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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.

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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.

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