Author's response to reviews

Title: Do we want more cancer patients on clinical trials? If so, what are the barriers to greater accrual?

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Author's response to reviews: see over
Editor

Many thanks for forwarding Mike Clarke's comments. Please believe me that it is not just gratuitous sucking up when I say that it was a delight to get a peer review that was actually helpful, and that was less about the peer reviewers pumping themselves up than about trying to improve the scientific literature.

My responses to each comment are given below, along with a description of the changes that I have made in the light of the comment.

Yours

Andrew Vickers

Comment: 1. Abstract: the two parts of the sentence “The financial and regulatory problems ...up; it has been estimated ... conducted abroad” do not necessarily support each other. Since the second part is the current situation and you provide no information on what proportion of US-sponsored trials were conducted abroad before the financial and regulatory problems. Do you have data on that? Does the article you cite in the main text (reference 9) make the comparison over time?
Response: I accept that I implicitly drew a causal relationship between increasing regulation and the increasing proportion of trials conducted outside of the US, and that this relationship was not well justified. I have changed this part of the text to read:

It has been estimated that nearly half of all US-sponsored trials are being conducted abroad, and it is plausible that excessive regulation is at least partly responsible.

Comment: 2. Discussion, How do get more patients on clinical trials, paragraph 1: you should reference the “one estimate” that 95c of every dollar of cancer research funding goes to basic research.
Response: I have slightly amended this sentence and added a reference.

Comment: You should also reference the statement that the funding of the co-operative groups has been flat for years.
Response: This reference has been added.

Comment: Discussion, How do get more patients on clinical trials, paragraph 3: your statement “I do not believe ...requirements” is very sweeping. Do you really not believe that anyone has noticed this?
Response: I have removed this sentence.

Comment: Introduction: can you add a reference to the statement that about 5% of cancer patients participate in clinical trials.
Response: Yes, and I did.

Comment: Discussion, paragraph 2: you appear to be critical of phase 2 trialists for not being prepared to go on to do phase 3 trials. In some cases, the skills needs for phase 2 and phase 3 trials are quite different and perhaps the challenge to phase 2 trialists (and the funders of phase 2 trials) should be that they should more actively promote the uptake of their results in phase 3 trials. What do you think?
Response: Not much! I don’t think a full reading of the literature really supports the view that there are a bunch of Phase II trialists out there who want to move on to Phase III but just don’t have the skills.

Comment: Discussion, How do get more patients on clinical trials, paragraph 2: you mention the need to spend a week on the “paperwork” for a single patient. How much of this is generated by regulation and how much is generated by poor design (e.g. excessive data collection) by the researchers?
Response: This is a fair point. I have added the following:

In other words, it takes about an entire work week to manage the paperwork of a single clinical trial patient. It is true that, in some cases, one might lay at least some of the blame for excessive paperwork on poor design and unnecessary data collection; nonetheless, one cannot help but speculate as to how much researcher time might be freed up were regulatory requirements to be liberalized.

Comment: Conclusions: are you able to give any reference to support the lack of sufficient randomised evidence for radiotherapy versus surgery for men with prostate cancer? For example, is there a systematic review that identifies this gap?
Response: Yes there is, and I have added the reference.

Comment: Are you able to include any examples of the “right clinical trials”.
Response: I could, but I am not sure how it would really help matters. This is especially because there have been, of course, a very large number of the “right” clinical trials.

Comment: Discussion, How do get more patients on clinical trials, paragraph 2: I was surprised to read that even a single centre trial would have to go through so many committees. If there is space in your editorial, would you be able to expand this to provide the reader with an illustration of the things that each of these committees would oversee for the trial.
Response: I think doing so would be somewhat distracting for the reader, and not particularly key to the main argument. (it might also sound like me whinging).

Comment: You might wish to mention initiatives in other places to facilitate randomised trials. For example, the European Union funded TENALEA project
(www.tenalea.com) is providing an online, 24 hour registration and randomisation service for clinical trials.

**Response:** This is an interesting initiative that I was not previously aware of. However, I am not sure where I could fit this into this short editorial.

**Comment:** Some other articles that are relevant to your work on the need for more phase 3 trials and sources of the questions for these, you might like to look at: Djulbegovic B, Kumar A, Soares HP, Hozo I, Bepler G, Clarke M, Bennett CL. Treatment success in cancer: new cancer treatment successes identified in Phase 3 randomized controlled trials conducted by the National Cancer Institute-sponsored Cooperative Oncology Groups, 1955 to 2006. Archives of Internal Medicine 2008;168(6):632-42; and Clarke L, Clarke M, Clarke T. How useful are Cochrane reviews in identifying research needs? Journal of Health Services Research and Policy 2007;12(2):101-3.

**Response:** I have added the first of these citations in the section where I discuss the point that what really matters is Phase III trials.

**Comment:** 12. Do you want to add anything to the article to comment on the definition of clinical trials used by the National Cancer Research Institute in the UK which was used in achieving the government target that 10% of cancer patients would be in “clinical trials”.

**Response:** I think this would have been more for the original paper, right?