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Pragmatic Randomised Controlled Trials for Complex Therapies

Key Words

Randomised controlled trial · Study design · Methodology · Combined modality treatment

Summary

In order to be able to 'predict' the extent or likelihood of success of an intervention, it is essential to know that exposure and effect are causally related. The randomised controlled clinical trial (RCT) is commonly referred to as the golden standard to establish causality. Apart from ethical constraints or rare diseases it is rarely impossible to do an RCT. Sometimes, however, RCTs may not be feasible (at least at first glance) due to e. g. patients' or therapists' reluctance to participate, lack of funding, organisational limitations, or because technical skills to deliver a therapy are not available. A variety of design alternatives have been proposed to overcome these problems, e. g. clinician-preferred treatment, single consent design, double consent randomised design, prerandomisation, cluster randomisation, and response-adaptive designs ('play the winner'). For complex ('combined modality') therapies it seems reasonable to study the effect of the whole treatment package on the patient rather than the value of individual components. Change to open label or optional cross-over allow 'individualized treatment' as well as 'individualized outcome' within the framework of the RCT. For clinicians and researchers it seems wise to put more emphasis on the search for a suitable and appropriate design for their current problem rather than to artificially tailor their study to an awkward standard design (or even abandon the idea to seek an answer to an open question): Much more alternatives exist than one would imagine.

Schlüsselwörter

Randomisierte kontrollierte Studie · Studiendesign · Methodologie · Komplexe Therapien

Zusammenfassung

Pragmatische randomisierte kontrollierte Studien in der Erforschung komplexer Therapiesituationen

Um das Ausmass oder die Wahrscheinlichkeit des Erfolges einer Intervention a priori einschätzen zu können, ist es essentiell zu wissen, ob zwischen Intervention und Effekt eine Kausalbeziehung besteht. Die randomisierte kontrollierte klinische Studie (RCT) wird gemeinhin als methodischer Goldstandard zum Nachweis von Kausalbeziehungen betrachtet. Abgesehen von ethischen Problemen und seltenen Erkrankungen ist ein RCT fast immer möglich. Nicht selten jedoch ist ein RCT nicht realisierbar, z. B. weil Patienten und/oder Therapeuten nicht teilnehmen wollen, weil Mittel oder Einrichtungen oder Know-how fehlen. Eine Palette von Design-Alternativen kann einige dieser Probleme beheben helfen, u. a. «clinician-preferred treatment», «single consent design», «double consent randomised design», «prerandomisation», «cluster randomisation» und «response-adaptive designs» wie «play the winner». Für komplexe Therapien scheint es sinnvoll, den Effekt des Gesamtpakets auf den Patienten zu untersuchen statt auf die Bedeutung einzelner Komponenten zu fokussieren. «Change to open label» oder «optional cross-over» erlauben sogar die Untersuchung «individualisierter Therapien» bzw. «individualisierter Therapieziele» im Rahmen eines RCT. Es scheint für Kliniker wie Wissenschaftler lohnenswert, sich intensiv um die Suche nach einem geeigneten Design für ihr aktuelles Problem zu bemühen, anstatt ihre Studie mit Gewalt auf ein wenig adäquates Design zurechtzuschneidern (oder gar die Forschungsfrage ganz aufzugeben): Es gibt mehr Alternativen, als man sich gemeinhin vorstellt.

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'What is more unwise than to mistake uncertainty for certainty, falsehood for truth?'
Cicero, 'De Senectude XIX'

Introduction

Medicine has many facets and is often referred to as an art and a science. The personality of the 'health care provider' and his/her individual ability to establish an inter-relationship with the 'health care receiver' are doubtlessly important competents of any therapeutic success. When talking about medicine, however, one has to put emphasis on those components in the first place, which are not a function of personality but a function of skills, i. e. only those components that can reliably be taught (and, thus, reproduced), or, in other words, those components that can be expected to be offered by anyone with positive intention and sufficient training. In order to be able to 'predict' the extent or likelihood of success, it is essential to be sure that exposure (intervention) and effect are causally related.
This year we will celebrate the 50th anniversary of the 'official' debut of the randomised controlled trial (RCT), which is said to have been introduced by the British Medical Research Council (MRC) in 1948 into biomedical research. Up to now there is an ongoing debate on whether RCTs are necessary or even useful. Protagonists claim that it is the only valid method to establish causality between an exposure or intervention and an outcome or effect [19] and that other approaches, in comparison, run desperately short [18]. There are advocates of non-randomised trials as well who strongly argue in favour of alternatives to RCTs [2].
What clinicians concerns most is the feasibility of a research design [12] suggested by brave academic methodologists with little imagination of the 'real world'. This is even more an issue when the therapeutic approach is complex in nature and/or control conditions cannot simply be created by leaving the supposedly active ingredient out of a neatly prepared, indistinguishable placebo. Moreover, is the *placebo* controlled trial, is double blinding always appropriate to investigate the clinical usefulness of an intervention?

Blinding

A common misconception of authors of clinical research papers is the role of double blinding. Although often perceived as the maximum of rigorousness, double blinding does neither guarantee validity of results nor is it a reliable predictor of the quality of a clinical trial. Double blinding is just the measure of choice for quantifying the specific effect of an intervention. Its reputation may derive from the fact that quantification of the specific effect is the main goal of most drug trials.
When other hypotheses (in particular overall effectiveness) are to be tested, double blinding may even be inappropriate. In particular, when a therapy has to be applied by a therapist (e. g. psychotherapy, massage, or acupuncture), overall clinical effectiveness (and, in consequence, cost-effectiveness) may not be a function of the specific effect, yet the most important criterion for the availability of that therapy within a health care system.

Randomisation and Controls – Why and When

Clearly, the RCT is not the natural first step in the course of research concerning a given problem, it is usually the final, sometimes the ultimate one. Typically clinical research starts with somebody's curiosity about a personal or a reported observation (case report), deemed unexpected but not irrelevant. Sometimes a satisfactory answer or explanation is available from the literature, more often available evidence is scare and/or unreliable. Then 'hypothesis-generating research' is the logical next step, e. g. single case studies, retrospective studies, surveys of all kinds, open, uncontrolled, and/or non-randomized prospective trials [14].
Qualitative research methods are appropriate to assess, for instance, prevalence, attitudes, demand, time trends or belief systems in order to enhance our knowledge of an area of interest and to provide a proper basis for doing the right research (methodological skills will then help to do the research right).
Besides a sound methodology, hypothesis testing ('establishing causality') requires two fundamental preconditions: proper randomisation and a control intervention ('Randomized Controlled Trial', 'RCT'). Randomisation is a formal requirement technically relatively easy to be realized [8], whereas the latter profits considerably from know-how and medical experience of the investigator. The necessity of a control intervention is obvious, since any comment on an exposure being 'as effective *as*' or 'more effective *than*' demands a second sample for comparison [6, 17]. From a clinical perspective the main focus is on questions whether an intervention works at all (if there is no other treatment available for which efficacy has been shown before) or whether a new intervention is superior to an established one (if efficacy of the latter has been shown before). This implies some 'pragmatism' concerning trial methodology [15].

Methods to Increase the Feasibility of RCTs

Apart from ethical constraints or rare diseases it is rarely impossible to do an RCT. However, often RCTs do not seem feasible (at least at first glance) due to e. g. patients' or therapists' reluctance to participate, lack of funding, organisational limitations, or because technical skills to deliver a therapy are not at hands. Yet many smart solutions have been suggested to overcome some of those problems and increase the feasibility of RCTs.

Clinician-Preferred Treatment
For a situation where clinicians feel uncomfortable with randomizing patients into two different treatment arms, Korn and Baumrind suggested a 'clinician-preferred treatment' [11]. If objective

parameters and/or screening by a panel of clinicians resulted in one of the two treatments being considered more appropriate for a given patient, he/she would deliberately be allocated to the respective arm and followed-up. Informed consent would be sought only from the remainder. These patients would than be randomised and treated by the clinician who prefers the respective treatment.

Patients' Consent

Zelen proposed a 'single consent design' with a 'best standard treatment' as the control intervention. Patients randomised to the control arm would not have to be asked, since they would receive the supposedly optimal therapy anyway. Patients randomised to the interverntion arm would get this treatment if they agreed, otherwise they would get the control treatment [23]. Similarly, in a 'double consent randomized design' patients randomized to treatment A would get this treatment if they agreed, otherwise they would get treatment B or another treatment, whereas patients randomized to treatment B would get this treatment if they agreed, otherwise they would get treatment A or another treatment [16].

Randomisation Alternatives

Another smart approach is prerandomisation, which is essentially a modified Zelen technique. Here patients would be assigned either to the experimental or to the control group. Patients who consent would receive the therapy they were randomized to, patients who refuse would not get the respective therapy [5]. The term prerandomisation refers to the fact that patients are randomized before consent is sought. Patients who consent and who don't are thus subsamples of the respective trial arms.

Several design alternatives aim at minimizing the patients' risk to be assigned to the arm with the supposedly 'inferior' therapy. Capelleri and Trochim proposed a model in which patients below a predefinded threshold of severity would automatically be allocated to the 'inferior' arm, those above a second, higher threshold to the 'superior' arm. Only patients within the two cut-off points would be randomized [4].

It has been shown that patient' refusal rate for informed consent or for consent after randomisation to new treatment is lower the worse the outlook [9].

Response-Adaptive Designs

'Response-adaptive designs' have a similar intention [16]. The idea is that information produced in the ongoing trial may be used to optimize the forthcoming patients' chance to get the better of the two (or more) treatments tested.

The 'randomized play-the-winner' design makes use of an urn for randomisation. Depending on the pre-existing evidence, it can contain equal numbers of balls of two colours or any ratio (e. g. 2 : 1, 3 : 1). When a patient is available for assignment, a ball is drawn at random. It is *replaced*, however, as soon as the outcome becomes clear, with a ball of the same colour if the outcome was considered positive, and with a ball of the other colour if the outcome was negative [21].

In 1969, Zelen proposed the play-the-winner rule in an impressingly elegant form: Only the first patient would have to be randomised, the consecutive patient would receive the same therapy as the previous one if it was successful, and the other treatment modality if it was unsuccessful [22]. This design was, for instance, used in a pioneering trial on extracorporeal membrane oxygenation (ECMO), a surgical procedure for newborns with respiratory failure, where one baby died with conventional therapy (known to be associated with an average survival rate of 20%) and the next 12 all received ECMO, because the first and all consecutive patients survived [1].

It has to be considered, however, that 'adaptive' designs require a dichotomous outcome (e. g. success of failure) with a large likelihood to occur soon after the intervention.

Cluster Randomisation

Sometimes the feasibilty of an RCT can be greatly increased by making the therapist or even a geographic region rather than the patient the unit of randomisation [3]. This form of randomisation is referred to as 'cluster randomisation' and requires a multicentre setting.

Problems Specific to Complex Therapies

'Complex therapies' are typically associated with complex problems, e. g. chronic disease, disorders with unknown or poorly understood aetiology and pathogenesis, and diseases manifesting as a variety of different symptoms at a time (often referred to as 'syndrome'), or the prevalence of several different diseases at a time. Complex therapies may include drugs, physical therapy (electro-, mechano-, thermotherapy, light), psychotherapy, placebo (perception, hope/fear, expectation, confidence), health education, coping, metaphysical and/or other unknown factors.

Combined modality therapy is common, usually established empirically, even if there is some evidence of effectiveness for single components. Multivariate statistical models try to identify relevant and redundant components, yet the validity of the respective model may be uncertain, particularly if the situation is quite different from the one for which the model has been developed. On the other hand, a systematic approach would require a multitude of classic RCTs to quantitatively establish the relative relevance of all components, and therefore possibly an unforeseeably long time to identify better alternatives.

Main Outcome Measure

Many patients with serious health problems require help now. Where firm evidence of the effectiveness of a straightforward intervention is lacking, empirically derived regimens are often the only choice. It seems therefore ethically justified to scrutinize those 'pragmatic alternatives' regardless of their theoretic foundation and/or plausibility. Even 'individualized treatment' is not an obstacle against a proper clinical trial. As the Dutch epidemiologist Paul Knipschild stressed, 'if all patients were really unique we could never learn from their experience of treatment' [20].

Sometimes so little is known about the mode of action of an intervention that it proves difficult to sensibly choose a main clinical ('objectively measurable') outcome parameter. This is typically the case with essentially subjective complaints like migraine or other pain syndromes, or mood disorders.

Perceived Effectiveness

Provided that the patient is relevantly affected, the 'COLA design' may be a promising strategy [10]. Two or more different therapeutic strategies can be tested at the same time. Patients would be randomized into the different treatment arms and would be treated accordingly as long as they remain satisfied with the treatment. Otherwise they would opt to change to open label, i. e. to leave the study. The therapist would then be free to apply any other treatment considered promising. Main outcome parameter is the time patients feel fine with their study intervention, presuming that this is a reliable indicator of perceived effectiveness, and that the treatment modality with the highest perceived effectiveness has the longest 'survival time'.

Recently, we proposed the 'optional cross-over design', where patients (and, when possible, the therapist) can decide to 'try' the other treatment arm if they suspect to be in the arm with the 'inferior' therapy or in the placebo arm [7]. They would then have a second chance to get back to the previous treatment arm. Starting with 50% of the patients in either arm, the balance will increasingly tend to the 'better' arm. A high frequency of changes would, in addition, suggest limited effectiveness of both therapies, a low frequency of chances a clinically relevant effectiveness of both therapies.

Conclusion

The classic RCT methodology is well developed. It may be less than optimal in areas other than the ones it was developed for. Adaptation of existing or development of new methodologies may be necessary in those instances. Since solutions are more likely to have already been developed for simple than for complex problems, the latter are more likely to be the challenge of the future. Methodologies for these problems are presumably more complex and complicated, less straightforward in interpretation, for a narrower range of problems, and also likely to be less easily accessible.

It would habe been beyond the scope of this article to provide a review of all useful and/or relevant alternatives to conventional trial design strategies. Therefore, only some designs were introduced as examples (yet all based on published serious biometrical concepts). These few examples may stimulate clinicians and researchers to look for a design that seems suitable and appropriate for their current problem rather than to artificially tailor their study to an awkward standard design (or even abandon the idea to seek an answer to an open question) [13]. Much more alternatives exist than one would imagine.

As physicians, we are obliged to give our best: Medicine, as an art *and* a science, requires skills *and* knowledge.

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