REVIEW ARTICLE

Explanatory and pragmatic clinical trials

A primer and application to a recent asthma trial

David L. Sackett

Kilgore S. Trout Research & Education Center, Irish Lake, Ontario, Canada

KEY WORDS

effectiveness, efficacy, explanatory trial, management trial, pragmatic trial

ABSTRACT

Most clinical trials assessing the role of a specific intervention attempt to answer an explanatory question: under ideal circumstances of risk and responsiveness, can the expert care of individual with a particular condition reduce their risks of a relevant but restricted set of outcomes? Such explanatory trials (also called efficacy trials) are of direct relevance to expert clinicians and their highly compliant patients. Another question, potentially of broader clinical or health care policy relevance is: Does this treatment improve patient-important outcomes when applied by typical clinicians to typical patients? Answering this latter question is the goal of pragmatic trial, also labeled by some as "management" or "effectiveness" trial. The methodological and organizational differences between explanatory and pragmatic trials include, among others, patients eligibility (restricted to highly responsive and compliant patients in explanatory trials vs. everyone with condition of interest in pragmatic trials), experimental and comparator intervention (blinded and inflexible with strict instructions vs. flexible with cross-over permitted and no blinding), types of practitioners (only those with documented high expertise vs. all who usually provide given mode of care), and outcome measurement (often limited to biologic effects vs. broad overall health effects sometimes based on administrative data bases on mortality and utilization). Those aspects of study design and conduct and their role in determining a place of an intervention in clinical practice are reviewed in this paper.

Prelude In 1960, the prevailing expert opinion was that a patient with persistent blood pressures of 240/125 and no major target organ damage probably did not benefit from – and might be harmed by – antihypertensive drugs (as a medical resident I was cautioned that my "reckless" decision to treat such a patient might cause him to suffer a stroke).[1]

Trial 1 Accordingly, it was ethical and highly relevant in 1963 for a group of trialists led by Edward Fries[2] to ask the PICOT question:

P: Among hospitalized United States veterans with persistent diastolic pressures 115–129 who were free of important target organ damage or secondary hypertension, and who displayed high compliance with appointment-keeping and placebo-taking as outpatients over a 2–4 month period,

I: can "stepped care" with 3 antihypertensive drugs applied under close follow-up by aggressive medical clinicians,

C: compared to identical-appearing placebos given by these same clinicians under identical circumstances,

O: reduce the risk of catastrophic clinical events (such as death, dissecting or ruptured aortic aneurysms, cerebral or retinal hemorrhages, rapidly progressive renal failure, or diastolic pressures >135)

T: over the next 2 years?

Interlude Subsequent investigators have generated powerful randomized controlled trial (RCT) evidence that prescribing and taking antihypertensive drugs can reduce death and target organ damage. Unfortunately, they have also generated powerful observational evidence that lots of clinicians do not detect and treat hypertension, and that lots of patients do not take their medicine.

Correspondence to:
David L. Sackett MD, MSc, FRCP (Ottawa, London, Edinburgh), Kilgore S. Trout Research & Education Center, 154 Pinewood Drive, RR 1, Markdale, Ontario, Canada N0C 1H0, e-mail: sackett@bmts.com
Received: August 9, 2011.
Accepted: August 10, 2011.
Conflict of interest: none declared.
Pol Arch Med Wewn. 2011; 121 (7-8): 259-263

Trial 2 Accordingly, it was ethical and highly relevant in 2007 for a group of trialists led by Janusz Kaczorowski[3] to ask the PICOT question:

P: Among mid-sized Ontario communities,

I: does a highly organized, community-based program that combines offering blood pressure assessments to everybody ≥65 years old with education and referral of all new or uncontrolled hypertensives to a source of continuing care,

C: compared to the absence of this community-based program,

O: raise community rates of antihypertensive treatment and reduce community rates of hospitalization for cardiovascular disease

T: over the next 2 years?

These 2 trials differed in many ways, but the all-embracing reason behind these differences, and the theme for this paper, was formulated by a pair of French trialists, Daniel Schwartz and Joseph Lellouch, in their landmark 1967 paper: "Generally speaking, the treatments to be studied have to be administered in a 'context' made up of the mode of administration, side-effects and their treatment, diet, auxiliary care, associated treatments, etc. The levels of these contextual factors may be fixed in several different ways, of which two may be clearly distinguished – the levels in the two treatment groups may be equalized if we require information on the true effects of the treatments (we aim at acquiring information) [they labeled these explanatory trials, and we often refer to them as efficacy trials], or they may be separately optimized, taking into account the 'cost' of the treatments in the broadest sense*, if what we require is to choose between two modes of therapy (we aim at making a decision) [they called these pragmatic trials, and we often refer to them as effectiveness or management trials]."[4]

Thus, they proposed that the function served by a trial ought to determine its structure. The trial structure in Case 1 served an explanatory function: Under ideal circumstances of risk and responsiveness, can the expert care of individual, severely hypertensive patients reduce their risks of a relevant but restricted set of outcomes? For example, before they could enter the trial, eligible patients were prescribed placebos laced with riboflavin and given a series of clinic appointments. If, on more than one occasion, they missed an appointment, returned more than 10% (or less than 5%!) of their prescribed pills, or their urine failed to display riboflavin fluorescence under ultraviolet light, they lost their eligibility. This "faintness of heart" strategy rejected almost half of them! The "survivors" were randomized to increasing doses of active antihypertensives or corresponding placebos, closely followed, and observed for a restricted set of clinical events and death. No surprise, in retrospect, that this explanatory trial was crash-stopped after catastrophic events occurred (within an average of 16 months) in 14 placebo patients but in no patients on active drugs (indeed, this difference in outcomes was so great that a "worst-case scenario" analysis assigning dire outcomes to lost experimental patients and rosy outcomes to lost placebo patients still generated a risk reduction at $P = 0.001$).

The trial structure in Case 2 served a pragmatic function: Under the usual circumstances of hypertension detection and treatment that prevail in mid-sized Ontario communities, does adding a community-organized offer to identify, educate, follow, and link untreated and uncontrolled hypertensives to family physicians increase antihypertensive care and reduce cardiovascular admissions to hospital? Their "knowledge translation" or "KT" interventions, although extremely comprehensive and highly integrated, were simply offered to everyone in the experimental communities, and patients and health professionals were free to use or ignore them. All the more remarkable, then, that in experimental communities, half-again as many patients were started on antihypertensive drugs ($P = 0.02$), and fewer citizens were hospitalized for heart attack (rate ratio 0.87, 95% confidence interval 0.79 to 0.97; $P = 0.008$) or congestive heart failure (0.90, 0.81 to 0.99; $P = 0.029$). The investigators concluded that extrapolating their program results would result in about 5000 fewer hospital admissions for cardiovascular disease throughout Ontario, 30,000 fewer in the United Kingdom, and 120,000 fewer in the United States, and are proceeding to an economic analysis.

The explanatory/pragmatic formulation of Daniel Schwartz and Joseph Lellouch (which they expanded into a book)[5] is widely shared and applied (sometimes unknowingly and often incorrectly) by trialists and other students of health care, although sometimes renamed. Five years after their landmark paper, Archie Cochrane championed pragmatic trials as the means for determining the "effectiveness" of health care, coupling it with "efficiency" in his landmark book.[6] Others, mere mortals,[7] have also coined synonyms that better suited their clinical teaching and application of these notions, using "efficacy" in the place of "explanatory," and "effectiveness" or "management" in the place of "pragmatic".

For at least 2 reasons, explanatory trials often constitute the initial attempt to determine the usefulness of new treatments. First, by restricting their scope to surrogate or compound outcomes among high-risk, highly responsive individuals, they can generate a quicker, cheaper answer to the question: Can this new treatment work under ideal conditions? Second, if this answer is "no", their investigators and sponsors can cut their losses, not throw more good money and effort after bad, and get on to the next candidate treatment. On the other hand, a "yes" answer from an explanatory trial leaves some ambiguity. Although it might help expert clinicians and their highly compliant patients select individual

* That is, two alternative overall approaches to the management of a health condition might be compared (as in Trial 2 above), and this comparison might include an economic analysis such as cost-effectiveness.

TABLE Trial elements, illustrating the extremes of the explanatory – pragmatic continuum

Element	Explanatory (or efficacy) trial	Pragmatic (or effectiveness or management) trial
the question	Can this Rx work under ideal circumstances?	Does this Rx benefit under usual circumstances?
participant eligibility	Strict: restricted to high-risk, highly-responsive, highly compliant.	Free: everyone with the condition of interest.
experimental intervention	Inflexible, with strict instructions for every element. Both participants and practitioners are usually blind. Cross-overs are prohibited.	Highly flexible, as it would be used in routine health care. Nobody is blind. Cross-overs are permitted.
comparison intervention	Inflexible, with strict instructions (often employs a placebo). Both participants and practitioners are usually blind. Cross-overs are prohibited.	Usual care for this condition in this setting. Nobody is blind. Cross-overs are permitted.
practitioner expertise	Only practitioners and settings with previously documented high expertise.	Full range of practitioners and settings in which a successful intervention would be applied.
participant compliance with interventions	Closely monitored, and may be a prerequisite for study entry. Both prophylactic strategies (to maintain) and "rescue" strategies (to regain) high compliance are used.	Unobtrusive (or no) measurement of compliance. No special strategies to maintain or improve their compliance.
practitioner adherence to protocols	Close monitoring into how well clinicians and centers are adhering to the trial protocol and "manual of procedures," triggering vigorous interventions whenever deficient.	Unobtrusive (or no) measurement of practitioner adherence. No special strategies to maintain or improve their adherence.
follow-up intensity	Frequent, highly intense, with extensive data collection.	Usual intensity for this condition and setting, or restricted to administrative data bases on mortality and utilization.
primary outcome	A restricted set of events, composite outcomes, or surrogate outcomes, often determined by blinded experts and adjudicators.	A broad set of events of importance to participants, determined in the routine course of health care.
primary analysis	Might try to justify excluding non-compliers or non-responders.	Never deviates from "intention-to-treat" analysis of all participants who entered the trial.

treatment options, it does not answer the broader clinical or health care policy question: Does this treatment improve patient-important outcomes when applied by typical clinicians to typical patients? Answering this latter question is the goal of the pragmatic trial.

Pragmatic trials constitute the "proof of the pudding" for promising results from explanatory trials and are (or bloody well ought to be) a major focus of comparative effectiveness research. A "yes" answer to a pragmatic trial – if it tested the new treatment when it is applied by typical health professionals to typical patients for the prevention or relief of outcomes that are important to patients – can provide a powerful evidence-base for its general implementation, especially when accompanied by an economic analysis.

Elsewhere in this issue you will find a trial of leukotriene antagonists as first-line or add-on asthma-controller therapy.[8] The investigators concluded that the 2 regimens were equivalent at 2 months, but not at 2 years. I agree with them up to this point in their paper, but suggest that their subgroup analysis (of just those patients who stayed on their original treatments), their concerns about the absence of a placebo control group, their distress that differences in adherence would hamper "assay sensitivity," their "regrets" that some patients crossed-over to the alternative treatment, and their worry about the resulting "bias toward equivalence" are examples of the inappropriate application of irrelevant explanatory trial ways of thinking to pragmatic trials. Indeed, I suggest that their report, and the accompanying Statistics in Medicine commentary,[9] are examples of the misconceptions that led Daniel Schwartz and Joseph Lellouch to write that landmark paper: "It is the thesis of this paper that most therapeutic trials are inadequately formulated, and this from the earliest stages of their conception. Their inadequacy is basic, in that the trials may be aimed at the solution of one or other of two radically different kinds of problem; the resulting ambiguity affects the definition of the treatments, the assessment of the results, the choice of subjects and the way in which the treatments are compared."

I encourage readers to apply the descriptions in the **TABLE** to the leukotriene trial and decide for themselves whether the authors' post-hoc analyses and misgivings are consistent with their stated objective of determining "the real-world effectiveness" of these asthma treatments. After doing so, they can compare their conclusions with mine.**

** When I do so, their subgroup analysis (of just those patients who stayed on their original treatments) destroys both the validity created by random allocation and their ability to generate a pragmatic answer, their concerns about the absence of a placebo control group are irrelevant in a pragmatic trial, their distress that differences in adherence would hamper "assay sensitivity" (the ability to determine whether a treatment is superior to no treatment) inappropriately invokes an explanatory trial notion where it doesn't apply, their "regrets" that some patients crossed-over to the alternative treatment are, in fact, minor triumphs of their pragmatic design, and their worry about the resulting "bias toward equivalence" is no bias at all, but a valid, important conclusion.

REFERENCES

1 Perera GA. Antihypertensive drug versus symptomatic treatment in primary hypertension: Effect on survival. JAMA. 1960; 173: 11-13.

2 Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension: Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. JAMA. 1967; 202: 1028-1034.

3 Kaczorowski J, Chambers LW, Dolovich L, et al. Improving cardiovascular health at population level: 39 community cluster randomised trial of Cardiovascular Health Awareness Program (CHAP). BMJ. 2011; 342: d442.

4 Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutical trials. J Chron Dis. 1967; 20: 637-648.

5 Schwartz D, Flamant R, Lellouch J. Clinical Trials. London: Academic Press, 1980.

6 Cochrane AL. Effectiveness and efficiency: random reflections on health services. Nuffield Provincial Hospitals Trust, 1972.

7 Sackett DL, Gent M. Controversy in counting and attributing events in clinical trials. N Engl J Med. 1979; 301: 1410-1412

8 Price D, Musgrave SD, Shepstone L, et al. Leukotriene antagonists as first-line or add-on asthma-controller therapy. N Engl J Med. 2011; 364: 1695-1707.

9 Ware JH, Hamel MB. Pragmatic trials – guides to better patient care? N Engl J Med. 2011; 364: 1685-1687.

Poznawcze i pragmatyczne badania kliniczne

Wprowadzenie do zagadnienia na przykładzie niedawnego badania dotyczącego astmy

David L. Sackett

Kilgore S. Trout Research & Education Center, Irish Lake, Ontario, Canada

SŁOWA KLUCZOWE

badanie postępowania, badanie poznawcze, badanie pragmatyczne, efektywność, skuteczność

STRESZCZENIE

Większość badań klinicznych oceniających rolę jakiejś interwencji odpowiada na pytanie objaśniające: czy w warunkach idealnych pod względem ryzyka i odpowiedzi na daną interwencję, opieka eksperta nad osobą w konkretnym stanie klinicznym jest w stanie zmniejszyć ryzyko wystąpienia istotnego, ale ograniczonego zestawu punktów końcowych? Takie badania poznawcze (zwane też badaniami skuteczności [*efficacy*]) dotyczą bezpośrednio lekarzy-ekspertów i pacjentów ściśle przestrzegających zaleceń. Inne pytanie, potencjalnie ważniejsze dla praktyki klinicznej i zdrowia publicznego, brzmi: czy ta metoda leczenia wpływa korzystnie na punkty końcowe istotne dla pacjentów, gdy jest stosowana przez typowych lekarzy u typowych chorych? Odpowiedź na takie pytanie jest celem badań pragmatycznych, określanych też jako badania sposobu postępowania lub efektywności (*effectiveness*). Pod względem metodologicznym i organizacyjnym badania poznawcze i pragmatyczne różnią się m.in. doborem pacjentów (ograniczonym w badaniach poznawczych do chorych bardzo dobrze reagujących i ściśle przestrzegających zaleceń, a w badaniach pragmatycznych – obejmującym wszystkich chorych z danym stanem), sposobem porównywania interwencji badanej i kontrolnej (w pierwszym przypadku z zastosowaniem ślepej próby i rygorystycznym przestrzeganiem ściśle zdefiniowanej procedury, a w drugim – z uwzględnieniem możliwości zmiany metody leczenia, bez ślepej próby), doborem lekarzy (albo tylko eksperci, albo wszyscy, którzy zwykle zajmują się stosowaniem danej metody) oraz oceną efektów (w pierwszym przypadku często ograniczoną do efektów biologicznych, a w drugim – obejmującą wszechstronny opis wpływu na stan zdrowia, czasem w oparciu o administracyjne bazy danych demograficznych i ekonomicznych). W niniejszym artykule omówiono wpływ tych aspektów planowania i prowadzenia badań na określenie miejsca danej interwencji w praktyce klinicznej.

Adres do korespondencji:
David L. Sackett MD, MSc, FRCP (Ottawa, London, Edinburgh), Kilgore S. Trout Research & Education Center, 154 Pinewood Drive, RR 1, Markdale, Ontario, Canada N0C 1H0, e-mail: sackett@bmts.com

Praca wpłynęła: 09.08.2011.
Przyjęta do druku: 10.08.2011.
Nie zgłoszono sprzeczności interesów.
Pol Arch Med Wewn. 2011; 121 (7-8): 259-263
Tłumaczył lek. Łukasz Strzeszyński