

**PART 1:**

Journal Name:	<a href="#">British Journal of Medicine and Medical Research</a>
Manuscript Number:	MS: 2013_BJMMR_3208
Title of the Manuscript:	The Necessity of Randomized Clinical Trials

General guideline for Peer Review process is available in this link:

<http://www.sciencedomain.org/page.php?id=sdi-general-editorial-policy#Peer-Review-Guideline>

- This form has total 9 parts. Kindly note that you should use all the parts of this review form.

**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)
<b>Compulsory REVISION comments</b>		
<b>Minor REVISION comments</b>	<p>1) I think some clarity may be needed on the author's definition of "intervention." Is this term being used to describe the investigation of a novel agent, comparative efficacy, sociobehavioral trials, medical devices?</p>	<p>1) We thank the reviewer for this comment. We have now in our revised manuscript specified that we mean any kind of health-care intervention plus included references to article describing different types of interventions, i.e., investigational medical products, medical devices, surgery, physiotherapy, psychology, psychiatry, comparative research (head to head trials), etc.</p> <p>Line 43: "We will in the following paragraphs consider if randomized clinical trials always are necessary and the best clinical study design to assess any kind of health-care intervention, including drugs, medical devices, surgery, psychotherapy, etc. [8-12]. We are convinced that Thomas C. Chalmers was correct when he stated that we should always randomize the first patient [13]. However, we also acknowledge the difficulties that randomized clinical trials may cause and that they too may show erroneous results. We will, therefore, in the second part of the manuscript provide a list of the typical issues that represents a perceived or real hindrance for the conduct of</p>



	<p>2) In their discussion of prospective evaluation, the authors provide a discussion of type I and type II errors, but they do not note that key advantage of RCT is ability to evaluate/quantify these.</p>	<p>randomized clinical trials and we will suggest some remedies to reduce these hindrances.</p> <p>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 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>2) We thank the reviewer for this important comment. We have now revised our manuscript accordingly:</p> <p>Line 446:  “Observational studies can sufficiently assess associations between certain interventions and outcomes, but the randomized clinical trials are</p>
--	---	--



	<p>3) In their discussion of integration of research results into clinical practice, the authors reference the use of observational studies to access to global market. Perhaps they could provide examples of when observational data is used to guide clinical practice. They reference Cochrane in this discussion as well, and could note that in the establishment of evidence based guidelines meta-analyses of RCTs are the gold standard, followed by single RCTs and then observational data.</p>	<p>always needed to avoid falsely negating (type I error) or falsely confirming (type II error) the null hypothesis and to assess causality between interventions and outcomes, i.e., randomized clinical trials are needed to sufficiently validate intervention effects.”</p> <p>3) We thank the reviewer for this comment. We have now included an example and a reference to the evidence hierarchy.</p> <p>Line 140:          “If an intervention offers more benefit than harm compared with previous treatment options, it is an ethical obligation and hence necessary to get that intervention offered to as many patients as possible, as fast as possible. In the discussion about choice of design for assessing new interventions, investigators often claim that it is important to conduct a quick observational study so it can reach the global market fast if ‘proved’ effective [20]. Many medical devices have, for example, been implemented into clinical practice on the basis of observational evidence alone [21].”</p> <p>Line 558:          “We must as rational clinicians realize the uncertainty of our knowledge if randomized clinical trials have not been conducted and remember the validity of the evidential hierarchy [77]. Systematic reviews of randomized clinical trials is and should be</p>
--	--	---



	<p>4) In their discussion of integration of clinical research into practice, the authors also note that clinical trial data is more complex. They should describe how this data is more complex, and also how this is more extensive/credible.</p>	<p>considered the highest level of evidence followed by single randomized trials [77]. We should not, necessarily, stop using all interventions not based on results from randomized clinical trials. However, we believe that patients most often should be treated with interventions that have been proved effective in randomized clinical trials. Regarding many conditions it might be best not to intervene unless randomized clinical trials with low risks of systematic errors ('bias'), low risks of design errors ('bias'), and low risks of random error ('play of chance') have shown more benefit than harm [1,36]."</p> <p>4) We agree with the reviewer that it was unclear what we meant with the term 'complex'. We have now included a more thorough description of the complexity of conducting randomized trials and revised our manuscript:</p> <p>Line 38:  "Conducting observational studies require much less work and resources than conducting randomized clinical trials, and randomized clinical trials are often perceived as bureaucratic and difficult to conduct. Therefore, it is no surprise that many investigators choose observational studies to try to assess intervention effects."</p> <p>Line 371:  "Conducting randomized clinical trials generally</p>
--	--	--



	<p>5) In their discussion of risk/benefit analysis, the authors provide a discussion about use of observational studies for rare events/effects may be better suited within the introduction or within the discussion on selection of trial design, as the selection of the appropriate trial design (RCT vs observational) is an important point of discussion.</p>	<p>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]. Besides the need of informed consent it is generally not necessary to use narrow criteria for selecting trial participants, as this may impair the external validity [46]. We acknowledge all of these difficulties regarding randomized clinical trials.”</p> <p>5) We agree with the reviewer and we are happy that the reviewer also believes that this is an important point of discussion. We have now moved our considerations about the use of observational studies assessing rare events to the section about selection of trial design.</p> <p>Line 119:  “Large well-conducted observational studies</p>
--	--	---



		<p>can sometimes provide useful information about rare adverse events and intervention effects [15]. We acknowledge a few historical instances where observational evidence validly have demonstrated benefits of new interventions (e.g., insulin for diabetic coma and ether for anaesthesia) [5].”</p> <p>Line 512: “Observational studies can be the only 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</p>
--	--	---



	<p>6) In their discussion on risk/benefit analysis, the authors provide examples in Box 1. I'm unclear as to the utility of these examples to illustrate risk/benefit analysis without further integration into the argument outlined in the text. For example both arguments illustrate that to adequately determine an effect size you need a "control group," Theoretically you can do a case control study, and still have a comparator group, but what makes RCTs so valuable is the randomization process.</p>	<p>randomized clinical trials are necessary to assess their effects."</p> <p>6) We thank the reviewer for this important point. We have now clarified this point in the revised manuscript.</p> <p>Line 177:          "It is theoretically possible to quantify a beneficial intervention effect size via observational evidence if the disease is stable and without any fluctuation in symptoms and if the intervention effects are large enough to be recognized by 'observation'. However, very few diseases show such stability and interventions with large easily observable effects occur extremely rarely [14]. Most interventions have no beneficial effects or relatively small effects. It is among the latter we shall find the interventions of tomorrow. Moreover, large 'surprising' beneficial effects shown in observational studies may be due to random errors, systematic errors, or confounding. Randomized clinical trials are, therefore, needed to assess when potential beneficial effects outweigh the potential harmful effects. Randomization is able to construct the perfect control, which, at baseline, becomes fully comparable to the experimental group regarding all known and all unknown prognostic factors — provided that the randomized groups become large enough. Without randomization and without an appropriate control group it is often unclear if a change in symptoms is caused solely by an intervention effect — or if some, or all, of the</p>
--	--	--





	<p>7.) In their discussion of clinically relevant outcomes, the authors begin their argument with a discussion of for blinding/randomization help to mitigate bias, especially in subjective assessments. Perhaps this is better suited to the initial discussion of the benefits of clinical trials?</p>	<p>change is a natural fluctuation of the symptoms (often a combination of 'regression towards the mean' and the natural fluctuation of the symptoms). Observational studies including some kind of matched control group do not provide valid information about effect sizes, because the participants in the control group will almost never be fully comparable to the participants in the experimental group [18]. It is therefore impossible to quantify and have an overview of the relative effect sizes via observational evidence only (<b>Box 1</b>)."</p> <p>7) We agree with the reviewer that blinding is a very important issue and essential advantage regarding randomized clinical trials. We have mentioned this in the section about Balance between beneficial and harmful effects.</p> <p>Line 247:          "Studies have shown that observational studies compared to randomized clinical trials often overestimate benefits and underestimate harms, i.e., produce biased results [16-18]. To accurately and objectively assess the balance between benefits and harms, we need randomized clinical trials with blinded outcome assessment. Blinded randomized clinical trials compared to unblinded randomized clinical trials show significantly less biased results [31,32]. A valid and unbiased assessment of benefits and harms are impossible to achieve in an observational design where blinding usually is impossible."</p>
--	---	---



	<p>8.) In “Indications for an Intervention” the authors should expand on this idea of subgroup analysis and treatment thresholds, and again integrate the examples into the discussion, as this is a very important point.</p>	<p>We still believe that considerations about blinding are important to mention also in the section about clinically relevant outcomes. We have now revised the section:</p> <p>Line 316: “Intervention effects on patient relevant and clinically relevant outcomes such as psychological distress, quality of life, patient satisfaction, and pain are impossible to assess accurately by ‘observation’ (<b>Box 2</b>). Such outcomes should be reported and assessed by the patient and not by a clinician and are by nature subjective, fluctuating, and a placebo effect can be significant [27]. Therefore, randomized clinical trials enabling blinding of all parties (participants; investigators; health-care providers; outcome assessors; data managers; statisticians; conclusion drawers) are mandatory to validly assess patient relevant and clinically relevant outcomes [1].”</p> <p>8) We agree with the reviewer and thank for this important comment. We have now revised the section about indication for interventions and we have referred to the examples in the text:</p> <p>Line 342: “Randomized clinical trials are necessary to determine the most optimal indication for an intervention — when to treat or when not to treat. We have illustrated this in the two examples in <b>Box 3</b>. Randomized clinical trials, with low risk of bias, low risk of design errors,</p>
--	--	---



	<p>9) Table 1: This table presents some interesting arguments, but they need to be addressed in greater depth or at least referenced in the discussion. Perhaps to better integrate this table into the paper the authors could add an additional column about observational studies and how each perceived or realized issue applies to observational studies.</p>	<p>and low risk of random errors can via prospectively planned subgroup analyses suggest such indications [1,36]. However, because of concerns of multiplicity and of small sample sizes often involved, subgroup analyses should be viewed only as hypothesis generating exercises [37,38]. If subgroup analyses show effect in only one or more of the subgroups, then new confirmatory randomized clinical trials on these subgroups ought to be conducted [39].”</p> <p>9) We agree with the reviewer. We now refer to Table 1 in the discussion (see below). However, we do not believe that Table 1 should include another column. Table 1 is already very large and we do not believe that another column will add more clarity. We have now revised the section about typical hindrances so the information in Table 1 is better integrated and addressed in the manuscript.</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.,</p>
--	---	---



		<p>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]. Besides the need of informed consent it is generally not necessary to use narrow criteria for selecting trial participants, as this may impair the external validity [46]. We acknowledge all of these difficulties regarding randomized clinical trials. Nevertheless, the establishment of academic industry independent trial units with know-how about evidence-based medicine [47] can lessen and solve some of the many problems conducting randomized clinical trials [48-53]. Furthermore, regional, national, international, and global research collaboration between trial units and clinical sites (e.g., The European Clinical Research Infrastructures (ECRIN), <b>The UK Clinical Research Collaboration (UKCRC)</b> Clinical Trials Units Network [54], and The Nordic Trial Alliance (NTA)[55]) may reduce problems with recruitment of a sufficient number of trial participants etc. [56,57]. Well-conducted multicentre clinical trials also offer better external validity than well-conducted single centre trials. It must be recognized how much health-care costs can be reduced if patient treatment becomes more effective through evidence-based research. It has been calculated that investment in randomized clinical trials usually gives a reasonable or high</p>
--	--	---



	<p>10.) In their discussion the authors note that RCTs are “always needed,” however they should develop this idea, as it can be argued that in certain circumstances observational studies are a better study design.</p>	<p>return on investment [58]. Politicians and decision makers must be taught the key positions of the randomized clinical trial and of systematic reviews of such trials in clinical intervention research.”</p> <p>We have in <b>Table 1</b> listed typical issues and misconceptions that are perceived or realized as obstacles for the conduct of randomized clinical trials and pointed out how the problems may be minimized.”</p> <p>Line 447:  “Observational studies can sufficiently assess associations between certain interventions and outcomes, but the randomized clinical trials are always needed to avoid falsely negating (type I error) or falsely confirming (type II error) the null hypothesis and to assess causality between interventions and outcomes, i.e., randomized clinical trials are needed to sufficiently validate intervention effects. Typical issues hindering the conduct of trials can be overcome (Table 1).”</p> <p>10) We thank the reviewer for this valid comment. We have now in our revised manuscript clarified that observational studies sometimes can be the only possible option:</p> <p>Line 119:  “Large well-conducted observational studies can sometimes provide useful information about rare adverse events and intervention effects [15]. We acknowledge a few historical instances where observational evidence validly</p>
--	---	--



		<p>have demonstrated benefits of new interventions (e.g., insulin for diabetic coma and ether for anaesthesia) [5]. However, we cannot a priory identify such rare instances. It is only in retrospect it may be concluded that interventions have been validly assessed by observational studies [5], and evidence based on observational evidence will in most circumstances be uncertain [16-18]. Observational studies will often either grossly overestimate or underestimate intervention effects and adjustment with statistical analyses (logistic regression or propensity score) only seem to increase the problem [18]. If an intervention is implemented into clinical practice based on observational evidence and seems to work, it can be difficult to justify and to conduct randomized clinical trials assessing the correct balance between benefits and harms. In this situation, we may never know the 'true' balance between benefits and harms. If an intervention does not look rewarding in an observational study we will likely stop further assessment of the intervention and therefore risk 'throwing the baby out with the bath water'. Intervention research during the development of drugs, devices, and other interventions are in essence a prospective process and the correct research design has to be selected prospectively [19]. The correct design ought to be the randomized clinical trial [13]."</p> <p>Line 512:  "Observational studies can be the only possible option regarding assessment of very rare adverse events, very late occurring effects, or of very long-term interventions. Observational</p>
--	--	---



		<p>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><b>Optional/General comments</b></p>	<p>This paper details the authors' argument for the superiority of RCTs to observational studies, as well as a list of the common problems in the conduct of RCTs. While an important discussion, two main thematic issues must be addressed:</p> <p>1.) The superiority of RCTs has been well established, however the authors should detail what is the scope of RCT as a superior design. As always in science, theories are valid within certain limits, and in the present case we would like to capture where are the limits of the theory stating that RCT are superior to observational studies. There are many conditions in which an observational design is superior, for example in the evaluation of rare events. Also, observational studies are superior when an RCT is logistically not feasible, such as a in the evaluation of a very long term outcome or when running an RCT is cost prohibitive.</p>	<p>1) We agree with the reviewer that the superiority of trials may be seen as having limitations. It is a matter of wording and definitions if rarities of adverse events or costs make other designs threaten the superiority of randomised clinical trials. In both instances, we would still advocate that the randomised clinical trial is superior but maybe not feasible due to the required size or the required sum of money. We have now specified these considerations in the revised manuscript</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</p>
---	---	---





		<p>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 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.”</p> <p>2) We thank the reviewer for this important comment. We have included a description of this important advantage regarding the</p>
--	--	---



	<p>2.) The key advantage of RCTs, a point that should be a focal point of this paper, is their ability to establish causation, as opposed to correlation, through the randomization process. The authors need to expand a discussion on how RCTs offer a superior design for specific types of studies.</p>	<p>randomized trial in the revised manuscript</p> <p>Line 447: “Observational studies can sufficiently assess associations between certain interventions and outcomes, but the randomized clinical trials are always needed to avoid falsely negating (type I error) or falsely confirming (type II error) the null hypothesis and to assess causality between interventions and outcomes, i.e., randomized clinical trials are needed to sufficiently validate intervention effects. Typical issues hindering the conduct of trials can be overcome (Table 1).”</p>
--	---	--