Why is conducting pragmatic clinical trials so important?

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PRACTICAL SCENARIO

Researchers in Finland have designed a randomized clinical trial (RCT) in which adults older than 65 years of age will be randomized (1:1) to receive either high-dose or standard-dose of a quadrivalent influenza vaccine. The main outcome is cardiorespiratory hospitalizations up to 6 months post-vaccination. They propose to use a pragmatic design and implement follow-up for up to 11 months post-vaccination using the Finnish national health registries. Here, we analyze the design of this pragmatic clinical trial (PCT) to discuss its importance in evidence-based decision-making.[1]

PCTS: ADVANTAGES AND DIFFERENCES FROM EXPLANATORY CLINICAL TRIALS

RCTs are the gold standard study design to determine the safety and efficacy of new interventions. However, the "ideal scenario" in which clinical trials are conducted may be far removed from the true needs and the decision-making process of health personnel and the population. RCTs can be classified as explanatory trials (also called phase III of drug development), in which the main objective is to confirm a clinical or physiological hypothesis in a very controlled environment, or as pragmatic trials, as part of the post-marketing phase or the so-called phase IV, with the objective of testing the new intervention in real-world scenarios, thus helping understand the true impact of the introduction of the drug or technology under study.[2]

Choosing a PCT over an explanatory clinical trial (ECT) depends on the stage of development of the intervention and the level of pragmatism desired to increase the generalizability of the results. This decision implies modifications to typical aspects of RCTs to improve the feasibility of the study.

ECTs are usually carried out in research centers with trained professionals, while PCTs can be carried out in multiple types of health care centers (hospitals, clinics, and private practices) and by different health professionals, several of whom without prior research training; in our example, the study takes place in over 40 health care stations.[1] This increases the generalizability of the results.

Participants in PCTs, as those in our example, tend to be a heterogeneous population with minimal criteria for

Table 1. Differences between explanatory clinical trials and pragmatic clinical trials.

	Explanatory clinical trials	Pragmatic clinical trials
General		
Objective	Efficacy and safety of a new intervention.	Effectiveness and long-term safety. Optimization of generalizability of trial results.
Recruitment	Active recruitment is needed.	Less strict. May utilize disease registries.
Participants	Highly selected (many exclusion criteria)	Similar to patients who would receive the intervention if it became standard of care.
Study design		
Delivery of the intervention	Requires frequent study visits for intervention administration and safety evaluations.	Trial procedures and data-collection requirements are minimized. Intervention is administered as in normal practice.
Safety endpoints	Precise collection and description of adverse events.	Long-term safety data in some cases, often less complex and similar to standard of care.
Randomization	Present. Removes significant differences between groups.	Can be more complex. Could be performed on a patient, cluster, or clinician level.
Risk of bias	Minimal.	Higher due to less control over other variables. Can be addressed.
Other		
Ethical considerations	Participants' informed consent, and Institutional Review Board and regulatory entities' approval are required.	Less complicated. Requirements may be waived in some cases
Funding	Usually by industry.	Variable. Co-financed by industry and government.

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their selection and with a wider age range, whereas participants in ECTs are frequently more homogeneous and highly selected or share a common pathology.[2]

Both types of clinical trials use a control group; however, PCTs usually utilize another active arm group, many times a standard-of-care group instead of a placebo group. In our example, the high-dose group is being compared against the standard-dose group. Endpoints in PCTs are usually patient-centered such as deaths, hospitalizations, symptoms, disability, and quality of life, which facilitates data collection with a more flexible surveillance system.[2] The follow-up of participants in ECTs typically requires multiple visits to the study site, while the follow-up in PCTs is less strict; in our example, the researchers periodically collect registry data provided by electronic health records of the public health care system. Other major characteristics of both studies are summarized in Table 1.

Due to concerns about adherence and less stringent follow-up in PCTs, high-quality data collection, robust statistical design, and blinding when defining and adjudicating the study endpoint are key to obtaining reliable results.[2] The Pragmatic Explanatory Continuum Indicator Summary (PRECIS-2)[3] is a useful tool on how to conduct and increase the robustness of PCTs.

KEY POINTS

1. PCTs are increasingly in use in clinical research because they offer evidence about interventions under real-life circumstances.
2. PCTs provide information of paramount importance for new interventions, development processes, and public health decision-making, informing clinical practice.
3. The correct implementation of PCTs with a robust statistical design, high-quality data collection, and follow-up are essential to increase their validity.

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