Journal of Clinical Epidemiology 103 (2018) 10−21

Journal of Clinical Epidemiology

ORIGINAL ARTICLE

Patients and investigators prefer measures of absolute risk in subgroups for pragmatic randomized trials

Eleanor J. Murray[a,*], Ellen C. Caniglia[a], Sonja A. Swanson[a,b], Sonia Hernández-Díaz[a], Miguel A. Hernán[a,c]

[a]*Harvard T. H. Chan School of Public Health, 677 Huntington Ave, Boston, MA 02115, USA*
[b]*Department of Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands*
[c]*Harvard-MIT Division of Health Sciences and Technology, Boston, MA 02139, USA*

Accepted 15 June 2018; Published online 30 June 2018

Abstract

Objectives: Pragmatic randomized trials are important tools for shared decision-making, but no guidance exists on patients' preferences for types of causal information. We aimed to assess preferences of patients and investigators toward causal effects in pragmatic randomized trials.

Study Design and Setting: We (a) held three focus groups with patients (n = 23) in Boston, MA; (b) surveyed (n = 12) and interviewed (n = 5) investigators with experience conducting pragmatic trials; and (c) conducted a systematic literature review of pragmatic trials (n = 63).

Results: Patients were distrustful of new-to-market medications unless substantially more effective than existing choices, preferred stratified absolute risks, and valued adherence-adjusted analyses when they expected to adhere. Investigators wanted both intention-to-treat and per-protocol effects but felt methods for estimating per-protocol effects were lacking. When estimating per-protocol effects, many pragmatic trials used inappropriate methods to adjust for adherence and loss to follow-up.

Conclusion: We made four recommendations for pragmatic trials to improve patient centeredness: (1) focus on superiority in effectiveness or safety, rather than noninferiority; (2) involve patients in specifying a priori subgroups; (3) report absolute measures of risk; and (4) complement intention-to-treat effect estimates with valid per-protocol effect estimates.

Keywords: Pragmatic trial; Per protocol; Adherence adjustment; Intention to treat; Patient preferences; Health communication; Causal inference

1. Introduction

Patient involvement in making medical decisions, or shared decision-making, has been shown to be important for patient satisfaction, treatment adherence, and health outcomes [1−3], and a large literature exists on methods for improving doctor-patient communication and shared decision-making [3−7]. However, neither preferences of patients and investigators nor current practices regarding choice of causal contrasts have been systematically characterized in pragmatic randomized trials, which are designed to address real-world questions about health-care options.

For example, nonadherence and loss to follow-up in pragmatic trials compromises the interpretability of the usual intention-to-treat effect estimates, which may need to be complemented by other measures of causal effect, such as the per-protocol effect, that is, the effect that would have been observed if patients and clinicians had fully adhered to the study protocol. The preferences of patients and investigators regarding per-protocol effects are largely unknown.

To help fill these knowledge gaps about preference of causal contrasts, we (a) conducted focus groups with patients to determine their preferences; (b) interviewed and surveyed principal investigators of pragmatic trials to determine their preferences and their perceived barriers to estimating and reporting causal contrasts; and (c) conducted a systematic literature review of pragmatic trials published

Funding: This study was supported through a Patient-Centered Outcomes Research Institute (PCORI) award (ME-1503-8119) and grant number T32 AI007433 from the National Institute of Allergy and Infectious Disease. All statements in this report, including its findings and conclusions, are solely those of the authors and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute (PCORI), its Board of Governors or Methodology Committee.

Conflicts of interest: none.

* Corresponding author. Harvard TH Chan School of Public Health, 677 Huntington Ave, Suite 911, Boston, MA 02115, USA.
E-mail address: emurray@mail.harvard.edu (E.J. Murray).

https://doi.org/10.1016/j.jclinepi.2018.06.009
0895-4356/

What is new?

Key findings

- Patients prefer new-to-market medications only when substantially more effective or safer than existing choices.
- Patients prefer absolute risks in subgroups, and, when they expect to adhere, adherence-adjusted results, such as per-protocol effects.
- Investigators prefer both intention-to-treat and per-protocol effects but want better methods for per-protocol effect estimation.
- Pragmatic trials which estimated per-protocol effects used approaches which may result in bias, and no trials used adequate methods to adjust for bias due to loss to follow-up.

What this adds to what was known?

- Previously, no clear guidance was available on the preferred types of causal information for medical decision-making.
- We assess preferences of patients and investigators toward causal effects of interest in pragmatic randomized trials.

What is the implication and what should change now?

- Pragmatic trials should focus on a goal of superiority in effectiveness or safety, rather than noninferiority.
- Pragmatic trials should involve patients and patient advocates in specifying a priori subgroups to ensure relevance for shared decision-making.
- Absolute measures are the most interpretable and should be included in all trial reports.
- Per-protocol effects are of interest but clearer guidance on their estimation is needed, including appropriate adjustment for loss to follow-up.

in major medical journals to describe current practices for conducting and reporting causal effects.

2. Methods

2.1. Patient focus groups

We conducted three focus groups of patients aged 18 years or older with a chronic medical condition requiring regular medication or physician visits, with no restrictions on the type or duration of the condition. Participants were recruited from neurology, psychology, gastroenterology, and renal outpatient clinics at Brigham and Women's Hospital in Boston. Study pamphlets were placed throughout clinics and distributed through the Dana Farber Cancer Center social work group. A member of the study team (E.J.M.) was available to answer questions, assess eligibility, and enroll participants, or patients could enroll via phone or email. Patients were excluded if they could not sit for prolonged periods, could not make medical decisions due to a neurological condition, or were not available at scheduled group times (Fig. 1).

Focus groups comprised six to eight individuals, approximately 90 minutes long, and were conducted in English. Patients were compensated with a gift card. An experienced researcher from the Harvard Derek Bok Center for Teaching and Learning (Dr. Jenny Bergeron) moderated the focus groups. Patients were presented three vignettes, based on real-world trials designed to assess patients' preferences when deciding between medications with (a) nonadherence related to convenience; (b) nonadherence more common among people at higher risk for the outcome (heart attack); or (c) differing side effect risks (Appendix A). Each session was transcribed verbatim by an independent contractor.

2.2. Investigator interviews

We conducted five one-on-one telephone interviews with a convenience sample of principal investigators of one or more pragmatic trials, identified through the authors' professional networks. Potential investigators were contacted by email; those who were unavailable or unwilling were asked to suggest an alternate investigator. All but one investigator, who recommended a colleague, agreed to participate. All investigators had an affiliation with Harvard University and had previously collaborated with our research group. Four were based primarily in the Northeastern United States and one in Europe.

The interviewer (E.J.M.) followed a semi-structured guide (Appendix B) and began by asking for a definition or description of pragmatic trials. Interviewees were led through a series of questions on their research and their most recent pragmatic trial, followed by a discussion of conducting and reporting pragmatic trials. Interviews were transcribed by the interviewer.

2.3. Investigator surveys

We conducted an online survey (Qualtrics, Provo, UT) of principal investigators who had received funding from the Patient-Centered Outcomes Research Institute pragmatic trials mechanism ($n = 24$). Investigators were contacted by email up to three times and could enter a gift card raffle as incentive. The survey was conducted after the focus groups, interviews, and literature review and designed to target themes identified from those. In total, 12