

**PART 1:**

Journal Name:	British Journal of Medicine and Medical Research
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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)
Compulsory REVISION comments	<p>1)</p> <p>The authors have presented an excellent case of necessity of randomized clinical trials. However, this may cause more disarray in the field of evidence-based medicine and comparative effectiveness research which continues to evolve based on the opinions of methodologists and requirements of policy-makers. This manuscript will empower methodologists to state that none of the treatments work. In essence, we do not need any medicine.</p>	<p>1) We thank the reviewer for his very positive comment, that we have presented an excellent case of the necessity of randomised clinical trials.</p> <p>We are, however, surprised to learn that our manuscript should cause disarray in the field of evidence-based medicine and comparative effectiveness research. We actually think that the peer reviewer has misinterpreted our manuscript in this regard. Our intentions were the contrary – namely to underscore the necessity always to consider and use randomised clinical trials when evaluating new interventions or reassess old. This could cause disarray outside the field of evidence-based medicine and comparative effectiveness research – not within.</p> <p>We agree that evidence-based medicine and comparative effectiveness research continuous to evolve. However, we fear that much development will not come from the quarters of “opinions of methodologists” and “requirements of policy-makers”. First, innovation should not be opinion based but based on sound scientific principles evading the risks of systematic errors (through domains and designs) and the risks of random errors (through not respecting</p>




		<p>the laws of probability).</p> <p>We disagree with the points made, that “none of the treatments work” and “we do not need any medicine”. We think these points of views are far too nihilistic. On the contrary, we need to know which treatments do provide more benefits than harms. If results from observational studies no longer will be considered enough to recommend use of an intervention, we agree that fewer interventions may be used. However, we also believe - due to ethical and economical reasons - that we should not treat patients with interventions where we do not know the risks of benefits and harms. We have now specified this in the discussion and throughout our improved text of the manuscript:</p> <p>Line 552:</p> <p>“It may be frustrating for clinicians to realize that clinical experience and observational studies do not provide valid knowledge about intervention effects — especially because many interventions in clinical use have not been assessed in randomized clinical trials [68]. We aim to support the development and use of effective health-care interventions to the benefit of patients as well as health-care systems. This can be obtained by much wider use of randomized clinical trials for the proper assessment of benefits and harms. In times of austerity, the need of randomized clinical trials seems increasingly urgent. We must as rational clinicians realize the uncertainty of our knowledge if randomized clinical trials have not been conducted and remember the validity of</p>
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	<p>2) While the authors properly describe the necessity of randomized clinical trials, they have not described what a randomized trial is. There are multiple types of randomized trials, i.e., placebo-control, active-control, placebo-and active-control, dose-response, and various other combinations.</p>	<p>the evidential hierarchy [77]. Systematic reviews of randomized clinical trials is and should be 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>2) We thank the reviewer for these important comments.</p> <p>We have now specified what we mean with 'randomized clinical trial', described different types of trials, and included further considerations about different kinds of healthcare interventions.</p> <p>Please see Table 2 and:</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</p>
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	<p>3)</p> <p>The authors also do not define the role of placebo. It includes pure placebo, impure placebo. Further, in the modern world, methodologists continue to claim all active-control trials are worthless because they construe one of the treatments as placebo, i.e., injection of local anesthetic versus steroids into epidural space or</p> 	<p>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>3) We thank the reviewer for these important considerations. We agree that considerations about different types of placebo as well as different types of control interventions are extremely important. However, we believe that detailed considerations about different types of placebo are a little bit besides the intended topic of our manuscript. Nevertheless, we have now revised the manuscript and included further considerations about choice of control interventions (incl. different types of placebo) and the corresponding methodological strengths and limitations.</p> <p>Please see Table 1 and:</p> <p>Line 224. "Without an assessment of the balance between benefits and harms it is impossible to</p>
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		<p>assess the clinical significance of a preventive, prognostic, diagnostic, or therapeutic intervention. It is important to use the appropriate control group of a randomized clinical trial in order to make valid inferences. If a trial comparing the effects of two active interventions shows no difference in effect it is not on the face of it clear whether the two interventions are equally effective or equally ineffective. The interpretability of results from randomized trials using placebo as control intervention will on the face of it in a similar way be unclear because the placebo effects may be unknown. However, placebo has often very small effects or no effects compared with no intervention [27] and placebo-controlled trials will therefore often demonstrate the effects of the experimental intervention. Randomized clinical trials assessing the effects of experimental interventions versus placebo are therefore in general the optimal method to accurately assess effect sizes (Table 1). If effective treatments exist, then such treatments may either be used as the control intervention or as basis treatment for participants in all of the trial intervention groups, i.e., an experimental intervention may then be assessed as an add-on intervention to one of the intervention groups. Here The Declaration of Helsinki and medical regulatory agencies have been too kind to the product and ignored the patient [28-30].</p> <p>We have in Table 2 presented an overview of the different types of randomized trials and summarized the corresponding methodological strengths and limitations..”</p>
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	<p>4)</p> <p>Further, the authors also need to define what actual placebo is. Just because a placebo solution is injected into an active structure, it is not going to be inactive. There is substantial literature when sodium chloride solution or dextrose is injected into closed spaces, such as epidural space, discs over the nerve roots, facet joints, etc., they produce substantial response, leading to lack of understanding of actual placebo and misinterpretation of the evidence.</p>	<p>4) See the new Table 2 and see response to comment 3 above.</p>
	<p>5)</p> <p>The authors will do a great favor to the medical community even though they will not empower methodologists. If they clarify the role of placebo and necessity to design an appropriate placebo prior to embarking on placebo trials.</p>	<p>5) See the new Table 2 and response to comment 3 above.</p>
	<p>6)</p> <p>Basically, the authors should describe what they mean by randomized trial. It is extremely important that they show the potential, advantages, as well as disadvantages and facts and fallacies of each randomized type of controlled trial prior to embarking on the decision.</p>	<p>6) We thank the reviewer for these important comments.</p> <p>We have now specified what we mean with 'randomized clinical trial', described different types of trials, and included further considerations about different kinds of health-care interventions. We have also described many of the difficulties and limitations conducting randomized clinical trials.</p>



Please see Table 2 and:

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 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].”

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



	<p>7) The authors may want to expand the text further, along with the boxes explaining more practical scenarios rather than examples such as tracheostomy.</p>	<p>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>7) We have in former versions of the manuscript had more examples. We have carefully chosen the examples in the current version of the manuscript and do not believe that more examples will clarify the manuscript further. If the reviewer has concrete examples that are more relevant than the ones we have chosen we will be happy to include them.</p>
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	<p>8)</p> <p>The authors may want to expand the text overall and also describe the differences between evidence-based medicine and comparative effectiveness research. The authors in the discussion section describe about the Patient-Centered Outcomes Research Institute (PCORI). Obviously they are mixing evidence-based medicine with comparative effectiveness research. In comparative effectiveness research, mainly it is active-controlled trials rather than placebo-controlled trials. Methodologists tend to state that active-controlled trials are worthless, since basic treatment has not been proven in a randomized placebo-controlled trial.</p>	<p>8) The reviewer describes that it is only placebo-controlled that belongs under the term evidence-based medicine. We believe that evidence-based medicine is a collective term for the best research evidence. The choice of a placebo comparator or active comparator in a randomized clinical trial must be based on the developmental phase of interventions for a specific disease. Accordingly, evidence-based medicine contains both placebo-controlled trials and comparative effectiveness research. Please also see</p> <p>Centre of Evidence-based Medicine Toronto (http://ktclearinghouse.ca/cebm/intro/whatisebm): "Evidence-based medicine (EBM) is the integration of best research evidence with clinical expertise and patient values."</p> <p>Centre of evidence-based Medicine Oxford (http://www.cebm.net/index.aspx?o=1914): "Evidence-based medicine is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients."</p> <p>We have now included a reference (Sackett et al.) in the revised manuscript so our definition of evidence-based medicine is clear.</p> <p>Line 385: Reference : Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS (1996) Evidence based medicine: what it is and what it isn't. BMJ 312: 71-72.</p> <p>Please also see Table 1.</p>
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Minor REVISION comments		
Optional/General comments		