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Discussion

Is a controlled randomised trial the non-plus-ultra design? A contribution to discussion on comparative, controlled, non-randomised trials

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ABSTRACT

Background: Clinical studies provide formalised experience for evidence-based medicine (EBM). Many people consider a controlled randomised trial (CRT, identical to a randomised controlled trial RCT) to be the non-plus-ultra design. However, CRTs also have limitations. The problem is not randomisation itself but informed consent for randomisation and masking of therapies according to today's legal and ethical standards. We do not want to de-rate CRTs, but we would like to contribute to the discussion on clinical research methodology.
Situation: Informed consent to a CRT and masking of therapies plainly select patients. The excellent internal validity of CRTs can be counterbalanced by poor external validity, because internal and external validity act as antagonists. In a CRT, patients may feel like guinea pigs, this can decrease compliance, cause protocol violations, reduce self-healing properties, suppress unspecific therapeutic effects and possibly even modify specific efficacy.
Discussion: A control group (comparative study) is most important for the degree of evidence achieved by a trial. Study control by detailed protocol and good clinical practice (controlled study) is second in importance and randomisation and masking is third (thus the sequence CRT instead of RCT). Controlled non-randomised trials are just as ambitious and detailed as CRTs.
Recommendation: We recommend clinicians and biometricians to take high quality controlled non-randomised trials into consideration more often. They combine good internal and external validity, better suit daily medical practice, show better patient compliance and fewer protocol violations, deliver estimators unbiased by alienated patients, and perhaps provide a clearer explanation of the achieved success.

1. Introduction

1.1. Approaches to evidence based medicine

Clinical studies formalise medical experience for evidence-based medicine (EBM). Clinical studies range from retrospective evaluations of medical records over cohort studies, case-control studies up to controlled, randomised trials. These types of studies are designed for different types of questions and situations and contribute different degrees of evidence.

Formally, a controlled randomised trial (CRT) is the best design for a specific and precise hypothesis, especially to prove efficacy, in settings where most eligible patients give informed consent, and if the trial can be performed under suitable conditions. However, CRTs may not be appropriate in all cases and other designs may be more pertinent [1,2].

1.2. Advocacy

In court, two pleas are necessary to come to a decision: an advocacy of the prosecutor and one of the lawyer

Abbreviations: CnRT, Controlled non-randomised trial; CRT, Controlled randomised trial; EBM, Evidence-based medicine; GCP, Good clinical practice; RCT, Randomised controlled trial.

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representing the accused person. We give an advocacy for controlled, non-randomised studies and invite everybody to give the opposite advocacy.

1.3. Therapy is a complex procedure

The reasons for therapeutic success (or failure) are often summarised in three categories:

(1st) self-healing properties of the body and the disease having already passed the peak when the patient consulted the doctor,
(2nd) non-specific effects induced by the status as a patient, i.e. causes of the illness are reduced, the patient receives sympathy and compassion for his sickness, is relieved from daily work-load and stress, gains mental distance from personal problems, is encouraged by physicians and nursing staff, has trust in the therapist and is confident in the treatment setting and
(3rd) specific efficacy of physical or pharmaceutical intervention(s).

Therapeutic success with placebo results from self-healing and non-specific effects. The effectiveness of placebo treatment therefore involves many more elements than just the "placebo effect" itself.

1.4. Information affects the outcome

The placebo effect and many other non-specific treatment effects largely depend on the information given to the patient and the trial setting [3–6]. After being informed about a CRT for consent, patients are often concerned [7,8] and good evidence suggests that the information given affects expectations and therapeutic outcomes [9,10].

1.5. Estimation of effect sizes

For the best treatment of a patient the efficacy of the applied medication should be known. However, for both physicians and patients it is highly interesting to know what other effects are important for the outcome. The effect of the applied medication may be less important than other effects, for example. Controlled comparative studies are necessary to determine the most important effects on outcome, but randomisation is not always obligatory.

1.6. Fading of effects

If several CRTs investigate the efficacy of a certain medicinal product in similar patients over years, then the effect size decreases [11]. This fading shows how fragile therapeutic success can be.

2. Comparative and controlled studies

2.1. Meanings of control

In the context of clinical studies "control" has two meanings. One is that the study has a control group. We call this a comparative study. The other meaning is that the study procedures are governed by the study protocol and operating procedures. Some protocols give very few guidelines on the performance of the study (low control) while others regulate many details (high control).

2.2. Degree of control

The greatest degree of control is possible in laboratory experiments. In such experiments, all details are defined and reported. The experiment is then reproducible in other laboratories. In clinical studies, different degrees of control are possible. In highly controlled studies, all measures during treatment are fixed by protocol and the operating procedures stipulated, while in studies with little control many measures are performed as usual in the particular setting. Clinical studies can vary considerably from laboratory-like studies with a high degree of control to observational studies without any control (only observations and documentation are regulated).

2.3. Controlled non-randomised trials (CnRTs)

Often the terms "controlled" and "randomised" are mentioned together in one breath. However, control and randomisation are completely different procedures. Intensive control is possible for both randomised and non-randomised trials.

3. Internal and external validity act as antagonists

Internal validity means that the groups to be compared are not statistically different in any respect except for the treatment investigated. A randomised, highly-controlled study performed without major protocol violations has comparable groups and therefore excellent internal validity. If in such a study the outcome variable shows a significant difference between groups, then it can be caused only by the investigated treatment. If all groups have the same outcome, then an effect of the investigated treatment cannot be compensated for or hidden by other influencing variables. Hence, the results of a study with (perfect) internal validity can be interpreted. The keyword to describe internal validity is "laboratory-like conditions".

3.1. Measures to achieve internal validity

A study protocol regulating all the following aspects in detail and the performance of the study according to these regulations ensures internal validity:

- narrow criteria for patient enrolment,
- stratification of admitted patients for the most important confounders,
- randomisation of patients to treatment groups,
- standardisation of study therapy for each group,
- standardisation of all specific and unspecific measures of treatment, including the nurse's smile (this is mildly exaggerated of course),
- standardisation of measurements and a clear and detailed observation schedule, and
- reliable, objective and valid outcome variable(s).

All these measures – except randomisation – can also apply to CnRTs.

3.2. External validity

Clinical studies should represent daily practice in hospitals, out-patient care and daily life. This is not always the case in laboratory-like studies. If a study is performed with a highly selected sample of patients, treated under specific conditions and with efforts that are not possible for usual patient care, then the study has poor external validity. Its results cannot be transferred to daily practice and applied as standard care. The keyword to describe external validity is "practice-conditions".

3.3. Measures to achieve external validity

All patients, to whom the results of the study will be applied, should have the same chance of being enrolled in the study. Study procedures should reflect daily life in hospitals and out-patient care.

3.4. Internal versus external validity

Measures for internal validity and measures for external validity are often contradictory. It is quite easy to achieve excellent internal validity and it is quite easy to achieve excellent external validity, but it is difficult to achieve internal and external validity in the same study. Internal and external validity act as antagonists, like the sensitivity and specificity of a diagnostic procedure. A diagnostic procedure is only useful if both sensitivity and specificity are acceptable. In an analogous manner, a really useful study needs internal and external validity. Ethgen et al. [12] recommend reporting internal as well as external validity in all publications on controlled trials.

4. Randomisation and informed consent

4.1. Comparability of groups

Groups are comparable if they differ as little as possible and not more than randomly in structure, treatment (except the treatment under investigation) and observations (statistical equality of structure, of treatment and of observations). On evaluation of the study, a statistical test investigates whether the outcomes differ significantly between groups (i.e. if the difference in outcome between groups is larger than can be explained by chance). If, in a study with statistical equality of structure, treatment and observation, the outcome between groups is significantly different, this can only be due to the treatment investigated.

4.2. Effect of randomisation

Randomisation guarantees statistical equality of structure in the treatment groups. It balances for known and unknown covariates. However, this holds only if the study can be performed without dropouts and other major protocol violations. If variables other than the randomised treatments are evaluated, e.g. if the question is whether females and males have the same outcome, then randomisation (between treatment groups) has no effect. Statistical equality of treatment and of observation may be achieved by intensive control and monitoring [13].

4.3. Disadvantages of randomisation

The problem is not randomisation itself, as introduced to clinical trials by Bradford Hill in 1948, but the informed consent to randomisation and masking of therapies according to today's legal and ethical standards. In a randomised study, doctors have to declare that they do not know which of the therapies applied in the study is best for the particular patient. From the patient's point of view this means: "The doctor has no idea which therapy is best for me. He's throwing a dice or coin! He can't be a good doctor. I don't want to be treated by such a doctor." Randomisation and masking may appear disparaging to some – but not all – patients. Therefore, randomisation and masking disturb the mutual trust between these patients and the doctor. This reduces the therapeutic success in all groups and as a consequence the difference in outcome between groups [14]. Confidence in the therapy and adherence to the recommendations of the physician improve the patient's outcome — but are seriously affected by consent in a CRT [15]. In a non-randomised trial the informed consent must not cover randomisation and masking and therefore the patient–doctor-relationship is much less disturbed. Despite sophisticated recruiting strategies, it is becoming more and more difficult to recruit physicians and patients for CRTs. Often, many patients will not agree to randomisation. This can lead to a biased sample of patients giving informed consent and reduces external validity. The level of evidence achieved by a CRT depends on patient selection, as shown in simulations [16].

4.4. Randomisation is not always appropriate

In specific settings, randomisation biases results (in addition to the problem of informed consent already mentioned). This holds particularly if therapies cannot be masked and need the patient's cooperation [17]. Comparative, controlled, non-randomised trials are more suitable than CRTs for situations like the ones described in the following examples:

Physiotherapy. Some people like to be physically active; others do not. Randomisation into groups with and without exercises will lead to the situation where physically active patients will be active regardless of which group they are in, while lazy patients will be lazy in all groups.

Training against fear–tension–pain-syndrome during birth. It is well known that neonates from first-time mothers who have participated in a training-course according to Grantly Dick-Read (1890–1959) have a better Apgar-score for vitality (Virginia Apgar, 1909–1974) than neonates whose mothers have not undergone such training. The reason for this, besides the course itself, might be that the first-time mothers who participate spontaneously in such a course are more health-conscious, smoke less, are happier in their pregnancy, organise their life better around their pregnancy, take more care of themselves during pregnancy etc. than those who don't. A randomised study is practically impossible, simply because pregnant women will not consent to randomisation.

Specific diet for patients with rheumatoid arthritis. In a randomised study to investigate whether a low energy diet reduces rheumatic inflammation there will be many

non-compliant patients, but they will not confess to their non-compliance.

Anthroposophical medicine. Some people are followers of Rudolf Steiner (1861–1925) and his naturopathy. In a study to compare Steiner's anthroposophical medicine with scientific medicine anthroposophic patients randomised to scientific medicine will possibly have poor success because they are convinced of receiving the wrong therapy. Non-anthroposophic patients will reject the anthroposophical procedures because these procedures are strange for them.

5. Performance of controlled, non-randomised trials

5.1. Good clinical practice (GCP)

Today, a well-controlled trial will follow GCP, regardless of whether it is randomised or not [13]. Please keep in mind that CnRTs are just as ambitious, sophisticated and elaborate as CRTs.

5.2. Allocating procedures

The most serious problem of a CnRT is to obtain comparable groups. In a CnRT each patient usually selects his favoured therapy from those offered by the study. Instead of patient selection, matched pairs are also possible if there are few patients and plenty of potential controls. In a comprehensive cohort study, a patient is randomised if he agrees to randomisation — otherwise he can select one of the study groups. Narrow inclusion and exclusion criteria for patient selection increase comparability of groups. Many characteristics of the patients must be recorded to identify the relevant covariates and to enable adjustment for them. Informed consent is necessary as well, but is easier to obtain, because the most dissuasive issues, namely randomisation and masking, are not given.

Protocol violations are formally the same problem in CRTs and in CnRTs. Both types of studies have to be evaluated by intention to treat and according to protocol (patients without major protocol violation). However, it is reasonable to suppose that patients in CnRTs are more compliant and adhere better to the protocol than patients in CRTs, because they are treated per their choice rather than being forced to follow an unwanted procedure.

5.3. Evaluation

CnRTs may have more covariates and disease modifiers than CRTs but even CRTs sometimes require adjustment of covariates [18]. Statistical methods to adjust covariates and disease modifiers are (i) multiple regression analysis, (ii) propensity score-based analysis and (iii) instrumental variable approach. These are efficient and valid methods to evaluate CnRTs. There is comprehensive literature about these methods [19–21]. Internal validity of a CnRT needs adjustment of several covariates to become acceptable. However, it is possible that some covariates are not recorded or some dependencies not recognized. Thus internal validity of a CnRT may not be perfect despite adjustment of covariates.

5.4. Study results

CRTs are designed to answer one single question, while CnRTs often give broader information on therapeutic outcome because they investigate several predictor variables. Regression analysis of a CnRT can (i) find out which predictor variables and which covariates influence the outcome, (ii) give the sequence of importance of the predictor variables and covariates, (iii) deliver an estimate of how the outcome is influenced and how strong the influence is for each predictor variable and each covariate, (iv) provide information about which proportion of the variance of the outcome is explained by the model and (v) indicate how strong the common influence of all the variables not investigated is (error-term). Hence, after evaluation of a CnRT with a regression model we know much more about the outcome than only whether the investigated therapy is efficient. However, a CRT can also be evaluated with a regression analysis and deliver the same information as a CnRT, provided it has the same sample size and co-variables as the corresponding CnRT. But for a CRT it will be more difficult to reach the required sample size than for a CnRT.

5.5. Reporting

The CONSORT statement is a well-known guideline for reporting CRTs. Reeves and Gaus [22] give a guideline for reporting CnRTs.

6. Examples of controlled, non-randomised trials

Serafini et al. [23] reported a CnRT on treatment of rotator cuff calcific tendonitis. “After local anesthesia was induced, two 16-gauge needles were inserted into the calcific deposit. Saline solution was injected through one needle, and the dissolved calcium was extracted through the other needle.” This treatment was applied to 219 patients, 68 patients refused this therapy and were evaluated as controls. After one year, 5 years and 10 years of shoulder joint function was assessed by using Constant scores, and pain was assessed by using a visual analogue scale. We consider this as a good trial to investigate efficacy of the described therapy with a CnRT. Randomisation would have led to a non-selection rate of at least $68 / (219 + 68) = 24\%$ with a serious risk of introducing bias.

Carlsson et al. [24] compared anthroposophical with conventional care on quality of life and life satisfaction for patients with breast cancer. She built 36 matched pairs and followed them over one year. As already mentioned, such an investigation would have been impossible as a CRT because women are either convinced by anthroposophy or not. However, the observed difference in outcome may have been due to the different types of therapies or to the different attitudes of the patients.

Silverman et al. [25] treated obese postmenopausal women with a hypo-caloric diet ($n = 40$) or the same dietary scheme plus walking ($n = 46$) over 6 months. Outcome variables were bone mineral density and inflammation parameters. Again, for this topic, a CnRT might be more appropriate than a CRT.

Gramenzi et al. [26] evaluated the effect of interferon on the clinical course of compensated hepatitis C virus-related cirrhosis. Seventy-two cirrhotic patients treated with interferon were matched to untreated patients of a survey programme on natural history of cirrhosis. The outcome was the incidence of clinical complications (hepatocellular carcinoma, ascites, jaundice, variceal bleeding and encephalopathy) and death. Although a CRT would have been possible, we consider this CnRT to be superior with regard to ethics, external validity, costs, and time until results were available. In view of the objective and the "hard" outcome variables, the internal validity of this CnRT is adequate.

7. Conclusion

Randomisation guarantees statistical equality of structure in the randomised groups if only a few major protocol violations occur. However, informed consent to randomisation and masking of therapies is necessary according to today's legal and ethical standards. The patient's knowledge that his therapy is selected by a random procedure and that he might receive an inferior therapy will influence unspecific therapy components and decrease the patient's compliance, leading to more protocol violations. Some patients will not give informed consent and this may bias the sample of patients investigated.

7.1. Importance of design components

Ranking is difficult and not completely objective in many situations. But we think that the sequence controlling, randomisation, and masking is most logical. Without a control group (controlling) randomisation is not possible. Masking of therapies only makes sense if therapy is not selected but randomised. When a study is designed, the decision to have a group for comparison (controlling) has to be taken first. Then a decision on randomisation can be taken. Finally, a decision on masking is possible. At least the sequence controlling, randomisation, and masking is reasonable.

If a study has no group for comparison, nobody will ask about randomisation. If the therapy group is selected, nobody will ask for masking. Hence, we think that the sequence controlling, randomisation, and masking is also a justifiable ranking. We are convinced that the sequence CRT is more appropriate than the sequence RCT.

7.2. Advantages of CnRTs

Comparing a CnRT with a similar CRT (i) it is easier to find study patients, (ii) external validity can be much better, (iii) compliance of patients will be better, resulting in fewer protocol violations, (iv) fewer unconscious processes will influence the estimation of the investigated effect, (v) results are easier to generalise and to transfer to daily life, and (vi) several components of the achieved outcome are explained.

7.3. Disadvantages of CnRTs

Comparing a CnRT with a similar CRT (i) internal validity may be worse, (ii) sample size should be larger for adjustment of covariates, (iii) more potential covariates have to be recorded, and (iv) patients may select one of the therapy-groups less frequently than others, which decreases power. (Power depends mostly on the number of patients in the smallest group.) Researchers planning a CnRT are well advised to try to compensate for these problems as far as possible.

7.4. Evidence of results

A CRT delivers best evidence for a single specific and narrow question, in settings where most eligible patients give informed consent and results are not directly used for daily practice. However, it can be difficult to apply the result to other patients [27]. A comparative, controlled, non-randomised trial might be more suitable for broader problems and the results may be directly relevant for the daily work of physicians. Even Sacket et al. [28] say: "EBM is not restricted to randomised trials and meta-analyses". Best evidence will be achieved if a CRT and a CnRT investigating the same question deliver similar results. This also holds for comprehensive cohort studies [29,30].

The purpose of this manuscript is not to provide a teaching book with complete listings of the pros and cons of CRTs and CnRTs. This is a plea for dialogue, not a final judgment. In many circumstances the decision for randomisation is easy but in some circumstances this decision is more difficult. This paper should assist in the latter.

8. Key points

- A group for comparison (comparative study) is most important for the validity of results. Strict control of the performance of the study (controlled trial) is of secondary importance. Randomisation has rank three. We therefore prefer the sequence CRT (controlled randomised trial) instead of RCT.
- Randomisation is not the problem, but informed consent for randomisation and masking. However, today's legal and ethical standards require informed consent for such trials.
- Internal and external validity act as antagonists.
- Information on randomisation and masking will alienate some patients. This uncertainty will modify unspecific effects and may even affect the specific efficacy of treatment.
- Patients will be more compliant in a controlled non-randomised trial (CnRT) with fewer protocol violations than in a CRT.
- CnRTs deliver results about several components of the therapeutic success while a CRT is designed to investigate efficacy of only one measure.
- CRTs can be characterised as "laboratory-type" trials while CnRTs are "daily practice-type" trials.

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