Reviewer's report

Title: Exploratory trials, confirmatory observations

Version: 1 Date: 16 February 2011

Reviewer: Paul Cronin

Reviewer's report:

Comments:

Review BMC Medical Research Methodology
Manuscript 2002771554690506 - Exploratory Trials, Confirmatory Observations

General comments:

Major Strengths: A very interesting paper and counter argument to the current prevailing view in therapeutic clinical research that only randomized clinical trials are the most appropriate method to assess and confirm an intervention's efficacy.

Major weaknesses: None.

Keywords: None.

Comment 1: In the section “But the responses of different types of patients to a same intervention may be of different degree and even go in the opposite direction, so overall differences between the compared interventions can be diluted, making necessary large RCTs and megatrials to detect statistically significant differences. In other words, the strategy of large trials has not helped to solve the problem; indeed, it has worsened it.” I would also make the additional point that large RTCs can detect small effects that, although statistically significant, may have little practical benefit on patient outcomes.

Comment 2: And the additional point that large RCTs / megatrials designed specifically to answer a specific question of benefit or harm may not confirm benefit or excluded the possibility of harm.

Comment 3: In the section “The continued enlarge in sample size has dramatically increased RCTs' cost, even when researchers seek to answer simple questions. If the objective was to answer complex questions, which arise with most diseases, much larger samples would be required.” I would also discuss that these very expensive large-scale trials have historically had a substantial proportion of their funding from government and foundation grants but more recently these are now largely sponsored by industry with potential vested interests and the potential to influence outcomes, the interpretation of data, and nuances of the language used when writing manuscripts.
Comment 4: Please change “The continued enlarge in sample size has dramatically increased RCTs’ cost, even when researchers seek to answer simple questions” to “The continued increase in sample size has dramatically increased RCTs’ cost, even when researchers seek to answer simple questions.”

References: Appropriate and well referenced.

Summary Comment:

The debate addresses an important problem of interest, and presents a novel argument and insight into existing work. It is well argued and referenced with logical arguments and sound reasoning. The manuscript is written well enough for publication.

- Major Revisions

None.

- Minor Revisions

Comment 1: In the section “But the responses of different types of patients to a same intervention may be of different degree and even go in the opposite direction, so overall differences between the compared interventions can be diluted, making necessary large RCTs and megatrials to detect statistically significant differences. In other words, the strategy of large trials has not helped to solve the problem; indeed, it has worsened it.” I would also make the additional point that large RTCs can detect small effects that, although statistically significant, may have little practical benefit on patient outcomes.

Comment 2: And the additional point that large RCTs / megatrials designed specifically to answer a specific question of benefit or harm may not confirm benefit or excluded the possibility of harm.

Comment 3: In the section “The continued enlarge in sample size has dramatically increased RCTs’ cost, even when researchers seek to answer simple questions. If the objective was to answer complex questions, which arise with most diseases, much larger samples would be required.” I would also discuss that these very expensive large-scale trials have historically had a substantial proportion of their funding from government and foundation grants but more recently these are now largely sponsored by industry with potential vested interests and the potential to influence outcomes, the interpretation of data, and nuances of the language used when writing manuscripts.

- Discretionary Revisions

Please change “The continued enlarge in sample size has dramatically increased RCTs’ cost, even when researchers seek to answer simple questions” to “The continued increase in sample size has dramatically increased RCTs’ cost, even
when researchers seek to answer simple questions.”

Based on my assessment of the manuscript
- Accept after minor revisions.

Quality of written English
- Very good.

Statistical review
- N/A.

Declaration of competing interests
- None. I declare that I have no competing interests.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.