What makes a trial more pragmatic? A conceptual introduction

March 27, 2023
Gardeners' Grove meeting

Dr. Merrick Zwarenstein

Departments of Family Medicine and Epidemiology/Biostatistics
IC/ES, Western University, Ontario, Canada

Schulich MEDICINE & DENTISTRY

Western

Originally published in English as :

Pragmatic and Explanatory attitudes in Therapeutical Trials . Schwartz D, Lellouch Journal of Chronic Diseases, 1967.

Reprinted in facsimile form :

Explanatory and pragmatic attitudes in therapeutical trials Schwartz D, Lellouch J. J Clin Epi. 2009;62(5):499-505 (successor journal to Journal of Chronic Disease,

EXPLANATORY AND PRAGMATIC ATTITUDES IN THERAPEUTICAL TRIALS

DANIEL SCHWARTZ and JOSEPH LELLOUCH

Unité de Recherches Statistiques, Institut National de la Santé et de la Recherche Medicale, 94 Villejuif, France

(*Received* 6 *January* 1967; *in revised form* 24 *March* 1967)

"It is the thesis of this paper that most trials are inadequately formulated. Their inadequacy is basic, in that trials may be aimed at the solution of one or other of two radically different kinds of problem."

Content

Intention/aim/purpose of RCT is dichotomous:
Explanatory: test a hypothesis about a mechanism of action of an intervention
Pragmatic: provide evidence for decision-makers to choose between interventions

Intention (for each estimand) is dichotomous but design is ordinal- more pragmatic vs more explanatory design- 9 domains of **design choices**, each on a spectrum, from pragmatic to explanatory.

Relationship between pragmatic and explanatory design choices, and well known concepts of internal and external validity in RCTs

How to match the design choices for each domain to intention for your RCT, using PRECIS-2

Randomization with allocation concealment ensures Internal Validity

Bothwell LE, Greene JA, Podolsky SH, Jones DS. Assessing the Gold Standard--Lessons from the History of RCTs. N Engl J Med. 2016 Jun 2;374(22):2175-81. doi: 10.1056/NEJMms1604593. PMID: 27248626.

Randomization with allocation concealment guarantees INTERNAL validity of effect estimate (within bounds of chance and only for trial participants, in trial setting, during RCT).

Randomization: Tends to equalize distribution between trial arms of **confounders** (known and unknown) and of of **non-specific causes** (regression to mean) so only difference between arms is the treatment **effect**).

INTERNAL validity vital for all RCTs to be meaningful but INTERNAL validity alone **does not create EXTERNAL** validity/applicability**.**

Both Internal and External Validity needed for decision-making

External validity depends on designing RCT sufficiently similar to a specific situation in which findings are to be applied. No RCT is universally applicable so local decisionmakers decide.

Decisionmakers prefer pragmatic design choices because they **need RCT** findings to be directly applicable to their own situation to be useful- to their own providers, patients and settings.

Trialmakers with pragmatic intention should design RCT to minimize traditional distortions that narrow applicability to external settings- e.g., arbitrary age limits, excluding common multimorbidities, cointerventions, monitoring

Bothwell LE, Greene JA, Podolsky SH, Jones DS. Assessing the Gold Standard--Lessons from the History of RCTs. N Engl J Med. 2016 Jun 2;374(22):2175-81. doi: 10.1056/NEJMms1604593. PMID: 27248626.

Traditional RCT design choices undermine external validity

Selected patients, providers, site

- Patients more severe, no comorbidity, narrow age range, good adherers
- Trial sites or clinicians with more experience, better outcomes

Distorted delivery of care

Obscure outcomes

Confusing comparators

Traditional RCT design choices undermine external validity

Peculiar patients, clinicians, sites

Modified delivery of care

- Usual care fixed by rigid protocols for investigation or treatments
- RCT adds co-interventions, extra visits, atypical setting
- RCT undertakes Intensive, intrusive data collection with increased visits

Obscure outcomes

Confusing comparators

Traditional RCT design choices undermine external validity

Peculiar patients, clinicians, sites

Distorted delivery of care

Lab-style outcomes

- Outcomes short term
- Not patient-centred

Confusing comparators

Traditional RCT design choices undermine external validity

Selected patients, clinicians, sites

Distorted care processes

Distracting outcomes

Obscure comparators

Compare to low dose, outmoded drug or placebo

Can we improve external validity while maintaining internal validity?

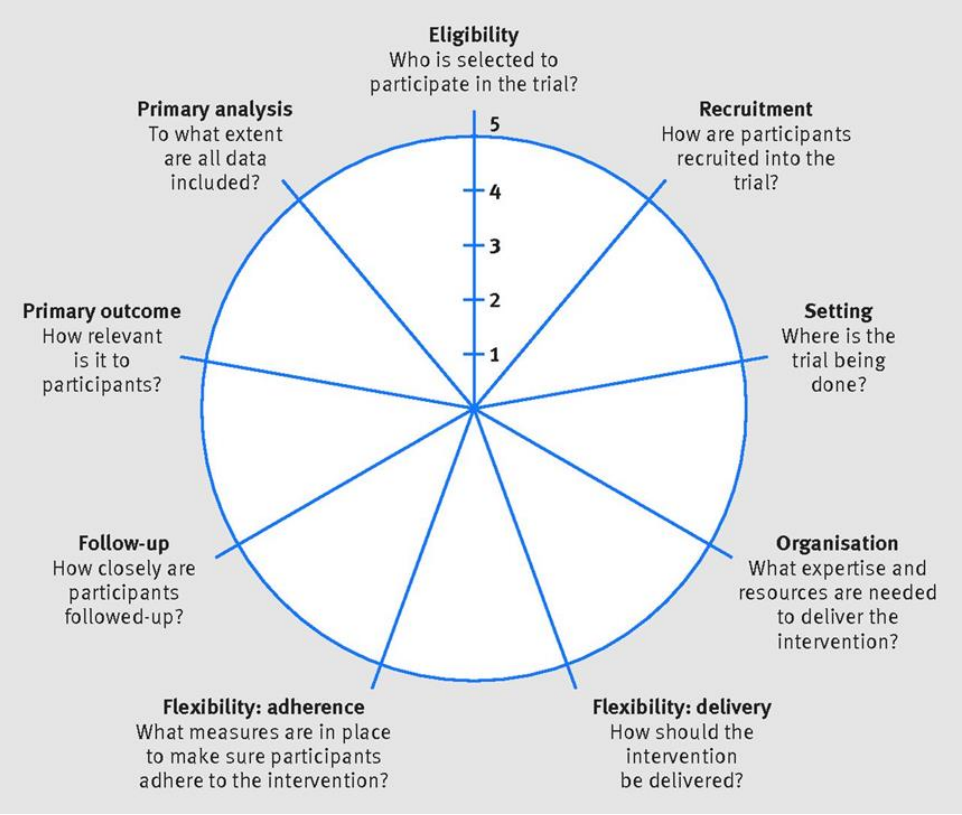
Internal validity depends on randomization allocation concealment and no loss to follow up.

External validity depends on similarity of RCT to participants, care, setting in which finding will be applied.

Determinants of Internal validity ARE independent of external validity determinants

Efforts to increase usefulness for decisionmakers, increase external validity/ applicability/ pragmatism of RCT have no impact on internal validity- **NO TRADEOFF.**

PRECIS-2 wheel



thebmj | *BMJ* 2015;350:h2147 | doi: 10.1136/bmj.h2147

Loudon K. Treweek S, Sullivan P, Donnan P, Thorpe KE, Zwarenstein M.

The PRECIS-2 tool: Designing trials that are fit for purpose. *BMJ* 2015;350:h2147.

Download tool kit for designing your own pRCT, or critical appraisal of existing RCT from:

PRECIS-2 Website: www.PRECIS-2.org

Explanatory Versus Pragmatic Clinical Trials

Explanatory

Pragmatic

Originally published in English as :

Pragmatic and Explanatory attitudes in Therapeutical Trials . Schwartz D, Lellouch Journal of Chronic Diseases, 1967.

Reprinted in facsimile form :

Explanatory and pragmatic attitudes in therapeutical trials Schwartz D, Lellouch J. J Clin Epi. 2009;62(5):499-505 (successor journal to Journal of Chronic Disease,

EXPLANATORY AND PRAGMATIC ATTITUDES IN THERAPEUTICAL TRIALS

DANIEL SCHWARTZ and JOSEPH LELLOUCH

Unité de Recherches Statistiques, Institut National de la Santé et de la Recherche Medicale, 94 Villejuif, France

(*Received* 6 *January* 1967; *in revised form* 24 *March* 1967)

"Most trials done hitherto have adopted the explanatory approach without question; the pragmatic approach would often have been more justifiable".