*Policy paper

The Necessity of Randomized Clinical Trials

Janus Christian Jakobsen [1,2*], Christian Gluud [1]

[1]The Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark
[2]Acute department, Holbæk Hospital, Denmark

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ABSTRACT

Aims: To assess if observational evidence under some circumstances can validate intervention effects.
Methodology and Results: We present five arguments demonstrating the fundamental need of randomized clinical trials to sufficiently validate intervention effects. Furthermore, we argue that issues that can hinder the conduct of randomized clinical trials can be lessened through education, collaboration, and other measures. These arguments validate why the randomized clinical trial should and must be the study design evaluating new 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 cannot sufficiently validate intervention effects — randomized clinical trials are always needed.

Keywords: evidence-based medicine; observational studies; clinical experience; intervention research.

* Corresponding author: Janus Christian Jakobsen Tel.: +45 26186242.
E-mail address: jcj_ctu@icloud.com

1. INTRODUCTION

Observational studies, such as non-randomized cohort studies or patient series, are usually viewed as producing results with less evidential weight compared to the results from randomized clinical trials [1,2]. However, a number of publications state that observational studies in some circumstances can adequately validate intervention effects [3-6]; and clinicians often argue that their clinical experience sufficiently can assess the effects of some interventions [7]. Conducting observational studies require much less work and resources than conducting randomized clinical trials, and randomized clinical trials are perceived as complex and bureaucratic.

We will in the following paragraphs consider if randomized clinical trials always are necessary and the best clinical study design to assess intervention effects. We also offer a list of the typical issues that represents a perceived or real hindrance for the conduct of randomized clinical trials and provide some remedies to reduce these hindrances.

2. METHODS AND RESULTS

2.1 Five arguments demonstrating the fundamental need of randomized clinical trials to validate intervention effects

2.1.1 Development of interventions is a prospective process subheading

It is important to make the correct choice of study design before the initial assessment of a new intervention. The optimal indication, effect size, and balance between harmful and beneficial effects (see the paragraphs below) will remain unknown if randomized clinical trials are not conducted before an intervention is implemented into clinical practice. When a researcher wants to assess if an intervention is effective or not, an observational design should therefore never be used. We fully agree with T.C. Charmers when he in 1977 wrote "Randomize the first patient" [8].

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) [4]. However, we cannot a priory identify such rare instances. It is only in retrospect it may be concluded that interventions would have been validly assessed by observational studies [4], and evidence based on observational evidence will in most circumstances be uncertain [9,10]. Observational studies will often either overestimate or underestimate intervention effects [11], and both circumstances will pose problems after an initial assessment. When an intervention is already implemented clinically and seems to work, it can be difficult to justify and conduct randomized clinical trials assessing the correct balance between benefits and harms. When an intervention does not look rewarding in an observational study we risk 'throwing the baby out with the bath water'. Intervention research and development of drugs, devices, and other interventions are in essence a prospective process and the correct research design has to be selected prospectively [12].

2.1.2 Implementation of scientific results into clinical practice

If an intervention offers more benefit than harm and is superior to previous treatment options, it is 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 if 'proved' effective [13]. However, if only observational evidence backs the intervention it may be difficult to reach clinical consensus about a given

intervention effect because clinicians might rightly question the validity of such results. It is much more easy to reach clinical consensus based on results from randomized clinical trials preferably assessed in systematic reviews ad modum those conducted by The Cochrane Collaboration [1]. Even if an intervention has an almost parachute-like beneficial intervention effect [14], a fast way to the global market might be blocked if the intervention is only assessed in observational studies. Although more complex, the results of randomized clinical trials will be more readily accepted than results from observational studies and will therefore probably offer a faster access to a larger market compared to market implementation via an observational design.

2.1.3 Balance between beneficial and harmful effects

Large well-conducted observational studies can provide useful information about rare adverse events and intervention effects [15], and it is theoretically possible to quantify a beneficial intervention effect size via observational evidence if a disease is stable and without any fluctuation in symptoms. However, very few conditions show such stability and randomized clinical trials are needed to assess when potential beneficial effects outweigh the potential harmful effects. Without randomization and 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 change is a natural fluctuation of the symptoms (often a combination of 'regression towards the mean' and a natural fluctuation of the symptoms). It is impossible to quantify and have an overview of the relative effect sizes via observational evidence only (Box 1). If one is not able to assess the balance between benefits and harms it is impossible to assess the clinical significance of a preventive, prognostic, diagnostic, or therapeutic intervention.

BOX 1

It can be 'observed' that an operation for heartburn can normalize pH in the oesophagus,[16] but the procedure also carry some risks.[17,18] Observational evidence cannot assess when the degree of heartburn justifies an operation with possible harmful effects.[18] Furthermore, without a control group it is unclear whether a change in symptoms is caused by the operation or by other factors.

Long-acting beta$_2$-agonists can improve lung function in asthma patients,[19] but after a large number of participants have been assessed evidence has indicated that long-acting beta$_2$-agonists also cause a small overall increase in mortality.[19] Such rare harmful effects would be impossible to detect without randomized trials. It would be unclear whether the relatively few deaths were caused by the long-acting beta$_2$-agonists or by other factors.

Studies have shown that observational studies compared to randomized trials often overestimate benefits and underestimate harms, i.e., produce biased results [9-11]. 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 on the same interventions show significantly less biased results [20,21]. A valid and unbiased assessment of benefits and harms are impossible to achieve in an observational design where blinding is impossible.

2.1.4 Clinically relevant and patient relevant outcomes

Intervention effects on clinically relevant and patient relevant outcomes such as psychological distress, quality of life, patient satisfaction, and pain are impossible to assess accurately by 'observation' (Box 2). 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 [22]. Therefore, randomized clinical trials enabling blinding of all parties (participants; investigators; health-care providers; outcome assessors; data managers; statisticians; conclusion drawers) are mandatory [1].

BOX 2

It can be 'observed' by a clinician that a laser can reduce redness of the otherwise non disappearing 'port-wine stain' on the skin of a patient;[23] or that chemotherapy seems to prolong survival in incurable cancer patients.[24] 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[23] and 'quality of life' and QUALY (quality adjusted life years) of the cancer patients.[25] These outcomes are impossible or difficult to assess only by clinical 'observation'.

Indications for an intervention

Most diseases have varying degrees of severity. When diseases are on the borderline between severe and 'not severe', only randomized trials can determine if we should intervene or not. Randomized clinical trials are necessary to determine the most optimal indication for an intervention — when to treat or when not to treat **(Box 3)**. Randomized clinical trials, with low risk of bias, low risk of design errors, and low risk of random errors can via prospectively planned subgroup analyses suggest such indications [1,26]. If such 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 [27].

BOX 3

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.[28] Without randomized clinical trials it is, e.g., not apparent how severe the hypoxia should be before performing tracheostomy.[28]

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.[29]

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

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

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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 randomised clinical trials.	**Potential solutions:** Trialists 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 trial units is essential.
Practical issue: Difficulties recruiting enough trial participants.	**Potential solutions:** A 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 rather than single centre trials and through the use of broad inclusion criteria and appropriately selected exclusion criteria trials.[30]
Methodological issue: Lack of methodological know-how and lack of practical experience conducting randomized trials.	**Potential solutions:** Establishment of industry independent trial units and infrastructures of such units with know-how about evidence-based medicine and trial design can lessen and solve some of the many problems conducting randomized trials.
Ethical issue: It can be difficult to ethically justify the conduct of a randomized trial especially if the control group is no intervention	**Potential solutions:** It is unethical to treat patients with interventions that are not evidence-based. Furthermore, if an evidence-based treatment exists then all intervention groups should receive this treatment. A new experimental intervention can then be assessed as an add-on intervention in one of the intervention groups. All participants will receive the treatment that previous evidence has shown offers more benefits than harms and the trial can easily be ethically justified.
Typical misconception: Trial participants differ from patients in common clinical settings.[3,31,32] 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.[3,31,32]	**Counter argument:** It is not necessary to use narrow criteria for selecting trial participants.[33] Using fewer inclusion and exclusion criteria will also make trial populations more similar to patients in the clinic. Moreover, patients that receive similar treatments and interventions within and outside randomized clinical trials seem to have similar prognosis.[34,35]
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 trial participants (and hence the trial results) compared to	**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.[34,35,38] Moreover, it is not necessary to use strict treatment protocols in a randomized trial.[33] It is possible to randomize participants to, e.g., a non-standardized care versus 'no

patients in the clinic.[3,36,37]	intervention'.
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.[13,39]	**Counter argument:** Standardized interventions based on evidence-based practice are most often superior to non-standardized interventions.[40-43] Furthermore, it is possible in a randomized 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 trial using a given outcome.
Typical misconception: It is costly to conduct randomized clinical trials.	**Counter argument:** It has been calculated that investment in randomized clinical trials usually gives a reasonable or high return on investment.[44] 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 becomes, the cheaper it will be.

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. We acknowledge all of these difficulties. Nevertheless, the establishment of industry independent trial units with know-how about evidence-based medicine can lessen and solve some of the many problems conducting randomized trials [45-50]. Furthermore, regional, national, international, and global research collaboration between trial units and clinical sites (e.g., The European Clinical Research Infrastructures (ECRIN), The UK Clinical Research Collaboration (UKCRC) Clinical Trials Units Network [51], and The Nordic Trial Alliance (NTA)[52]) may reduce problems with recruitment of a sufficient number of trial participants and other problems [53,54]. Well-conducted multicentre 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 return on investment [44]. Politicians and decision makers must be taught the key position of the randomized clinical trial in clinical intervention research.

3. DISCUSSION

We believe that clinical experience and observational studies cannot and should not validate intervention effects. The randomized clinical trials are always needed to sufficiently validate intervention effects.

A report from the Patient-Centered Outcomes Research Institute was recently published for public comment [55]. This report claims that the use of observational studies to make causal inference is potentially much stronger than it has been in the past [55], and similar arguments are often published in highly esteemed journals [56]. We believe that the fundamental construct of the observational studies limits the reliability of the results from observational studies. To assess if an intervention causes more benefit than harm randomized trials are, in practical terms, always needed. Deeks and colleagues have in a comprehensive report compared results from randomized trials and observational studies [11]. This report showed that results from observational studies can be seriously misleading and that adjusted results in observational studies may even appear more misleading than unadjusted results [11]. Compared to small randomized trials, small observational studies often showed effects that were far from the true intervention effect [11]. Ioannidis and colleagues have also observed that significant discrepancies do occur between the results of randomized clinical trials and observational studies [9,11] — and that results from observational studies are more often contradicted than results from randomized trials [57]. As mentioned, it may be possible to present a few historical examples where intervention effects have been sufficiently validated by observational evidence. However, this does not justify that observational evidence should be used prospectively to validate intervention effects. Regarding the vast majority of present-day interventions, randomized clinical trials are necessary to assess their effects.

It may be frustrating for clinicians to realize that clinical experience does not provide valid knowledge about intervention effects — especially because many interventions have not been assessed in randomized trials. But as rational clinicians we must consequently realize the uncertainty of our knowledge if randomized trials have not been conducted. This does not necessarily mean we should stop using all interventions not based on results from randomized 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 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 [1,26].

4. CONCLUSION

Clinical experience or observational studies cannot sufficiently validate intervention effects — randomized clinical trials are always needed. We therefore strongly disagree with authors claiming that observational designs can be employed for assessing new interventions.

ACKNOWLEDGEMENTS

We have received no funding.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

AUTHORS' CONTRIBUTIONS

Both authors conceived the study and contributed to the writing of the paper. JCJ is guarantor.

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