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Pragmatic trials – what are they?

PERSPECTIVES

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Pragmatic clinical trials are based on data from unselected patients recruited from common clinical practice. These trials therefore bridge the gap between evidence-based medicine and clinical practice.

The concept of *pragmatic trials* was proposed by Schwartz and Lellouch in 1967 and helped problematise two key aspects of trials of new therapies: *understanding* and *decision* (1). Traditional explanatory trials seek to enhance our *understanding* by showing whether a treatment is efficacious per se, often under optimal conditions with carefully selected participants and outcome measures. Pragmatic trials, on the other hand, seek to investigate whether a treatment works in the clinical setting, preferably on all types of relevant patients. A broader patient sample can potentially make it more difficult to identify clinically relevant differences between groups, and for this reason the trials often need to include a large number of patients.

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An ideal pragmatic trial includes an unselected group of patients who are candidates for a type of clinical treatment, with end points and follow-up that to the greatest possible extent take place within common clinical practice. The results provide us with real-world data that can inform the *decision* on whether or not to introduce a new treatment on a general basis. Pragmatic trials are of interest to decision-makers because these trials also aim to answer questions on the cost-effectiveness of new treatments that are to be introduced in the healthcare service.

An artificial dichotomy

Pragmatic trials have attracted increasing attention in recent years (2, 3). Enhancing the competence in this area is a key priority in the national action plan for clinical trials (4). The number of hits in PubMed produced by the search term 'pragmatic' has increased exponentially since the 1990 s, and large Scandinavian trials with a pragmatic design have been published in prestigious journals in recent years (5, 6). Explanatory and pragmatic trials are often portrayed as polar opposites, but such a dichotomy is not useful and does not enable us to develop and conduct the best clinical trials. Few or no clinical trials are completely pragmatic, and all will be found somewhere on a continuum from explanatory to pragmatic. Where the trial ends up on this continuum is not essential. The research question and the way in which it can best be answered will decide the choice of methodology. It will serve no purpose to be as pragmatic as possible if a different type of trial will provide a more precise answer to the research question.

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The pragmatic approach

Despite the fact that the boundaries between explanatory and pragmatic trials can be blurred, there are tools available that can quantify the degree of pragmatism in clinical trials. PRECIS (Pragmatic-Explanatory Continuum Indicator Summary) was developed in 2009 both as a scoring system and a visual representation to assess pragmatic features of clinical trials. In 2015, PRECIS-2 (7) was launched, containing nine different domains with a score from 1 (very explanatory, optimal conditions), to 5 (very pragmatic, clinical setting). With such a comprehensive quantification, most trials will have pragmatic features, and very few will be exclusively explanatory or pragmatic. It is important for both clinicians and researchers to understand the potential inherent in pragmatic trials, the features that define the pragmatic trials and how pragmatic elements can be used in their own research.

In trials of new treatments, the most pragmatic approach would be to include all relevant patients who initiate contact with the health service, be it hospitals, outpatient clinics or primary healthcare services. Traditional explanatory trials will typically have a strict selection of patients, which reduces the generalisability to common clinical practice. The Norwegian national quality registries are unique resources for recruitment to pragmatic clinical trials in that they make it possible to include and follow up patients directly in the established registries, without the need for trial-specific follow-up visits (8).

If the objective is to investigate the treatment of patients with acute heart failure in various local hospitals, patients in highly specialised university hospitals cannot be included – and vice versa. In this case, it is desirable to conduct the trial as closely as possible to the common clinical practice. In this context, single-centre trials will have less information value and lower degree of pragmatism, especially if the trial results are to be applied to other clinical settings.

The pragmatic element is reduced if a trial requires specific training, resources or expertise that are not routinely available in the health service. The most pragmatic approach is to use personnel and resources that are already available in the health service. A new treatment can then be compared to a control group that receives the standard treatment. A drug trial can be pragmatic if, for example, the patients are randomised to a drug-based intervention or not, where the decision of dosage and choice of trial drug is left to the doctor responsible for treatment. An example of this is found in the Norwegian BETAMI trial (BEtablocker Treatment After Acute Myocardial Infarction) (9), where patients who have been revascularised after a myocardial infarction are randomised to either beta blocker treatment or not. The doctor responsible includes the patient in the trial and chooses the specific type of beta blocker and the dosage. The patients in the control group do not receive any placebo medication.

The opposite of this type of pragmatic trials will entail, for example, specific drugs in specific dosages and dose intervals, where the treatment effect is compared to a placebo control group.

Interpretation

The interpretation of the trial results will be affected by patient adherence to the prescribed treatment and the degree of pragmatism will be decided by the flexibility permitted with regard to treatment adherence. With a pragmatic design, the doctor and the patient decide on the treatment without the researchers using any resources on monitoring adherence. In explanatory trials, considerable resources are spent on drug accounts to ensure that all trial drugs have been taken in the correct amounts, with the possibility of extra follow-up to increase adherence, and in the worst case exclude patients who have not achieved sufficient trial drug dosages.

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One of the most important features of pragmatic trials is their focus on end points that are meaningful for both patients and decision-makers. Death, morbidity, quality of life and hospitalisation are all end points that are important to the patients, in contrast to, for example, details of changes to the left ventricular ejection fraction or tumour size. Use of end points that require

considerable resources and specialised personnel (such as diagnostic imaging and laboratory analyses) makes the trial less pragmatic. There are two fundamental methods for analysing results in clinical trials: intention-to-treat and per-protocol analysis (10). In pragmatic trials, data are analysed by the intention-to-treat principle, meaning that all patients who were randomly assigned to the treatment are compared with all patients randomly assigned to the control group. This reflects the focus on treatment intention in pragmatic trials, where the randomisation decides to what group participants belong. Explanatory trials will to a greater extent use per-protocol analysis, and only patients with sufficient adherence will be included in the analysis. This permits analysis of biological effects under optimal conditions, but means that the results are less generalisable to all patients. In most cases, an analysis of intention-to-treat will increase the generalisability of the trial results.

Improved IT solutions are required

The national action plan for clinical trials recommends the use of health data in clinical trials, collaboration with industry and new trials with a pragmatic design (4). Identifying patients in national quality registries can provide a comprehensive basis for pragmatic trials, with the ability to recruit, randomise and follow up patients via the registry. Before such trials start, study-specific IT solutions may be needed. These might be both time-consuming and costly, but faster and more cost-effective inclusion would outweigh this over time.

Good infrastructure is needed to avoid duplicate registrations and ensure high data quality in pragmatic trials. Suitable clinical data systems that can both direct the flow of data and permit registration of data from electronic patient records and registries, in which the patients can administer their consent to research and quality projects, can be of great assistance. Effective solutions will also have a transfer value to future trials in other national registries and strengthen the national effort for pragmatic trials.

At Akershus University Hospital, we have established a central data warehouse. With assistance from the analysis department, researchers can retrieve information from the clinical systems for screening potential patients and collect systematically registered patient information. At an early stage of the COVID-19 pandemic, the data warehouse enabled both quick inclusion of patients for clinical trials and rapid clarification of potentially efficacious treatments of COVID-19 (11).

Consequences of pragmatic design

The pragmatic features that strengthen the external validity may do so at the expense of internal validity. The absence of a placebo control may increase the risk of patients withdrawing from trials and thereby affect patient-reported outcome measures. Heterogeneous patient groups with different treatment

responses and a varying degree of adherence may give rise to uncertainty about the results and increase the risk of type II errors, meaning that the analysis fails to identify a real treatment effect.

In the worst-case scenario, these challenges may make researchers reluctant to initiate and conduct trials with a pragmatic design, since there is a risk of negative findings with less scientific prestige. Despite the heightened focus on publication bias in medical research, young researchers who are at an early stage of their career will be even less interested in publishing studies with negative findings (12).

Different legal framework, the same objectives

Clinical practice, research and quality assurance are regulated by different legal frameworks. This presents a legal challenge, for example when research data are collected in pragmatic trials as part of clinical courses of treatment. Even though treatment, research and quality assurance are separate issues from a legal perspective, pragmatic trials highlight how closely treatment, quality registries and research are interlinked when using data already collected in the healthcare service. This affects application procedures for ethical approval and data protection, as well as the requirement for consent to use data from the electronic patient records and national quality registries.

> ***«Increasing the number of clinical trials with pragmatic features will improve the treatment of patients»***

Increasing the number of clinical trials with pragmatic features will improve the treatment of patients. Explanatory randomised trials provide the evidence base for the established treatment of patients, but should primarily inform us about biological effects under ideal conditions. Clinical trials with pragmatic elements reflect common clinical practice, have a higher generalisability and can provide us with real-world data that will help decision-makers, clinicians and patients to choose the best medical treatment.

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