them to suit to the reviewers. Place emphasis on these points so that the reviewer feels that you are generally following their guidance.

Demonstrate your (superior) understanding

On some issues, you may have a better understanding than the reviewer. Gently pointing out where the reviewer is wrong will strengthen your position. The key here is to be polite but firm. If you are right, then you need to say so. In Appendix A, there is a worked example of the author correcting a central misconception of the reviewer, politely and gently, but firmly.

Acknowledge when the reviewer is right

If the reviewer has raised a point, or misunderstood something in your paper, then it may be insufficiently clear to your readers as well. Acknowledge this and amend your manuscript to make the point more clear.

Use the “third way”

The “third way” is to avoid head-on confrontation and an adversarial approach between two parties, by appealing to a third party, such as an external source of data, or a third person. For example, you could appeal to an external source by citing the STROBE guidelines and explaining that you are conforming to them. Or you could appeal to a third party, such as saying that a reader may be confused if an aspect of the paper was changed, or suggesting that the editor might make a call on a particular issue. By appealing to an entity that is outside the author-reviewer relationship, conflict can be avoided.

The “third way” is to appeal to a third party or source

Use evidence

Consult widely and use references to back up your assertions. Make generous use of hard data, especially sensitivity analyses. When presenting the evidence, be respectful and explain that the “evidence shows ...” rather than “the reviewer is wrong because ...”.

Adding tables and figures to your response is excellent, and shows that you are going further than required. They are also a powerful visual tool indicating that you know what you're doing.

Using references and data to deflect a criticism of the reviewer is very powerful, and its impact cannot be over-stated. If you can't do something yourself, then try to find a paper that has done it.

For example, you may not have been able to validate a self-reported measure, but you could find another paper that has validated a similar measure.

Give them something extra

If appropriate, provide the reviewer with additional data on a related subject. This might include additional work that you have done during your research or analysis, or a part of a paper that you have not yet submitted for review. You might include additional work that is beyond the scope of the current paper, but is related to it. This shows that you know your stuff, you have access to a wide range of information and also that you're willing to work a bit harder to get your paper accepted.

This also involves the reviewer in the process of your paper, by giving them additional insight that is not available to the reader. This may increase their commitment to the success of the paper.

Accumulate answers to common issues

Reviewers raise common issues over and over again. You should be prepared with a list of responses to these issues, because you will see them throughout your research career. Here are a few of them:

- Central scientific contribution
- Validity of measures
- Categorisation of variables
- Representativeness of the sample
- Generalisability
- Missing data
- Loss to follow-up
- Confounding, bias, adjustment

In Appendix A, there is a worked example of responses to a reviewer's comments about common issues.

Be concise

Wordiness can look like defensiveness, so try to be concise wherever possible. On the other hand, don't be so brief that it looks like you're dismissing the views of the reviewer. Say as much as you need to make your point, and no more.

Conflicts can arise when there is a word limit for the article, but the reviewer is asking for lengthy additions to the manuscript. Sometimes the editor can tell you to shorten your paper when a reviewer is effectively telling you to lengthen it. In that case, you can politely refuse to make the additions, using phrases like:

- "... is beyond the scope of the present paper"
- "... is the subject of future research in this area and is not addressed here"
- "... would not do justice to this important issue"

Format your response cleverly

Visual signals in your response will strengthen your case. Ensure that your formatting is clear. Attempt to de-emphasise reviewer's comments, and emphasise your own, by putting the reviewer's comments in a plain font and in italics, which implies passiveness, while putting your own response in bold, which implies confidence.

Number each comment of the reviewer, to indicate thoroughness and completion, and to make it easier to refer to different parts of the response. For example, "As previously discussed in section 1.2 of our response ...". It is also useful to keep track of comments if the paper is sent back for a subsequent review.

Remember: people hate to be ignored or dismissed

At all costs you need to avoid the impression that you are giving perfunctory responses to the reviewer's comments, and are ignoring their viewpoint. No-one likes to be ignored or have their opinions dismissed without careful thought, and framing your wording with this in mind will increase the likelihood that your next attempt at getting your paper accepted will be successful.

When it isn't working

Occasionally the peer review process can drag on for years, with multiple reviews and re-submissions. If you are still getting useful feedback from reviewers, and not going around in a loop, then it is worthwhile to persist with the current journal.

On the other hand, if there is no progress towards resolution, the feedback is not helpful, you have fallen into a loop where one reviewer asks for a change and another reviewer wants that reversed and/or you have entered a third round of comments, then you may consider your options:

- ask the editor to make a final decision
- if the issue is with the editor, ask the Editorial Board to make a decision
- abandon the process and start again with a different target journal

Sometimes lower-ranking journals have poorer peer review processes with less-experienced reviewers than higher-ranking journals. Even if you do decide to abandon the current process and go to another journal, it doesn't mean that you have to move to a journal with a lower impact factor. You may find that you have targeted the wrong journal, and that your work will receive the recognition it deserves in a different journal.

Appendix A: Worked example

This appendix steps through the progression of a paper by one of the authors of this document, Prof Emily Banks, through the stages of peer review. This worked example demonstrates how the principles and approaches discussed in earlier sections can play out in the real world.

The paper in question had important, novel findings about the link between erectile dysfunction and cardiovascular disease. It was rejected by five journals, and was sent for peer review in two of these. One of them was PLoS Medicine, which provided extensive comments, including seven editorial comments. One reviewer then responded to the author's response, making it a lengthy and complex process. At the end of the process, the reviewer took the trouble to acknowledge that he had actually learnt something through the review process.

First, we look at the covering letter sent by the lead author, Emily Banks, with the first response to reviewer comments.

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Dr Barbara Cohen
 Acting Senior Editor
 PLOS Medicine

Dear Dr Cohen,

Re: Erectile dysfunction as a risk marker for two-year cardiovascular disease hospitalisation and all-cause mortality: prospective findings from 95,038 men (PMEDICINE-D-12-01783R1)

Thank you very much for your email and for the helpful and constructive comments by your editorial team and reviewers. We provide a point-by-point response to each of these below and have uploaded the amended paper. The editorial and reviewers' comments are given in italics.

We very much hope you will now find our paper suitable for publication in *PLOS Medicine*. Please do not hesitate to contact me at emily.banks@anu.edu.au or +61 2 6125 0328 if you require anything further.

With best wishes,

Yours sincerely,



Professor Emily Banks, on behalf of the authors

As is apparent, the covering letter is respectful and appreciative. It is polite but firmly confident.

Now we move to the detail of the response.

Correcting central misconception

E.2. The follow up duration is very short, which is a major limitation of the study. The authors make a point that for evaluation of a risk marker, short follow up is desirable. But in fact, the whole analysis is focused on demonstrating that erectile dysfunction is an independent predictor of outcomes and that it has the characteristics of a causal association (risk gradient, biological plausibility). It would be very useful to have long term follow up to determine whether the effect attenuates over the 4 years of follow up available for the men recruited in year one of the study. These data should be for the major atherosclerotic related CVD outcomes by year of follow up to permit assessment of the pattern of association.

A risk marker may be defined as an attribute that is associated with an increased probability of occurrence of a disease or other specified outcome and that can be used as an indicator of this increased risk. **It is not meant to be an "independent" risk factor that causes a disease.** For example, retinal manifestations of hypertension could be considered "risk markers" for adverse outcomes of hypertension (e.g. CHD, stroke), because they are essentially markers of disease severity. They would be expected to show a risk gradient and biological plausibility, in terms of their relationship to the specified outcomes, but these would not be used as evidence of a causal relationship and they would not be considered "independent" risk factors for hypertensive complications.

In the same way, conceptually, erectile dysfunction is a marker of risk because it is likely to relate to the severity of underlying atherosclerotic disease and particularly endothelial dysfunction. Current models suggest it is highly unlikely that erectile dysfunction *causes* CVD and our study does not set out to show that. We examine the risk gradient because this underlies the potential usefulness of the risk marker in predicting events and in discriminating at what level clinical concerns should be raised. We discuss biological plausibility because both risk markers and risk factors should demonstrate such plausibility. We adjust for additional factors with the aim of demonstrating how well the marker predicts risk above and beyond those additional factors.

As we have stated, long follow up is not required for examination of the relationship of risk *markers* to outcomes. The main reason for requiring long follow up in cohort studies is to examine the relationship of risk *factors* to outcomes, independent of other baseline factors. Longer follow-up is often necessary to avoid with issues relating to "reverse causality". For example, when examining the relationship of body mass index to mortality, it is often necessary to exclude those who are likely to have lost weight due to pre-existing disease (i.e. BMI as a "marker" of underlying disease), and an effective way of doing this is to exclude initial years of follow up.¹

In contrast, the aim with a clinically useful risk marker is to see how this marker relates to the immediate (or short-term) risk of the outcome of interest. The expectation is that reverse causality is present, in that the risk marker is closely related to underlying disease severity and one would expect this relationship to be *attenuated* over the years of follow up. Hence, short follow up is not an *a priori* limitation of a study of a risk factor, provided sufficient numbers of events are present. From the editorial comments we can see that this point is still insufficiently clear and have added to the relevant part of the discussion, to read:

"In studies of the relationship between risk factors and disease, short follow-up time is often seen as a limitation, particularly if there are issues with reverse causality. In contrast, where a risk marker is being considered, with the aim of measuring something that relates to the presence and severity of underlying disease, short follow-up time is often desirable, as is the case here. Provided there are sufficient numbers of health events, this allows quantification of the relationship of the risk marker to the immediate risk of disease. In particular, since erectile dysfunction status is likely to change increasingly with time since baseline, longer follow up might lead to reduced accuracy of prediction."

Furthermore, in order to directly address the editorial comments we show analyses separately according to follow up time. The relationship between ED and the major outcomes under examination does not differ significantly according to follow-up time (<2 years versus ≥2 years), however there are relatively few events and confidence intervals are wide in those with longer follow up.

Outcome	Degree of erectile dysfunction	≤2 y of follow up		>2y of follow up	
		no of events	RR (95%CI)	no of events	RR (95%CI)
IHD	none	289	1.00	69	1.00
	mild	219	1.05 (0.87-1.25)	52	1.07 (0.74-1.54)
	moderate	216	1.32 (1.09-1.59)	53	1.34 (0.91-1.97)
	severe	182	1.47 (1.18-1.84)	45	1.37 (0.86-2.20)
all CVD	none	850	1.00	195	1.00
	mild	570	0.95 (0.85-1.06)	138	1.01 (0.81-1.27)
	moderate	537	1.16 (1.03-1.30)	133	1.24 (0.98-1.58)
	severe	448	1.28 (1.11-1.48)	93	1.12 (0.83-1.52)

Rrs adjusted for age, tobacco smoking, alcohol consumption, marital status, income, education, physical activity, BMI, diabetes and current treatment for hypertension and hypercholesterolemia.

We have now amended mention this in the results:

"The relation of erectile dysfunction to subsequent CVD events did not vary materially according to duration of follow-up (i.e.<2 years versus ≥2 years, data not shown)."

The reviewer has a fundamental misunderstanding of the paper. In this case, the reviewer has mistakenly believed that the authors were arguing that erectile dysfunction was a risk *factor* for cardiovascular disease, rather than a risk *marker*. The authors were demonstrating that erectile dysfunction acts as a warning of cardiovascular disease, in much the same way that a canary in a mine acts as a warning of dangerous gases. In this context, erectile dysfunction is a “canary in the trousers”.

Here the author provides additional material to the reviewer that is not in the paper, thereby demonstrating that the author is taking the comments seriously. The author has accommodated the reviewers' comments, whenever possible, by amending the Results section.

The author has numbered the comments by the reviewer to ensure that they are all addressed. The formatting is designed to give maximum emphasis to the response: reviewers' comments in italics, and author's response in bold typeface.

Common issue: validity of measures

E.3. There is only a single self-report question measured only once using the question 'how often are you able to get and keep an erection that is firm enough for satisfactory sexual activity'. The question is said to perform well compared with a more complete questionnaire but it would be useful to have data on kappa coefficients and test-retest reliability from the 45 and Up study as well as the published citation. Typically questions that ask 'How often..' perform less well than those that ask 'In the last week?'

In large scale studies, it is typical to rely on other smaller scale work to validate measures.^{2,3} A previous study has compared a version of the single self-report question used here with the International Index of Erectile Function (IIEF) and has documented a correlation coefficient of 0.71 and a kappa score of 0.6.⁴ Because of the intermittent and variable nature of sexual activity, it has not been possible to frame general questions about erectile dysfunction in terms of “in the last week”, and hence the standard instruments do not phrase their questions in these terms.

Kappa coefficients can be used to assess agreement when individuals have reported data on the same measure in two different ways. In the 45 and Up Study we have only measured erectile dysfunction according to the single item in 95,000 men and are therefore not able to provide kappa coefficients. We have measured erectile dysfunction at a single time point and so do not have data from the 45 and Up Study on test-retest reliability. It should be noted that measurement error, in terms of poor validity and poor test-retest reliability, would tend to lead to an attenuation of the observed relative risks, so should not detract from the validity of the main findings outlined here. We have added the correlation coefficient and kappa score for the validation study to the discussion section.

The validity of the chosen measures is one of the common issues about which reviewers often comment.

Here, the author has used references to other published work to back up statements in the response. This is a powerful technique, as it draws in the wisdom of others to support the author's position.

The author has added additional information, and carefully clarified why it is not possible to meet the reviewer's request for kappa coefficients for the 45 and Up Study.

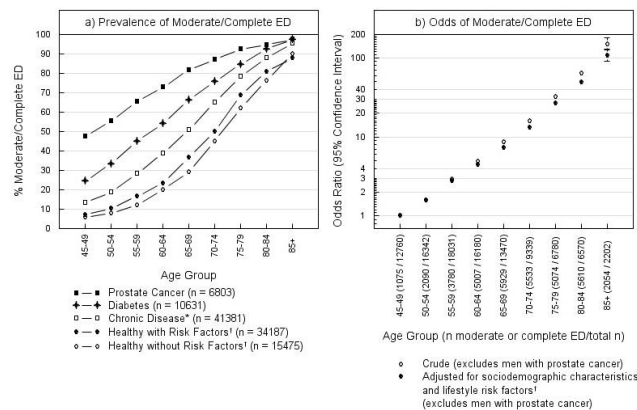
Common issue: contiguous versus categorical

1.1. My main problem is the categorization of the independent variables in the Cox regression. This is very rarely a good idea, and needs strong justification. For example, the categorization of drinking assumes that people who drink 1 drink per week are the same as those who drink 14, and that those who drink 15 are the same as those who drink a LOT. This is almost certainly false, and is an unnecessary assumption (similar for age, BMI and other continuous variables). This categorization is OK for display in tables, but should not be done in models. Nonlinear effects of the IVs can be modeled by polynomial terms or splines.

There are four covariates in our analyses that could potentially have been treated as continuous: age; body mass index; physical activity sessions and alcohol consumption. Categorisation of specific variables is a common approach which has the advantage of minimising certain assumptions about the nature of the underlying relationships between specific variables. In particular, categorisation minimises the impact of outlying values. We agree that such categorisation introduces certain assumptions. We also agree that, if each individual value given for each variable was equally reliable, then categorisation would potentially waste valuable information.⁵ However, certain responses given were, in effect, categorised by the respondent (i.e. for alcohol there was clustering at 7, 10 and 20 drinks per week), so treating this variable as continuous would give each individual values greater weight than could be justified.

Age is the key potential confounding factor in our data, with an increase in the risk of erectile dysfunction of 11% (95% CI 11.1-11.5%) per individual year increase in age after age 45 (see Figure 2, below). Age is not categorised in our analyses. It is used as the underlying time variable, in individual years and so is adjusted for extremely finely.

Figure 2. a) Prevalence of moderate/complete erectile dysfunction (ED) according to self-reported disease status and lifestyle risk factors in the 45 and Up Study. b) Odds ratios and 95% confidence intervals of moderate/complete ED by age.



Body mass index, physical activity and alcohol consumption are all relatively weakly related to erectile dysfunction (see Figure 1, above) and, as currently categorised, capture the observed variation in relative risk. In order to examine the robustness of our assumptions regarding categorisation, we have repeated our analyses for two major outcomes, adjusting for the potentially continuous variables as continuous. These are reproduced below.

Table 2. Sensitivity analysis for covariate classification. Relative risk (95%CI) of specific CVD outcomes in men with no previous CVD.

		erection	All categorical	BMI continuous	BMI, Alcoholic drinks continuous	BMI, Alcoholic drinks, pasessions continuous
IHD	Events		1125	1048	1030	995
	None		1			
	Mild		1.08 (0.92- 1.27)	1.05 (0.89- 1.24)	1.05 (0.89- 1.25)	1.04 (0.87- 1.23)
	Moderate		1.37 (1.16- 1.63)	1.35 (1.13- 1.61)	1.37 (1.15- 1.64)	1.36 (1.13- 1.63)
	Severe		1.60 (1.31- 1.95)	1.62 (1.32- 1.99)	1.67 (1.36- 2.06)	1.71 (1.38- 2.11)
All CVD	Events		2964	2773	2727	2617
	None		1			
	Mild		0.99 (0.90- 1.09)	0.96 (0.87- 1.07)	0.96 (0.87- 1.07)	0.96 (0.87- 1.07)
	Moderate		1.23 (1.11- 1.37)	1.23 (1.10- 1.37)	1.24 (1.11- 1.39)	1.24 (1.11- 1.39)
	Severe		1.35 (1.19- 1.53)	1.37 (1.21- 1.57)	1.38 (1.21- 1.58)	1.41 (1.23- 1.61)

RRs adjusted for age, tobacco smoking, alcohol consumption, marital status, income, education, physical activity, BMI, diabetes and current treatment for hypertension and hypercholesterolemia.

We found no material difference in the conclusions reached regarding the main findings, according to whether the remaining potential continuous variables (BMI, number of alcoholic drinks per week and physical activity) were categorised or left as continuous (i.e. variation in the relative risks was <10%), but confidence intervals became wider, and we have retained the original categorisation. We have also added the following to the text:

“No material differences in the main exposure-outcome relationships (ischaemic heart disease and all CVD) were observed when BMI, alcohol consumption and physical activity were modelled as continuous variables.”

Another common issue raised by reviewers, and shown in this same worked example, is arguing about whether variables should be modelled as contiguous or categorical. Here the author begins by acknowledging that the argument is a common one, and then goes on to gently point out where the reviewer is wrong, without stating that explicitly.

The author then provides additional data from her research, which was unpublished at the time. This demonstrates the author's knowledge and understanding of the material.

Finally, the author is able to show, using data and hard facts, that there is no material difference in the results, regardless of whether the variables were modelled as continuous or categorical. In order to acknowledge the contribution of the reviewer, the author has then added an additional sentence to the text of the manuscript, stating that there were no material differences.

Common issue: representativeness

3.8. The cohort has a mean age of 62 in their study and a mean BMI of 27 (significantly lower than most American cohorts) . We would expect that this cohort would have an overall incidence of ED of ~60% given previously work in American cohorts. The incidence is surprisingly low in this cohort and this should be commented on in the discussion. A significant limitation of the study is the lack of serum lipid values and/or BP measurements which would be required in any major CV health study.

The current analyses exclude men with cancer and previous prostatectomy so it is difficult to relate the prevalences of erectile dysfunction in this paper directly to population prevalences. Furthermore, cohort studies are generally not suitable for providing estimates of prevalence.

Using data from the cohort of 108,166 participants with data on erectile dysfunction, prior to exclusions due to a cancer diagnosis, 37.2% reported no erectile dysfunction, 24.1% had mild erectile dysfunction, 18.7% had moderate erectile dysfunction and 20.0% had severe erectile dysfunction. We observe, if anything, somewhat higher age-specific prevalences of moderate to severe erectile dysfunction in our study than the prevalences of moderate to severe erectile dysfunction reported in a representative population-based survey of Australian men.⁶ Given that the study has the stated exclusions and is not designed to measure the prevalence of erectile dysfunction we consider that it might be best to avoid reference to prevalence, to avoid confusing the reader. However, we are happy to take editorial advice on this matter.

Here the author refers to data to make a point, as well as gently correcting the reviewer on the difference between “prevalence” and “incidence”. Finally, the author uses the “third way” by appealing to the editor to make the final decision.

E.7. Reviewer response 3.8: It would be useful to refer to the relative prevalence of ED in this population vs the general population to address questions of whether this population is representative.

We have now done this and have added this paragraph to the discussion:

“Using data from the cohort prior to exclusions,16% of men aged 50-59, 34% of men aged 60-69 and 60% of men aged ≥70 years reported moderate or severe erectile dysfunction; this compares with 11%, 31% and 68% affected in the same age groups in a representative population-based survey of Australian men.[1] Hence, although representativeness is not necessary for valid and reliable estimates of relative risk from within-cohort comparisons,[2] the degree of erectile dysfunction within the cohort is broadly similar to that reported in the general population.”

The reviewer then responded to the author's response with a second set of comments and request for information. In this case, the author simply agreed to the request of the reviewer. Here we can see the value of having numbered comments and responses, in order to keep track of exactly what is being discussed.

Here the author was persistent in standing by the claims of the paper. By continuing to respond to further comments, the reviewers eventually conceded the point.

Common issue: unmeasured factors

3.18. Paragraph 7: PDE5i use could significantly confound this study and the authors should mention the specific usage rates in Australia. Also, the authors need to comment on potential bias introduced from a patient being admitted for another event ie sepsis that lead to MI as CVD is a common endpoint for many different disease processes. The authors need to further clarify how they made any effort to examine the temporality of the CVD events in relationship to other dx during admission.

We are not able to locate any accurate direct population-based information on the use of PDE inhibitors in Australia but basic indicators suggest use is uncommon. Data from a newspaper article on war veterans indicates that 5,000 out of 300,000 (1.7%) received sildenafil. In a Lancet publication on reproductive health in a representative sample of Australian men aged ≥ 40 years, 303/5990 (5%) reported ever having received medical treatment for erectile dysfunction.⁶ We have now added this to the paper. Moreover, since use of PDE inhibitors does not influence the risk of CVD, this cannot be seen as a traditional confounding factor.⁹ Even if substantial numbers of men who reported never having a problem getting an erection were taking PDE inhibitors, this would lead to a dilution of the underlying relative risks of CVD with increasing ED.

Here the author uses a newspaper article to provide data. Whilst peer-reviewed publications are much more powerful, it is better to have something in writing to back up the claim, rather than simply make an assertion such as “PDE use is uncommon”.

Disagreement

We recognise that there is an unresolved debate about the utility of this method, but, in the final analysis, we believe that this is largely a philosophical difference, and no amount of defence is likely to convince Reviewer 2 of its validity. Although we stand by our data and the methods we have employed, we could remove these results.

The author is faced with the dilemma of having a basic disagreement with the reviewer. Here the author acknowledges the disagreement and appeals to a third party, the editor, to make the final call. As far as possible, the author is conciliatory, and offers to make a change.

Acknowledgments

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