Alternative Approaches to Tuberculosis Treatment Evaluation: The Role of Pragmatic Trials

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Overview

- Definition of pragmatic and explanatory attitudes to trial design
- Main features of a pragmatic trial
- The pragmatic-explanatory continuum
- The PRECIS wheel – a tool for aiding trial design
- PRECIS applied to past TB trials
- Issues in TB trials

Definition of pragmatic and explanatory attitudes to trial design

- Explanatory trials investigate the maximum response achievable from a treatment
- Pragmatic trials investigate how well a treatment works in practice
- The design of an explanatory trial is highly restrictive in order to reduce variability
- Pragmatic trials are designed to mirror practice in order to maximise generalisability of results

Common features of pragmatic trial designs

- Less restrictive eligibility criteria
- Flexibility of changes/modification to treatments
- Limited or even no follow-up visits
- Participants may not be blinded to treatment
- Little or no measurement of treatment adherence and no attempt made to maintain or improve it
- Little or no measurement of protocol adherence
- Outcomes aimed at determining direct benefit to patients (e.g. QoL)
- Analysed using ITT approach only

Advantages & disadvantages of pragmatic trials

Advantages

- By comparing treatments in a realistic setting, the results of a pragmatic trial are more generalisable
- This can reduce the delay in acceptance and implementation of results into guidelines and thereafter into practice

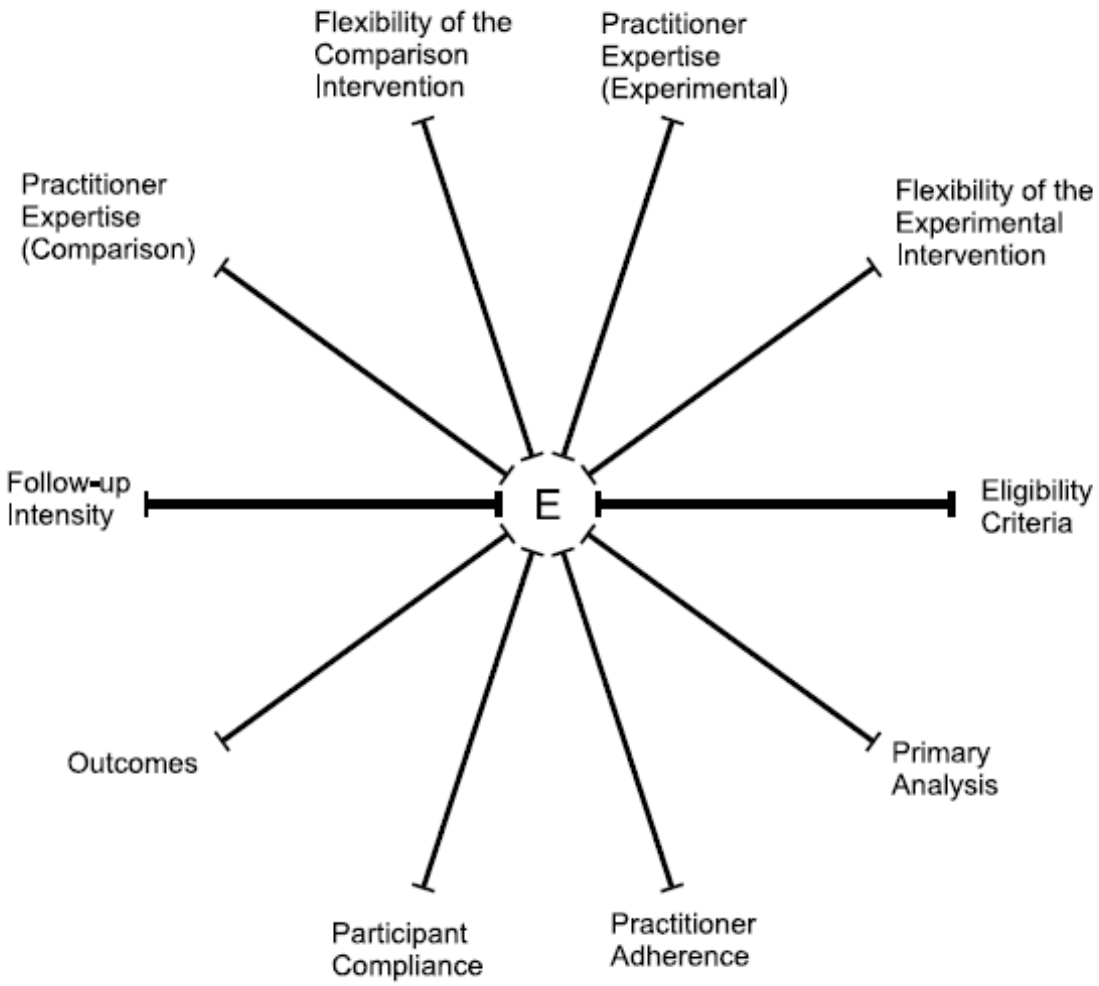
Disadvantages

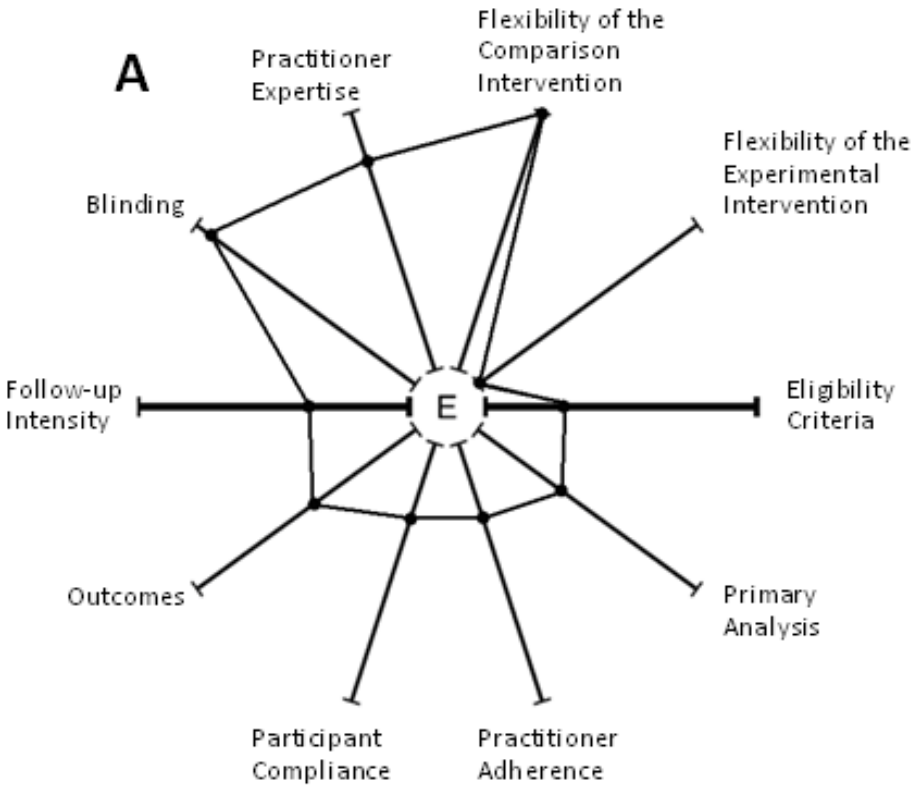
- By relaxing eligibility criteria and allowing greater freedom to physicians the between-patient variability is increased
  - larger sample size
  - implications for the length and cost of the trial

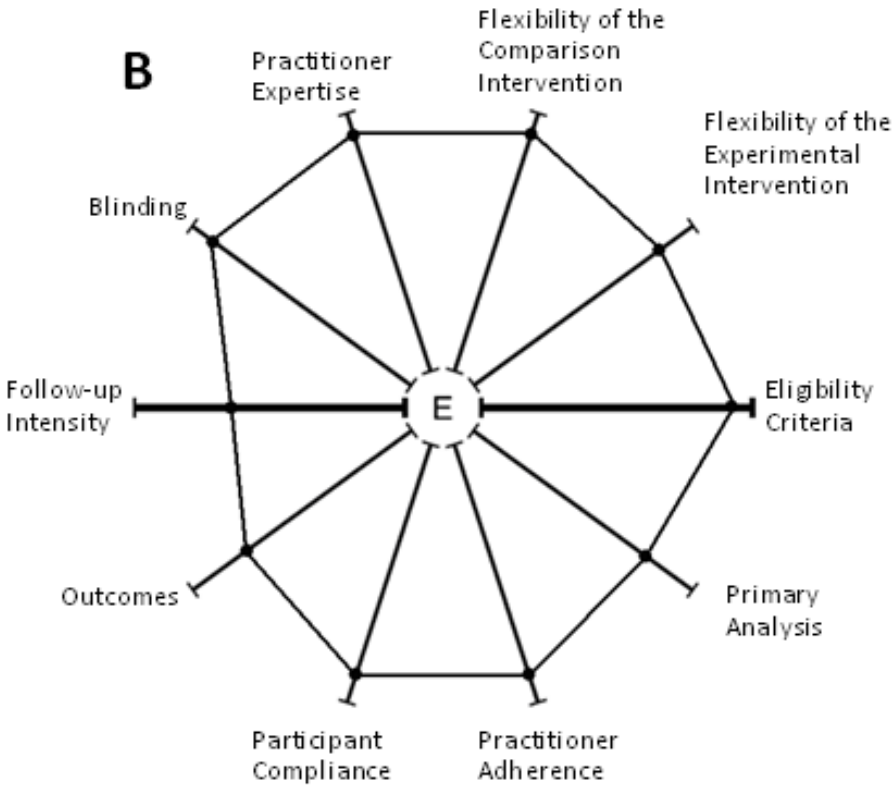
The Pragmatic-Explanatory continuum

- Most trials lie between the most extreme pragmatic and explanatory designs
- Hence a pragmatic-explanatory continuum for trial design exists
- The continuum is multidimensional due to the many aspects of trial design (e.g. treatments, outcomes, analysis etc)
- Until very recently there have been no published tools for assisting trialists in designing trials in line with their stated purpose
- In 2009 Thorpe and colleagues published such a tool - the PRECIS (pragmatic-explanatory continuum indicator summary) wheel

The PRECIS wheel







A: 1st East African/British Medical Research Council short-course trial (1972)
B: the Algerian Sahara study (1984)

Issues in TB trials

- There are considerable differences in the circumstances under which many TB trials are and have been conducted and routine practice.
- Patients are usually supervised and followed much more intensively in an RCT than in regular clinics – in several early studies they were kept in hospital to ensure adherence to their treatment, results were probably unrealistically good.
- More recent trials coordinated by the International Union Against TB & Lung Disease in collaboration with MRC CTU have been much more pragmatic in nature and closer to programme conditions.

Issues in TB trials

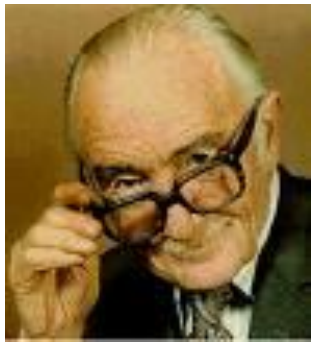
- In a recent large study failure and relapse rates on standard treatment were noticeably higher than in earlier studies.
- A notable exceptions was the Algerian Sahara study which included nomadic patients. “No attempt was made to persuade the nomads to change their way of life…chemotherapy was largely self administered”
- Future trials could be more pragmatic in nature to more accurately quantify treatment effectiveness in practice

"At its best a trial can show what can be accomplished with a medicine under careful observation and certain restricted conditions. The same results will not invariably or necessarily be observed when the medicine passes into general use."

Austin Bradford Hill 1984

"Between measurements based on RCTs and benefit in the community there is a gulf which has been much underestimated."

Archie Cochrane 1971



Conclusions

- Pragmatic trials investigate the effectiveness of treatments in practice
- Explanatory trials investigate a treatment's *potential* effectiveness
- There is a pragmatic-explanatory continuum for trial design
- The position of a trial on this spectrum can be illustrated using the PRECIS wheel
- Quite often the results observed in clinical trials are not replicated in practice. TB is one such area where this has been demonstrated
- The results of trials which take on more pragmatic designs are more generalisable, but the trial itself may be more costly and take longer to run
- By conducting more pragmatic trials the delay in getting new, effective treatments into practice may be reduced