Barts and The London
School of Medicine and Dentistry

Pride and Pragmatism: Celebrating 50 years of Pragmatic Trials

Some current issues in pragmatic trials: bias, outcomes and regulation

Sandra Eldridge

Pragmatic Clinical Trials Unit
Centre for Primary Care and Public Health
Blizard Institute

Queen Mary
University of London

PCTU

Outline

What and when?

Some current issues

Bias, outcomes, regulation

What's in a title?

….the story charts the emotional development of the protagonist… who learns the error of making hasty judgments and **comes to appreciate the difference between the superficial and the essential**….. (Wikipedia, about Pride and Prejudice, written by Jane Austen in 1813)

…. this arbitrary and recent division has been **transformed by pride and prejudice into a national distinction, universally established**….
(Gibbons, The History of the Rise and Fall of the Roman Empire, 1781)

PCTU

What is a pragmatic trial?

Definitions

- Schwartz and Lellouch (J. Chron. Dis.1967;20:637-48)
  - Pragmatic trials = to help choose between care options
  - Explanatory trials = to test causal research hypotheses

- Roland and Torgerson (*BMJ* 1998;316:285)
  - Pragmatic trials measure ***effectiveness***—the benefit the treatment produces in routine clinical practice
  - Explanatory trials generally measure ***efficacy***—the benefit a treatment produces under ideal conditions

PCTU

EXPLANATORY PRAGMATIC

How pragmatic/how explanatory?

RESEARCH METHODS & REPORTING

The PRECIS-2 tool: designing trials that are fit for purpose

Kirsty Loudon,[1] Shaun Treweek,[1] Frank Sullivan,[2] Peter Donnan,[3] Kevin E Thorpe,[4] Merrick Zwarenstein[5]

[1]Health Services Research Unit, University of Aberdeen,
[2]North York General Hospital, Toronto, ON M2K 1E1, Canada
[3]Division of Population Health Sciences, University of Dundee,

PRECIS is a tool to help trialists make design decisions consistent with the intended purpose of their trial. This paper gives guidance on how to use an

Key to this reward is that the trial can indeed support end user decisions in the ways intended by the trial design team. That this is not always, or even mostly, the case was highlighted nearly 50 years ago, by Schwartz and Lellouch in their paper on pragmatic and explana-

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	Primary outcome not relevant to participants
Primary analysis intention to treat	Primary analysis per protocol

PCTU

When do pragmatic trials arise?

PCTU

Drug trials

Translational pathway

BASIC SCIENCE

EXPLANATORY PRAGMATIC

“Ideal” conditions

In routine practice

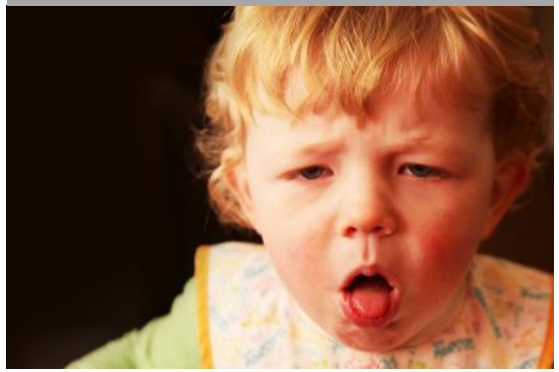
Can this treatment work?

Does this treatment work?

WAIT – Montelukast for pre-school wheeze

PCTU

Population



Intervention

Outcome

Unscheduled medical attendances for wheezing

Control

Placebo

STOP – Smoking cessation through pharmacies

PCTU

Population

Intervention

Training and support for pharmacists

Outcome (customers)

Control

No training and support

NESS - treating negative symptoms of schizophrenia

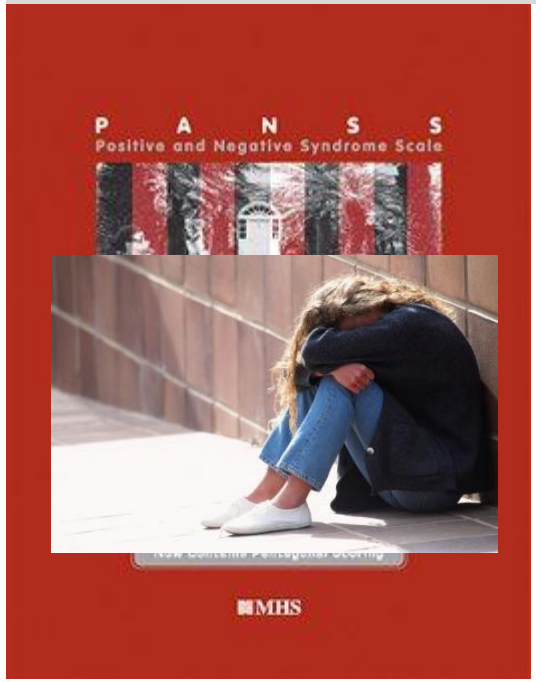
PCTU

Intervention

Population

People with schizophrenia

Outcome



Control (placebo)

When?

Translational research

helps to make findings from basic science useful for practical applications that enhance human health and well-being

Implementation research

is the scientific study of methods to promote the uptake of research findings

No other possibility

hypotheses not testable any other way

PCTU

Current *selected* issues

Outcomes

Regulation

Bias

Data collection

How much data?

Primary outcome??

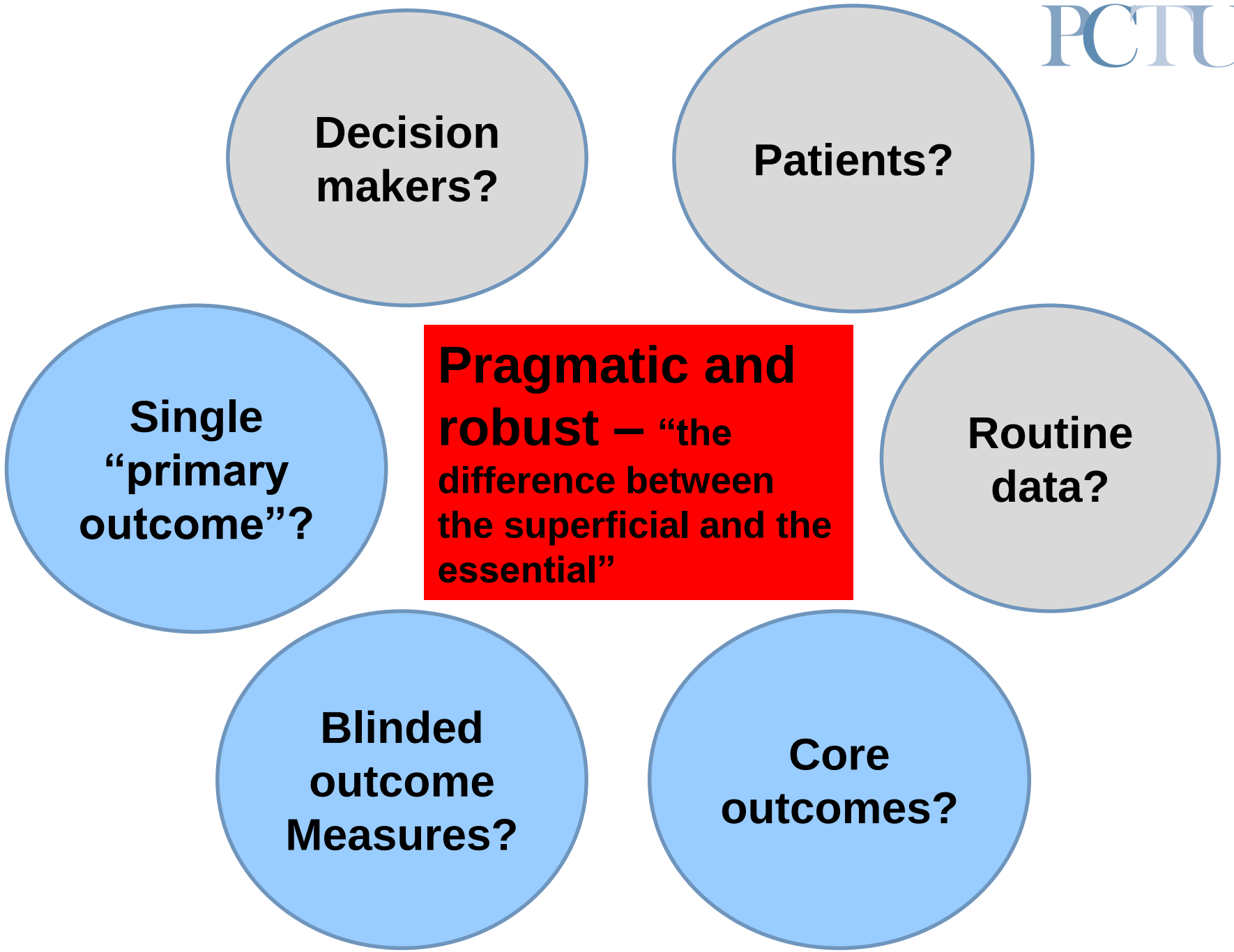
How long to collect data for?

Example – chronic pain

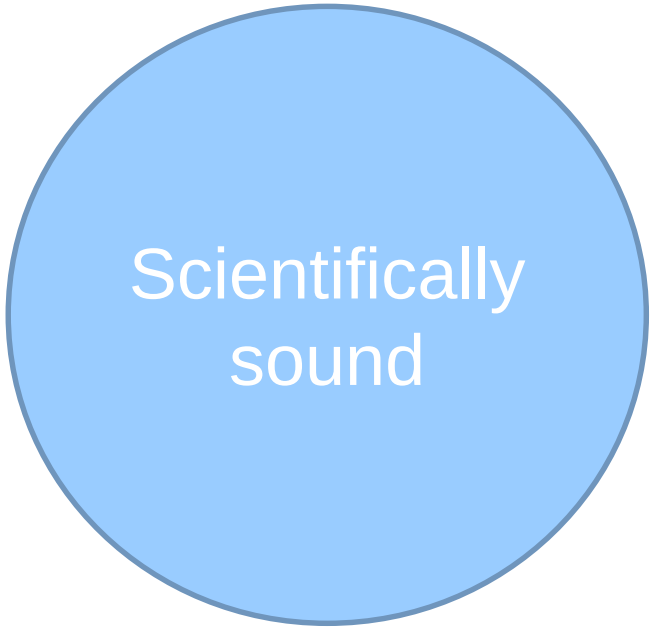
COPERs trial

Intervention: self-management groups for chronic pain

Outcomes: pain, self-efficacy to manage pain, depression, anxiety, social integration, pain related disability


Decision makers?
Patients?
Single "primary outcome"?
Pragmatic and robust – "the difference between the superficial and the essential"
Routine data?
Blinded outcome Measures?
Core outcomes?

Ethics and regulations



Pragmatic trials and regulations

UK MHRA

Good clinical practice (GCP) is a set of internationally-recognised ethical and scientific quality requirements that must be followed when designing, conducting, recording and reporting clinical trials that involve people.

UK Health Research Authority

….. **protects** and **promotes** the interests of patients and the public in health and social care research. We work to make the UK a great place to do research where more people have the opportunity to participate in **health** and **social care research** and continue to feel safe when they do.

Some issues: GCP training, adverse events, consent, adherence

Highly regulated, risk-averse, society
Scientists and ethicists, regulators need to talk to each other - “the difference between the essential and the superficial”

April 2017 - Feb 2021.

Developing a framework for the ethical design and conduct of pragmatic trials to improve the quality and value of health care systems and practices.

Canadian Institutes of Health Research: Project Scheme Operating Grant. $780,300.

Monica Taljaard (Nominated PI), Charles Weijer (Co-PI), Dean Fergusson (Co-PI), Terry Klassen (Knowledge User Co-PI). *Co-investigators*: Jamie Brehaut, Marion Campbell, Sarah Edwards, Sandra Eldridge, Bruno Giraudeau, Ian Graham, Jeremy Grimshaw, Karla Hemming, Spencer Hey, Vipul Jairath, Alex London, John Marshall, Lauralyn McIntyre, Joanne McKenzie, Alison Paprica, Merrick Zwarenstein. *Collaborator*: Allan Donner. *Knowledge Users*: Christopher Forrest, Susan Marlin. *Trainee*: Cory Goldstein.

Bias

Any tendency which prevents unprejudiced consideration of a question

What is your question?

Where could bias arise?

What is your question?

(1) The effect of assignment to the interventions at baseline (regardless of whether the interventions are received or adhered to during follow-up)?

(2) The effect of starting and adhering to the interventions as specified in the trial protocol?

https://sites.google.com/site/riskofbiastool/welcome

WAIT

Does parent-initiated montelukast prevent attendances for wheeze in pre-school children?

Where could bias arise?

Basic principle

- Bias occurs when individuals respond to information

Explanatory drug trial

- **Information on allocation** concealed through blinding (placebo & allocation concealment)

Pragmatic trial

- **Information on allocation** usually cannot be concealed from everyone (patient, deliverer, assessor)
- Some people have information – What is the potential for bias? Assessor? Chief investigator? Staff at sites? Research staff?

Concluding remarks

Thank-you to all those involved in the WAIT, STOP, NESS and COPERS trials

…. this arbitrary division into robust explanatory trials and less robust pragmatic trials **transformed by pride and prejudice into a distinction universally established** needs to be addressed by those who **appreciate the difference between the superficial and the essential**

PCTU

Barts and The London
Queen Mary's School of Medicine and Dentistry

P Pilot and
A Feasibility
F Studies
S Consort
Extension