



PART 1:

Journal Name:	British Journal of Medicine and Medical Research
Manuscript Number:	MS: 2013_BJMMR_3208
Title of the Manuscript:	The Necessity of Randomized Clinical Trials

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**PART 2: Review Comments**

	Reviewer's comment	Author's comment (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)
<u>Compulsory</u> REVISION comments	<p>1) The authors should better separate the various types of interventions : new drugs, monitoring systems, interventions, etc – obviously the needs are different</p> <p>The authors should also present the limits of RCTs (exclusion criteria, delays to start the intervention in some cases, patient selection related to the need of informed consent, etc)</p>	<p>1) We thank the reviewer for this important comment. It is clear that the details about assessment of benefits and harms differ between different types of interventions. However, the basic principles behind assessing different types of interventions are very similar, and we wish to focus on the general principles. We have now dealt with this issue. Please also see our response to Jacques Demotes Maynard.</p> <p>We also agree that conducting RCTs have several limitations.</p> <p>We have now clarified these points in our revised manuscript:</p> <p>Line 53: “Randomized clinical trials cannot only assess the effects of many different forms of experimental interventions, but also many different forms of control interventions, e.g., no intervention, placebo, ‘impure’ placebo, nocebo, or an active control intervention (i.e., a treatment backed by sufficient evidence). The latter trials compare the effects of two interventions (so-called head-to-head trials or comparative intervention research). It is clear that the inferences of the results from the different forms of trials differ accordingly. We</p>



		<p>will in the following paragraphs use the term 'randomized clinical trials' as a collective term for all kinds of trials, as we believe that the fundamental principles are similar regardless of type of experimental intervention and control intervention. The fundamental construct of the randomized clinical trial allows that any intervention using quantitative or qualitative outcomes can be assessed using the same basic principles [14]."</p> <p>Line 371: "Conducting randomized clinical trials generally require more resources than conducting observational studies. Researchers can be reluctant to conduct randomized clinical trials because they are costly and time consuming. Lack of methodological and statistical know-how can hinder the making of randomized clinical trials; it can be difficult to recruit enough trial participants, etc. Typical misconceptions about the usefulness of results from randomized clinical trials can also hinder that randomized trials are conducted. It is, e.g., often stated that trial populations are not representative of patients in the clinic [4,42,43]. Strict inclusion and exclusion criteria (e.g., the need of informed consent) are believed to put together trial populations not representative of patients in the clinic. The ethically need of informed consent can theoretically affect trial populations so they are different from the everyday patients, but such fears are often overestimated [44,45]."</p> <p>Line 512: "Observational studies can be the only</p>
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		<p>possible option regarding assessment of very rare adverse events, very late occurring effects, or of very long-term interventions. Observational studies can also have their place when it is difficult to include large enough sample sizes assessing extremely rare diseases or when lack of funds hinders the conduct of randomized clinical trials. Observational studies can of course have their place in such circumstances but their inferential power should always be considered threatened by random errors, confounding by indication, unmeasured confounding, and other systematic errors. Therefore, the randomized clinical trial would still in such circumstances be the optimal design regardless of hindrances making them infeasible. It may, as mentioned, be possible to present a few historical examples where intervention effects have been sufficiently validated by observational evidence [5]. However, these exceptions do not justify that observational evidence generally should be used prospectively to validate intervention effects. As it has been clearly expressed by Heiberg already in 1897 and reiterated by others both before and since [71-73] — regarding the vast majority of interventions randomized clinical trials are necessary to assess their effects.”</p> <p>Please also see Table 1: Misconceptions</p>
<u>Minor</u> REVISION comments		



<p>Optional/General comments</p>	<p>1) This is an interesting, provocative article, but of course not realistic. It is a bit the counterpart of our article stating the opposite (ref 3). There are many instances where RCT cannot be conducted (monitoring ECG, or monitoring arterial pressure in shock states, ventricular defibrillation in cardiac arrest, etc). If a surgeon wants to decrease the size of his incision, or for a horizontal rather than a vertical incision, he does not need to perform a RCT !</p>	<p>1) We thank the reviewer for being open-minded and for believing our manuscript is interesting. We are happy that the reviewer finds our article contrasting his points of view. This was exactly one of the objectives of our manuscript.</p> <p>We agree that it is not practically possible to conduct randomized trials for all kinds of interventions and in all situations. And we think we agree with the reviewer that randomized clinical trials are not the design coming to our mind when we think of monitoring ECG or monitoring blood pressure in shock. Furthermore, we acknowledge that some rare interventions (e.g., insulin for diabetic coma; penicillin for pneumonia; a few others) may have been validly proven by observational evidence. We now try to make this clearer – stressing to the reader that having a new and untested intervention in front of you, one should not embark on the ‘observational path’ but strive towards the proper path of randomized clinical trials right from the beginning.</p> <p>However, we do not agree that randomized trials are unnecessary when surgeons want to assess if a horizontal incision versus a vertical incision during an operation is the most effective operating technique. Surgeons, physiotherapists, psychiatrists, psychologists, etc. should all live in a world where interventions are being developed and assessed through randomised clinical trials.</p>
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		<p>It is practically impossible to assess every intervention, but if randomized trials have not been conducted we must realize the uncertainty of our knowledge.</p> <p>We have now revised our manuscript in response to the reviewer's important viewpoints:</p> <p>See our response to the compulsory comments in the paragraph above</p> <p>See also Box 3 and Table 1 (Counter arguments for misconceptions).</p>
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