

The Necessity of Randomized Clinical Trials

Janus Christian Jakobsen^{1,2*} and Christian Gluud¹

¹The Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
²Emergency Department, Holbæk Hospital, Denmark

ABSTRACT

Aims: The hierarchy of evidence-based medicine determines the inferential powers of different clinical research designs. We want to address the difficult question if observational evidence under some circumstances can validate intervention effects.

Methodology: Assessment of previous argumentation aiming at a clear conclusion for future decision-making.

Results: We present five arguments demonstrating the fundamental need of randomized clinical trials to sufficiently validate intervention effects. Furthermore, we argue that hindrance to the conduct of randomized clinical trials can be lessened through education, collaboration, infrastructure, and other measures. Our arguments validate why the randomized clinical trial should and must be the study design evaluating interventions. By choosing the randomized clinical trial as the primary study design, effective preventive, prognostic, diagnostic, and therapeutic interventions will reach more patients earlier.

Conclusion: Clinical experience or observational studies should never be used as the sole basis for assessment of intervention effects — randomized clinical trials are always needed. Therefore, always randomize the first patient as Thomas C Chalmers suggested in 1977. Observational studies should primarily be used for quality control after treatments are included in clinical practice.

Keywords: *evidence-based medicine; randomized clinical trials, observational studies; clinical research; clinical experience; intervention research*

* Corresponding author: Janus Christian Jakobsen Tel.: +45 26186242.
E-mail address: jcj@ctu.dk

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20 1. INTRODUCTION

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22 Observational studies, such as non-randomized cohort studies or patient series, are usually
23 viewed as producing results with less evidential weight compared to the results from
24 randomized clinical trials [1,2]. However, quite often clinicians argue that their clinical
25 experience sufficiently can assess the effects of some interventions [3], and some
26 publications state that observational studies can adequately validate intervention effects [4-
27 8]. Conducting observational studies require much less work and resources than conducting
28 randomized clinical trials, and randomized clinical trials are often perceived as bureaucratic
29 and difficult to conduct. Therefore, it is no surprise that many investigators choose
30 observational studies to try to assess intervention effects.

31

32 We will in the following paragraphs consider if randomized clinical trials always are
33 necessary and the best clinical study design to assess any kind of health-care intervention,
34 including drugs, medical devices, surgery, psychotherapy, in vitro diagnostic medical
35 devices, etc.[9-13]. We are convinced that Thomas C. Chalmers was correct when he stated
36 that we should always randomize the first patient [14]. However, we also acknowledge the
37 difficulties that randomized clinical trials may cause and that they too may show erroneous
38 results. We will, therefore, in the second part of the manuscript provide a list of the typical
39 issues that represents a perceived or real hindrance for the conduct of randomized clinical
40 trials and we will suggest some remedies to reduce these hindrances.

41

42 Randomized clinical trials cannot only assess the effects of many different forms of
43 experimental interventions, but also many different forms of control interventions, e.g., no
44 intervention, placebo, 'impure' placebo, nocebo, or an 'active' control intervention (the latter
45 being a treatment backed by convincing evidence from randomized clinical trials with
46 low risks of systematic errors due to bias; of systematic errors due to design flaws; or of

47 random errors due to play of chance). The latter trials compare the effects of two
48 interventions (so-called 'head-to-head' trials or 'comparative intervention research'). It is
49 clear that the inferences of the results from the different forms of trials differ according to
50 their design. We will in the following paragraphs use the term 'randomized clinical trials' as a
51 collective term for all kinds of trials, as we believe that the fundamental principles are similar
52 regardless of type of experimental intervention and control intervention. The fundamental
53 construct of the randomized clinical trial allows that any intervention using quantitative or
54 qualitative outcomes can be assessed using the same basic principles[15,16].

55

56 **2. METHODS AND RESULTS**

57

58 **2.1 Five arguments demonstrating the fundamental need of randomized clinical trials** 59 **to assess and validate intervention effects**

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61 **2.1.1 Development of interventions is a prospective process**

62

63 It is important to make the correct choice of study design before the initial assessment of a
64 new intervention. The optimal indication, effect size, and balance between harmful and
65 beneficial effects (see the paragraphs below) will remain unknown if randomized clinical
66 trials are not conducted before an intervention is implemented into clinical practice. We fully
67 agree with Thomas C. Chalmers when he in 1977 wrote that we should always randomize
68 the first patient[14]. Accordingly, when an investigator wants to assess if an intervention is
69 effective or not, an observational design should never be used for the initial assessment of
70 the intervention. We will in the paragraphs below consider if there are exemptions to this
71 rule.

72

73 Large well-conducted observational studies can sometimes provide useful information about
74 rare adverse events and intervention effects[17]. We acknowledge a few historical instances
75 where observational evidence validly have demonstrated benefits of new interventions (e.g.,
76 insulin for diabetic coma and ether for anaesthesia) [5]. However, we cannot a priory identify
77 such rare instances. It is only in retrospect it may be concluded that interventions have been
78 validly assessed by observational studies [5], and evidence based on observational
79 evidence will in most circumstances be uncertain [18-20]. Observational studies will often
80 either grossly overestimate or underestimate intervention effects and adjustment with
81 statistical analyses (logistic regression or propensity score) only seem to increase the
82 problem[20].If an intervention is implemented into clinical practicebased on observational
83 evidence and seems to work, it can be difficult to justify and to conduct randomized clinical
84 trials assessing the correct balance between benefits and harms. In this situation, we may
85 never know the 'true' balance between benefits and harms. If an intervention does not look
86 rewarding in an observational study we will likely stop further assessment of the intervention
87 and therefore risk 'throwing the baby out with the bath water'. Intervention research during
88 the development of drugs, devices, and other interventions are in essence a prospective
89 process and the correct research design has to be selected prospectively [21]. The correct
90 design ought to be the randomized clinical trial[14,16].

91

92 **2.1.2 Implementation of scientific results into clinical practice**

93

94 If an intervention offers more benefit than harm compared with previous treatment options, it
95 is an ethical obligation and hence necessary to get that intervention offered to as many
96 patients as possible, as fast as possible. In the discussion about choice of design for
97 assessing new interventions, investigators often claim that it is important to conduct a quick
98 observational study so the potential treatment canspeedily reach the global market if
99 'proved' effective [22]. Many medical devices have, for example, been implemented into

100 clinical practice on the basis of observational evidence alone[23]. However, if only
101 observational evidence backs the intervention it may be difficult to reach clinical consensus
102 about a given intervention effect because clinicians might rightly question the validity of such
103 results[18-20]. It is much more easy to reach clinical consensus based on results from
104 randomized clinical trials preferably assessed in systematic reviews ad modum those
105 conducted according to The Cochrane Collaboration Handbook [1]. Even if an intervention
106 has an almost parachute-like beneficial intervention effect [24], a fast way to the global
107 market might be blocked if the intervention is only assessed in observational studies. The
108 results of properly conducted randomized clinical trials will be more readily accepted by
109 more clinicians than results from observational studies and will therefore probably offer a
110 faster access to a larger market compared to market penetration via an observational
111 design.

112

113 **2.1.3 Balance between beneficial and harmful effects**

114

115 It is theoretically possible to quantify a beneficial intervention effect size via observational
116 evidence if the disease is stable and without any fluctuation in symptoms and if the
117 intervention effects are large enough to be recognized by 'observation'. However, very few
118 diseases show such stability and interventions with large easily observable effects are
119 extremely rare[15]. Most interventions have no beneficial effects or relatively small beneficial
120 effects. It is among the latter we shall find the interventions of tomorrow. Moreover, large
121 'surprising' beneficial effects shown in observational studies may be due to random errors,
122 systematic errors, or confounding. Randomized clinical trials are, therefore, needed to
123 assess when potential beneficial effects outweigh the potential harmful effects.

124 Randomization is able to construct the optimal control group, which, at baseline, becomes
125 fully comparable with the experimental group regarding all known and all unknown
126 prognostic factors—provided that the randomized groups become large enough. Without

127 randomization and without an appropriate control group it is often unclear if a change in
128 symptoms is caused solely by an intervention effect — or if some, or all, of the change is a
129 natural fluctuation of the symptoms (often a combination of ‘regression towards the mean’
130 and the natural fluctuation of the symptoms). Observational studies including some kind of
131 matched control group do not provide valid information about effect sizes, because the
132 participants in the control group will almost never be fully comparable to the participants in
133 the experimental group[20]. It is therefore impossible to quantify and have an overview of the
134 relative effect sizes via observational evidence only (**Box 1**).

135

136

137 **BOX 1**

138

It can be 'observed' that an operation for heartburn can normalize pH in the oesophagus[25], but the surgical procedure also carry some risks[26,27]. Observational evidence cannot assess when the degree of heartburn justifies an operation with possible harmful effects[27]. Furthermore, without randomization it is unclear whether a change in symptoms is caused by the operation or by other factors.

Long-acting beta₂-agonists can improve lung function in asthma patients[28], but after a large number of participants have been assessed evidence has indicated that long-acting beta₂-agonists also cause a small increase in mortality[28]. Such rare harmful effects would be impossible to detect without randomized clinical trials. It would be unclear whether the relatively few deaths were caused by the long-acting beta₂-agonists or by other factors.

139

140

141 Without an assessment of the balance between benefits and harms it is impossible to

142 assess the clinical significance of a preventive, prognostic, diagnostic, or therapeutic

143 intervention. It is important to use the appropriate control group of a randomized clinical trial

144 in order to make valid inferences. If a trial comparing the effects of two active interventions

145 shows no difference in effect it is not on the face of it clear whether the two interventions are

146 equally effective or equally ineffective. The interpretability of results from randomized trials

147 using placebo as control intervention will on the face of it in a similar way be unclear

148 because the effects of a placebo may be unknown. E.g., if trial results show no difference in

149 effect between a placebo intervention and an experimental intervention and the placebo

150 intervention does have significant effects, then the placebo effects can mask effects from the
151 experimental trial intervention. It is always of great importance to consider if a placebo
152 intervention (traditional placebo, nocebo, or 'active' placebo) might have a clinical effect. The
153 optimal 'placebo' is a substance which on the face of it is identical to the experimental
154 intervention but without any 'active' effects. Nevertheless, robust evidence has shown that
155 most placebo interventions have very small effects or no effects at all compared with no
156 intervention [29]. Therefore, placebo-controlled clinical trials will most likely demonstrate the
157 effects of the experimental intervention. Randomized clinical trials assessing the effects of
158 experimental interventions versus placebo are therefore in general the optimal method to
159 accurately assess the effects of an intervention (**Table 1**). If effective treatments exist, then
160 such treatments may either be used as the control intervention or as basis treatment for all
161 participants in all of the trial intervention groups, i.e., an experimental intervention may then
162 be assessed as an add-on intervention versus placebo or another intervention while all
163 groups receive the already known effective treatment. Here The Declaration of Helsinki and
164 medical regulatory agencies have been too kind to the product and ignored the patient [30-
165 32] – and even the 2013 suggested amendments to The Declaration seem to have missed
166 this point [33].

167

168 We have in **Table 2** presented an overview of the different types of randomized clinical trials
169 and summarized the corresponding methodological strengths and limitations.

170

171 Studies have shown that observational studies compared to randomized clinical trials often
172 overestimate benefits and underestimate harms, i.e., produce biased results [18-20]. To
173 accurately and objectively assess the balance between benefits and harms, we need
174 randomized clinical trials with blinded outcome assessment. Blinded randomized clinical
175 trials compared to unblinded randomized clinical trials show significantly less biased results

176 [34,35]. A valid and unbiased assessment of benefits and harms are impossible to achieve in
177 an observational design where blinding usually is impossible.

178

179 **2.1.4 Patient-relevant and clinically relevant outcomes**

180

181 Intervention effects on patient-relevant and clinically relevant outcomes such as
182 psychological distress, quality of life, patient satisfaction, and pain are impossible to assess
183 accurately by 'observation' (**Box 2**). Such outcomes should be reported and assessed by the
184 patient and not by a clinician and are by nature subjective, fluctuating, and a placebo effect
185 can be significant [29]. Therefore, randomized clinical trials enabling blinding of all parties
186 (participants; investigators; health-care providers; outcome assessors; data managers;
187 statisticians; conclusion drawers) are mandatory to validly assess patient relevant and
188 clinically relevant outcomes [1].

189

190

191 **BOX 2**

192

A clinician can observe that laser intervention can reduce redness of a 'port-wine stain' on the skin of a patient[36]; or that chemotherapy seems to prolong survival in incurable cancer patients[37]. However, the most clinically relevant outcomes in these two examples would likely be long-term patient satisfaction after the cosmetic laser treatment in patients with port-wine stains[36] and 'quality of life' and QALY (quality adjusted life years) of the cancer patients[38]. These outcomes are impossible or difficult to assess only by clinical 'observation'.

193

194 **2.1.5 Indications for an intervention**

195

196 Most diseases have varying degrees of severity. When a disease is on the borderline
197 between severe and 'not severe', only randomized clinical trials can determine if we should
198 intervene or not. Randomized clinical trials are necessary to determine the most optimal
199 indication for an intervention — when to treat or when not to treat. We have illustrated this in
200 the two examples in **Box 3**. Randomized clinical trials, with low risk of bias, low risk of design
201 errors, and low risk of random errors can via prospectively planned subgroup analyses
202 suggest such indications [1,39]. However, because of concerns of multiplicity and of the
203 small sample sizes often involved, subgroup analyses should be viewed only as hypothesis
204 generating exercises[40,41]. If subgroup analyses show effect in only one or more of the
205 subgroups, then new confirmatory randomized clinical trials on these subgroups ought to be
206 conducted [42].

207

208 **BOX 3**
209

Tracheostomy can be lifesaving for patients with risk of obstructed airways, but tracheostomy can also cause serious complications such as fatal bleeding and airway stenosis[43]. Without randomized clinical trials it is not apparent how severe the hypoxia should be before performing tracheostomy[43].

It can be observed that defibrillation can convert ventricular fibrillation to normal sinus rhythm in patients with cardiac arrest. However, randomized clinical trials are needed to determine when defibrillation for long-term cardiac arrest will lead to a meaningful life of the patient — and when it will not[44].

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211
212 **2.2 Typical hindrances for the conduct of randomized clinical trials and some**
213 **remedies to reduce these**

214

215 Conducting randomized clinical trials generally require more resources than conducting
216 observational studies. Researchers can be reluctant to conduct randomized clinical trials
217 because they are costly and time consuming. Lack of methodological and statistical know-
218 how can hinder the making of randomized clinical trials; it can be difficult to recruit enough
219 trial participants, etc. Typical misconceptions about the usefulness of results from
220 randomized clinical trials can also hinder that such trials are conducted. It is, e.g., often
221 stated that trial populations are not representative of patients in the clinic [4,45,46]. Strict
222 inclusion and exclusion criteria (e.g., the need of informed consent) are believed to put
223 together trial populations not representative of patients in the clinic. The ethically need of
224 informed consent can theoretically affect trial populations so they are different from the
225 everyday patients, but such fears are often overestimated [47,48]. Besides the need of
226 informed consent it is generally not necessary to use narrow criteria for selecting trial
227 participants, as this may impair the external validity of a trial [49]. We acknowledge all of

228 these difficulties regarding randomized clinical trials. Nevertheless, the establishment of
229 academic industry independent trial units with know-how about evidence-based medicine
230 [50] can lessen and solve some of the many problems conducting randomized clinical trials
231 [51-56]. Furthermore, regional, national, international, and global research collaboration
232 between trial units and clinical sites (e.g., The European Clinical Research Infrastructures
233 (ECRIN), The UK Clinical Research Collaboration (UKCRC) Clinical Trials Units Network
234 [57], and The Nordic Trial Alliance (NTA)[58]) may reduce problems with recruitment of a
235 sufficient number of trial participants, etc.[59,60]. Well-conducted multicentre clinical trials
236 also offer better external validity than well-conducted single centre trials. It must be
237 recognized how much health-care costs can be reduced if patient treatment becomes more
238 effective through evidence-based research. It has been calculated that investment in
239 randomized clinical trials usually gives a reasonable or high return on investment [61].
240 Politicians and decision makers must be taught the key positions of the randomized clinical
241 trial and of systematic reviews of such trials in clinical intervention research.

242

243 We have in **Table 1** listed typical issues and misconceptions that are perceived or realized
244 as obstacles for the conduct of randomized clinical trials and pointed out how the problems
245 may be minimized.

TABLE 1. Some hindrances of randomized clinical trials and possible solutions.

Typical issues perceived or realized as hindrances for the conduct of randomized clinical trials	Potential solutions and counter arguments
Practical issue: It is time consuming to conduct randomized clinical trials.	Potential solutions: Investigators must be taught the most effective way of conducting randomized clinical trials — how to use the resources in the most efficient way. Counselling from competent trialists or trial units is essential.
Practical issue: Difficulties recruiting enough trial participants.	Potential solutions: Realistic sample size estimation must be calculated based upon the primary outcome early on in trial planning. More participants will be recruited in multicentre trials compared to single centre trials and through the use of broad inclusion criteria and appropriately selected exclusion criteria [49,62].
Methodological issue: Lack of methodological know-how and lack of practical experience conducting randomized clinical trials.	Potential solutions: Establishment of academic industry independent trial units and infrastructures of such units with know-how about evidence-based medicine[50] and trial design can lessen and solve some of the many problems conducting randomized clinical trials.
Ethical issue: It can be difficult to ethically justify the conduct of a randomized clinical trial especially if the control group is receiving no intervention or placebo.	Potential solutions: It may be unethical to treat patients with interventions that are not based on evidence. Furthermore, if an evidence-based treatment exists, then all intervention groups should ideally receive this treatment (see text). A new experimental intervention can then be assessed as an add-on intervention in the experimental intervention group versus placebo or another add-on intervention in the control group. All participants will receive the treatment that previous evidence has shown offers more benefits than harms and the trial is ethically justified.
Typical misconception: Trial participants differ from patients in common clinical settings[4,45,46]. Strict inclusion and exclusion criteria are believed to put together trial populations not representative of patients in the clinic questioning the clinical relevance of results from randomized clinical trials[4,45,46].	Counter argument: It is not necessary to use narrow criteria for selecting trial participants[1,48,49]. Using fewer inclusion and exclusion criteria will also make trial populations more similar to patients in the clinic. Moreover, patients that receive similar interventions within and outside randomized clinical trials seem to have similar prognosis[47,48].
Typical misconception: Intervention effects in a trial setting are not representative of intervention effects in the clinic. Trial participants are often subjected to strict thorough treatment protocols and repetitive follow-up assessments of different kinds. It has been postulated that this might specifically benefit	Counter argument: Allocation to an experimental intervention in a trial setting compared to a similar treatment outside a trial setting has been shown to have similar effects[47,48,65]. Moreover, it is not necessary to use strict treatment protocols in a randomized clinical trial[1]. It is possible to randomize participants to, e.g., a non-standardized care versus 'no intervention'.

trial participants (and hence the trial results) compared to patients in the clinic[4,63,64].	
Typical misconception: Interventions cannot be standardized without compromising efficacy. It is believed that randomized trials cannot assess the effects of individualized patient treatment, where clinicians effectively treat each patient according to clinical expertise and experience[22,66].	Counter argument: Standardized interventions based on evidence-based practice are most often superior to non-standardized interventions[67-70]. Furthermore, it is possible in a randomized clinical trial to compare the effects of treating patients according to clinical experience with a standardized intervention or another comparator. Any intervention can be assessed in a randomized clinical trial using a given outcome.
Typical misconception: It is costly to conduct randomized clinical trials.	Counter argument: If you think clinical research is costly, consider clinical practice. It has been calculated that investment in randomized clinical trials usually gives a reasonable or high return on investment[61].Politicians and other decision makers must be taught the key position of the randomized clinical trial regarding knowledge about intervention effects. The more effective the healthcare system becomes, the cheaper it will be.

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249

250 **TABLE 2. Different comparisons in randomized clinical trials and associated methodological strengths and**
251 **limitations.**
252

Different types of control groups					
Experimental intervention versus no intervention		Experimental intervention versus placebo, impure placebo*, 'active' placebo (nocebo)**, or a sham intervention		Experimental intervention versus 'treatment as usual'***	
Strengths	Limitations	Strengths	Limitations	Strengths	Limitations
The beneficial and harmful effects of the experimental intervention can be assessed by the results.	Results of the trial may be biased due to lack of blinding of the participants. It may be ethically wrong to conduct the trial if an effective treatment exists.	Allows blinding of trial participants; investigators; treatment providers; outcome assessors; data managers; statisticians; and conclusion drawers. Allows assessment of experimental intervention effect sizes controlling for non-specific treatment factors****.	The 'effect' of placebo may be unclear in certain conditions. Participants can often because of beneficial effects or adverse effects figure out if they are treated with the active intervention or the control intervention.	The trial results demonstrate what a given average patient gains by an experimental intervention compared with the treatment the patient usually receive.	Treatment as usual most often contains some non-specific treatment elements with unknown effects. Results may be biased as no blinding is involved, unless one uses double placebo ('double dummy').
Co-interventions					
All three types of trials can include different kinds of co-interventions delivered similarly to all intervention groups. If there is no interaction between these co-interventions and the experimental and control interventions, the effects of the co-interventions will even out between the two comparison groups					

253 * A substances with pharmacological effects but not considered to have an effect on the condition being treated (e.g., antibiotics in viral infections or
254 vitamins for prevention of death).
255 ** A placebo preparation that mimics the adverse effects (nocebo) of the experimental intervention.
256 *** An intervention where participants are treated, as they would have been if they had not been included in the trial. Terms like treatment as usual,
257 standard care, or usual care (synonyms) are often collective terms used for different non-specific interventions.
258 **** Trial participants might benefit from, e.g., believing that an intervention is effective or just from being in contact with a treatment provider. Placebo-
259 controlled blinded trials can assess the specific effects of an intervention because the outcome of the control group will ideally show the effects of the non-
260 specific treatment factors.
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3. DISCUSSION

267 We have pointed out the dangers with observational evidence and concurred with others,
268 that the randomized clinical trial is the optimal design to use when new interventions are to
269 be assessed and when questions arise about the advantages of treatments already in use in
270 clinical practice. Our recommendations should not be surprising, as they represent the
271 opinion of drug regulatory agencies all over the globe. We just stress that these
272 recommendations should be expanded to all interventions. We acknowledge that conducting
273 randomized clinical trials is more difficult than conducting observational studies. However,
274 typical issues hindering the conduct of trials can be overcome (Table 1).

275

276 We believe that clinical experience and observational studies cannot and should not validate
277 the effects of interventions. Observational studies can sufficiently assess associations
278 between certain interventions and outcomes, but the randomized clinical trials are always
279 needed to avoid falsely negating (type I error) or falsely confirming (type II error) the null
280 hypothesis and to assess causality between interventions and outcomes, i.e., randomized
281 clinical trials are needed to sufficiently validate intervention effects. Observational evidence
282 should be used primarily to detect very rare adverse events, very late adverse events, or to
283 monitor the quality of medical treatments once they have been introduced in clinical
284 practice[71].

285

286 A report from the Patient-Centered Outcomes Research Institute was recently published for
287 public comment [72]. This report claims that the use of observational studies to make causal
288 inference is potentially much stronger than it has been in the past [72], and similar
289 arguments are often published in highly esteemed journals [3-7,73]. We believe that the
290 fundamental construct of the observational studies limits the reliability of the results from
291 observational studies[18,20]. To assess if an intervention causes more benefit than harm

292 randomized clinical trials are, in practical terms, always needed. Deeks and colleagues have
293 in a comprehensive report compared results from randomized trials and observational
294 studies [20]. They showed that results from observational studies can be seriously
295 misleading and that adjusted results in observational studies may even appear more
296 misleading than unadjusted results [20]. Compared to small randomized clinical trials, small
297 observational studies often showed effects that were far from the 'true' intervention effect
298 [20]. Ioannidis and colleagues also observed that significant discrepancies do occur between
299 the results of randomized clinical trials and observational studies[18]— and that results from
300 observational studies are more often contradicted than results from randomized clinical trials
301 [74]. Observational studies can be the only possible option regarding assessment of very
302 rare adverse events, very late occurring effects, or of very long-term
303 interventions. Observational studies can also have their place when it is difficult to include
304 large enough sample sizes assessing extremely rare diseases or when lack of funds hinders
305 the conduct of randomized clinical trials. Observational studies also have an important role in
306 monitoring the quality of medicine through use of patient registers and databases [71].
307 Observational studies have their place under such circumstances but their inferential power
308 should always be considered threatened by random errors, confounding by indication,
309 unmeasured confounding, and other systematic errors. Therefore, the randomized clinical
310 trial would still in such circumstances be the optimal design regardless of hindrances making
311 them infeasible. It may, as mentioned, be possible to present a few historical examples
312 where intervention effects have been sufficiently validated by observational evidence[5].
313 However, these exceptions do not justify that observational evidence generally should be
314 used prospectively to validate intervention effects. As it has been clearly expressed by
315 Heiberg already in 1897 and reiterated by others both before and since [75-77]— regarding
316 the vast majority of interventions randomized clinical trials are necessary to assess their
317 effects.

318

319 We acknowledge that randomized clinical trials may also get intervention effects wrong.
320 However, the likelihood of this occurring decreases with increasing sample sizes of the trials,
321 number of outcomes (reducing the risks of random errors), as well as with improved quality
322 of the methodology (reducing the risks of systematic errors)[1,34,35,39,78,79]. Moreover,
323 the conduct of systematic reviews assessing all randomized clinical trials on an intervention
324 as conducted by The Cochrane Collaboration reduces these risks [1,39,78,79]. We therefore
325 need to invest more in education in clinical research as well as in infrastructures for clinical
326 research and for systematic reviewing of randomized clinical trials.

327

328 Another group of arguments also exposes the weaknesses of observational studies. For
329 observational studies we do not yet have requirements of making public peer-reviewed
330 protocols before the epidemiologic work is started; we do not yet publish all data on
331 individual participants in observational studies on a repository; we do not yet have practices
332 of systematically reviewing all observational studies on a topic. Regarding randomised
333 clinical trials all of these issues have been solved or are in the making to be solved [1,80].

334

335 It may be frustrating for clinicians to realize that clinical experience and observational studies
336 do not provide valid knowledge about intervention effects — especially because many
337 interventions in clinical use have not been assessed in randomized clinical trials[72].

338 Randomized clinical trials or systematic reviews with low methodological quality (high risks
339 of systematic errors due to bias and design errors) and insufficient sample sizes (high risks
340 of random error) [81-85] should not be used to guide decision makers and clinicians about
341 which intervention to choose. We aim to support the development and use of truly effective
342 health-care interventions to the benefit of patients as well as health-care systems. This can
343 be obtained by much wider use of randomized clinical trials for the proper assessment of
344 benefits and harms. In times of austerity, the need of randomized clinical trials seems
345 increasingly urgent. We must as clinicians realize the uncertainty of our knowledge if

346 randomized clinical trials have not been conducted and remember the validity of the
347 evidence hierarchy [86]. Systematic reviews of randomized clinical trials is and should be
348 considered the highest level of evidence followed by single randomized trials [86]. We should
349 not, necessarily, stop using all interventions not based on results from randomized clinical
350 trials. However, we believe that patients most often should be treated with interventions that
351 have been proved effective in randomized clinical trials. Regarding many conditions it might
352 be best not to intervene unless randomized clinical trials with low risks of systematic errors
353 ('bias'), low risks of design errors ('bias'), and low risks of random error ('play of chance')
354 have shown more benefit than harm [1,39].

355

356 **4. CONCLUSION**

357

358 Clinical experience or observational studies cannot sufficiently assess and validate
359 intervention effects — randomized clinical trials are always needed. We therefore disagree
360 with authors claiming that observational designs can be employed for assessing
361 interventions. Observational evidence should be restricted to assess rare adverse events;
362 late adverse events; and the monitoring of quality in medicine.

363

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368

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370

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372

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377

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379

380 Both authors conceived the study, contributed to the writing of the paper, and are
381 guarantors.

382

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