Practical experience in pragmatic trials

Gardener's Grove 2023
Cultivating Large Pragmatic Trials to Improve Hemodialysis Care

Sandra Eldridge

Honorary Professor, Queen Mary University of London

Definition of pragmatic trials

Schwartz and Lellouch (J. Chron. Dis.1967;20:637-48)

Pragmatic trials = to help decisionmakers choose between care options	Explanatory trials = to test causal research hypotheses, understand mechanisms

But really a spectrum not a dichotomy, a single trial could have both pragmatic and explanatory aims

What will happen if the intervention is implemented outside a trial setting?

PRECIS-2 tool

(PRagmatic Explanatory Continuum Indicator Summary)

9 domains:

Each can be highly pragmatic,
highly explanatory, or in between

Pragmatic	Explanatory
Representative participants	Highly selected participants
Recruited in usual care, many centres	Recruited in another way, few centres
Setting where results apply	Different setting
Intervention “slotted” into usual care	Intervention requires additional resources
Flexibility in delivery	Very standardised delivery
Flexibility in adherence	Highly controlled adherence
Follow-up exactly as would be in usual care	More extensive follow up
Primary outcome relevant to participants, decision makers	Primary outcome not necessarily relevant to participants
Primary analysis intention to treat	Primary analysis per protocol

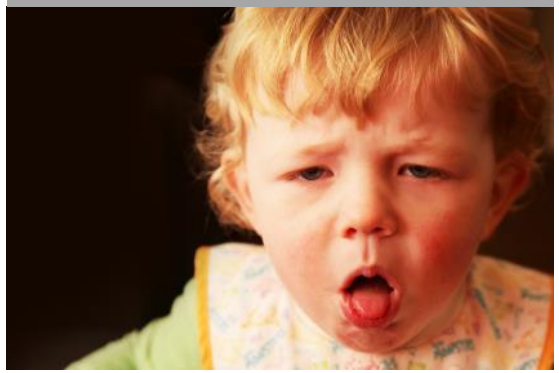
Examples – good and bad (sometimes anonymous!), mostly from Pragmatic Clinical Trials Unit

To introduce pragmatic trials:

1. Trial on drug translational pathway
2. Implementation trial (behavioural intervention)

WAIT – Montelukast for pre-school wheeze

Population



Intervention

Outcome

Unscheduled medical attendances for wheezing

Control

Placebo

STOP – Smoking cessation through pharmacies

Population

Intervention

Training and support for pharmacists

Outcome (customers)

Control

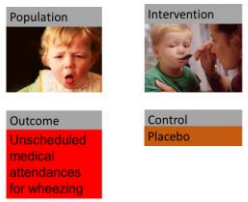
No training and support

Insights based on practical experience

Structure: Where? Who? What? How?

Where? (*Recruited in usual care, many centres*)

WAIT – Montelukast for pre-school wheeze



Around 2010

"Usual care"= general practices in UK
To get numbers, needed to also recruit in hospitals

Another trial, around 7 years later

"Usual care"= secondary care in UK
Press coverage of slightly related treatment
Changed environment for research in hospitals

Under-recruitment

Registry-based trials

"Barriers to participation were time and travel requirements associated with registry participation, data safety concerns, risks, side effects, and concerns that registry participation would impact current treatment."
Murphy, Sept 2021,BMC Trials

Who? (those working on the trial, institutions, regulatory bodies etc.)

Make sure your whole team knows about who does what, how long it takes and the pitfalls of the design that you are using

Institutions, regulators?

What? (the intervention, technology, *Primary outcome relevant to participants, decision makers*)

STOP – Smoking cessation through pharmacies

Evaluation of community-level interventions to increase early initiation of antenatal care in pregnancy: protocol for the Community REACH study, a cluster randomised controlled trial with integrated process and economic evaluations

Pilot indicated we needed to train counter staff as well as pharmacists, literature may also be useful in intervention development

Signal not strong enough in locations where data collected to use ipads for data collection…

RESEARCH ARTICLE 06/14/2016

Novel Three-Day, Community-Based, Nonpharmacological Group Intervention for Chronic Musculoskeletal Pain (COPERS)

In a randomized controlled trial, Stephanie Taylor and colleagues investigate the effectiveness of a group intervention for chronic musculoskeletal pain. Read the Author Summary.

Image credit: gyro2, Flickr

"COPERS intervention …….not effective for reducing pain-related disability over 12 mo (primary outcome)…… found sustained benefits on depression and social integration at 6 and 12 mo…."

How? (*Flexibility in adherence*, avoiding bias)

Adherence

I've just become aware that the adherence to the intervention in this trial is really bad, and

" the trial accomplished many of its demonstration project objectives…….uptake of the intervention was insufficient to determine whether longer sessions improve outcomes. Embedding trials into hemodialysis clinical care will require more effective strategies for engaging clinical personnel and patients."*Dember 2019 J Am Soc Nephrol*

don't have to make any changes to improve adherence?

That's right. However, you should still make sure you have some way of recording adherence so that you can interpret your results correctly.

Who knows what? – reducing bias in pragmatic trials

- Bias may occur when certain people have certain information ….
- In explanatory drug trials, placebo control ("blinding") prevents **a lot of individuals involved** from knowing who is in intervention group and who is in control group
- In pragmatic trials blinding **using placebo** often not possible, *and* not necessarily helpful
- BUT blinding certain people (who could potentially cause bias) to certain things may be useful and can usually be done
- Blind:
  - Chief investigators, trialists, those delivering the intervention from interim results by trial arm
  - Those involved in developing the analysis plan from any results (including anecdotal) by trial arm
  - Outcome assessors from knowing which participant is in which trial arm

How? (*Flexibility in adherence*, avoiding bias)

Bias in cluster randomised trial (conversation via management group teleconference)

Specific bias in specific design

Site recruiter via phone: *……so, I'm telling the participants which group they will be in…..*

Statistician in room: *Sorry, could you just repeat what you said? You're telling the participants which intervention they will receive when you recruit them?*

- Site recruiter via phone: *Yes that's right.*

Statistician in room: *Oh dear, I'm afraid that could potentially cause bias. Can we have another conversation about this and could we review recruiter training?*

Take home messages

Prepare as much as you can:

1. Context of recruitment important and environment may change
2. Think carefully about intervention, technology, outcomes, etc. and pilot if necessary

Be militant about communication!:

3. Team understanding is vital
4. Communication within organisational, institutional structures may also be important

Be aware of (and work for change in) wider environment:

6. Need more understanding between regulators and scientists
7. Need to be able to do research in clinical settings

Thank you for listening