Pragmatic trials – how pragmatic can we be?

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Pragmatic trials

- Pragmatic trials are designed to answer questions about comparative effectiveness to improve clinical decision making
- Eg better screening, diagnostic, or therapeutic decisions
- Not ‘does it work at all’ or ‘can it work’ but ‘what works best’ and ‘is it worthwhile’?

This needs Pragmatic trials - but what exactly are they? How do we assess pragmatism?

- Pragmatic trials are contrasted with explanatory trials
- They are said to be conducted in the ‘real world’

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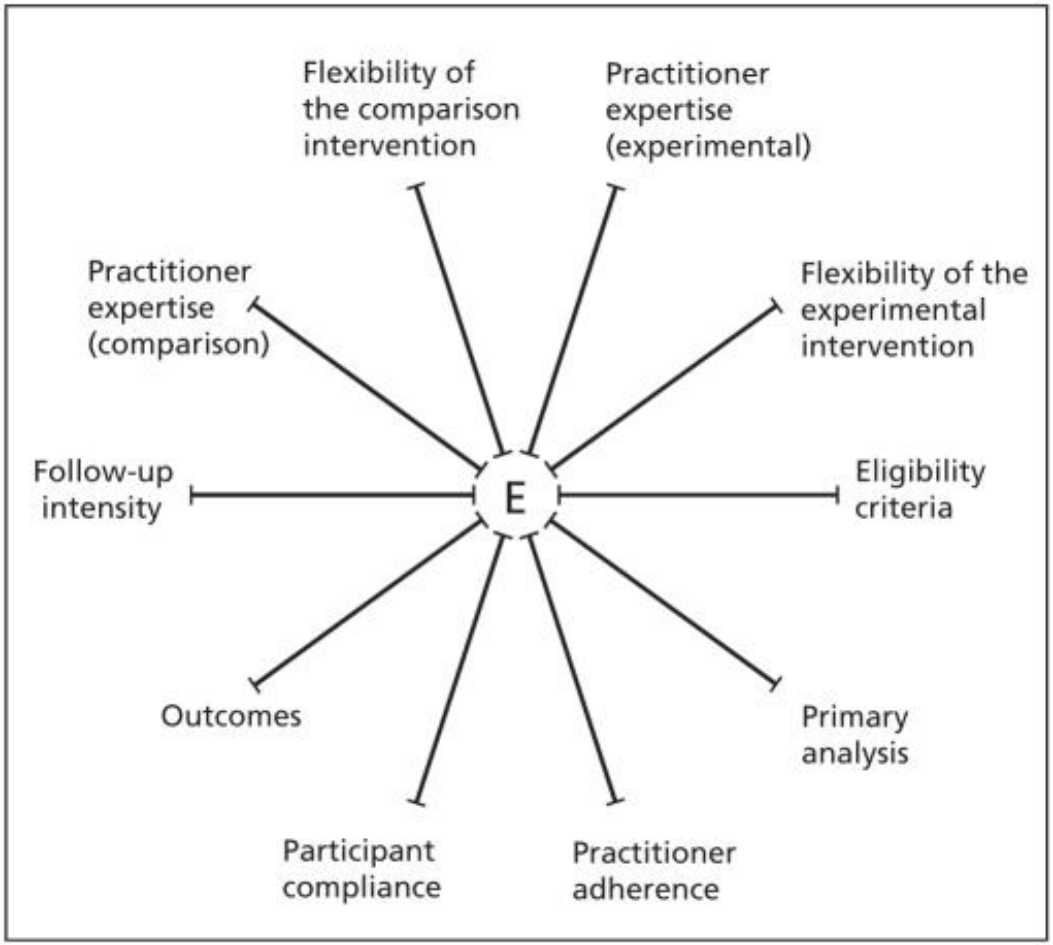
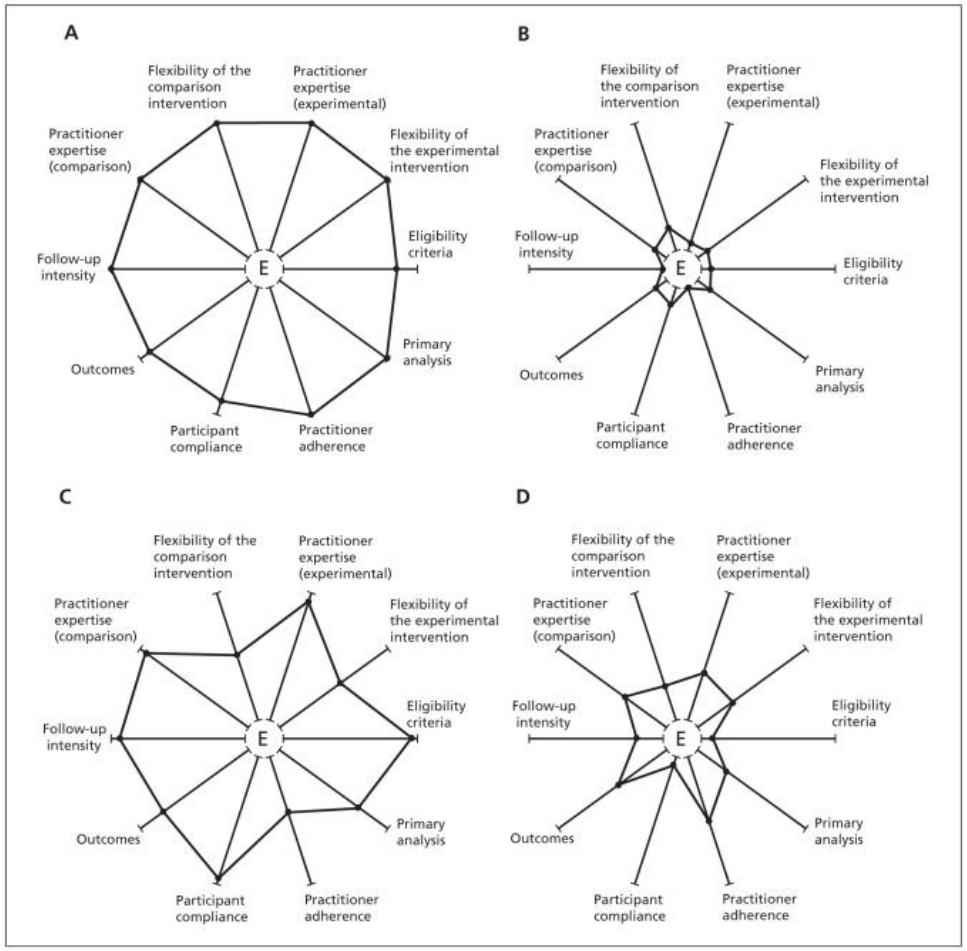
- They are said to be conducted in the ‘real world’ (rather than in the laboratory)

Some aspects of design can be made more or less ‘real’

Pragmatic trials – the PRECIS wheel
(Thorpe et al. J Clin Epi 2009; 464-)

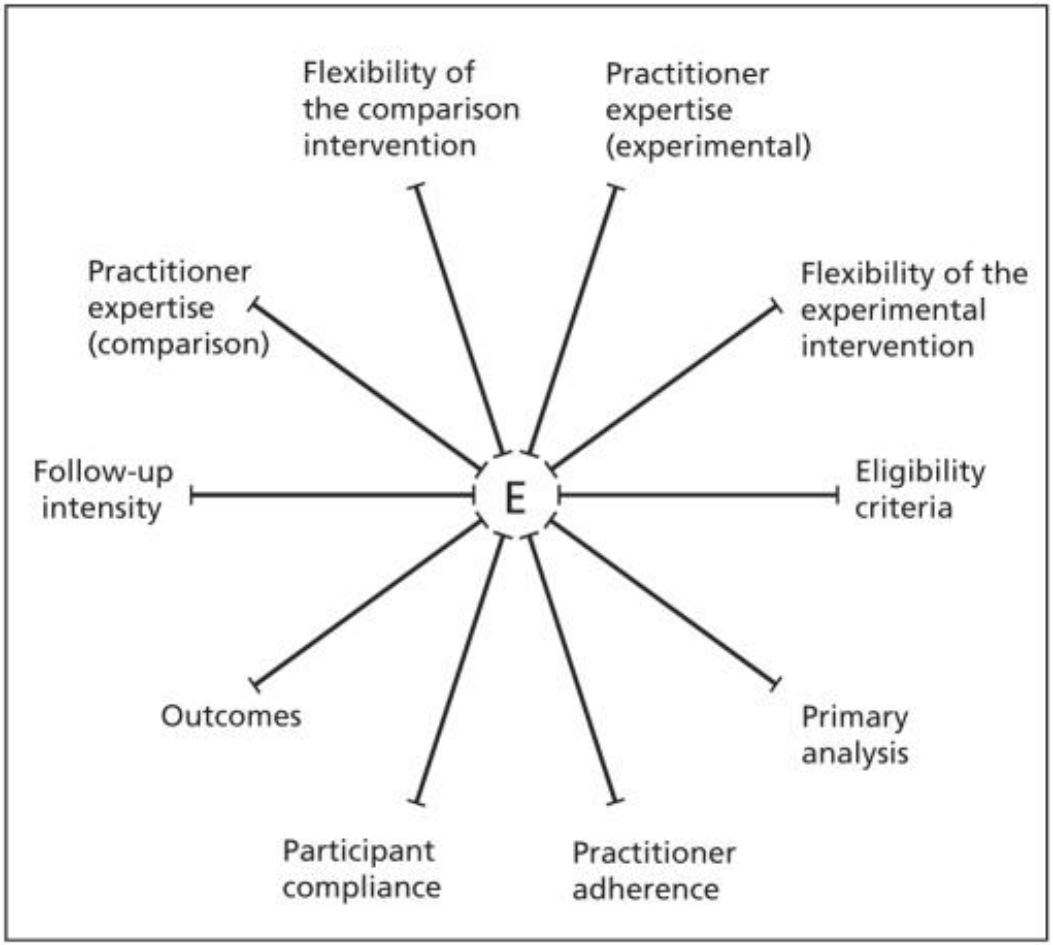


A. DOT TB trial
B. NASCET endarterectomy trial
C. Aspirin in pre-eclampsia
D. Aspirin in pre-eclampsia



Three missing spokes

1. The trial setting. Treatment effects may depend on the institution as well as the practitioner



Surprisingly the wheel omits the real world (setting) domain

2. Delivery of care

Some aspects of trials can't be made 'real' such as

- Randomisation to treatment
- Consent

And this can have a major impact on estimating real world effectiveness
- Consider emergency care

Time is the defining feature of emergency medicine

- Time can determine effectiveness
- Treatment benefit is typically time dependent
- Treatment harm is typically independent of time
- Effectiveness typically decreases with increasing time delay

Emergencies and critical care

- Recruitment and randomisation to trials in A&E and ICU can be difficult to organise

- Applying selection criteria, recruitment, allocation, baseline assessments, and treatment in emergencies is difficult and takes time

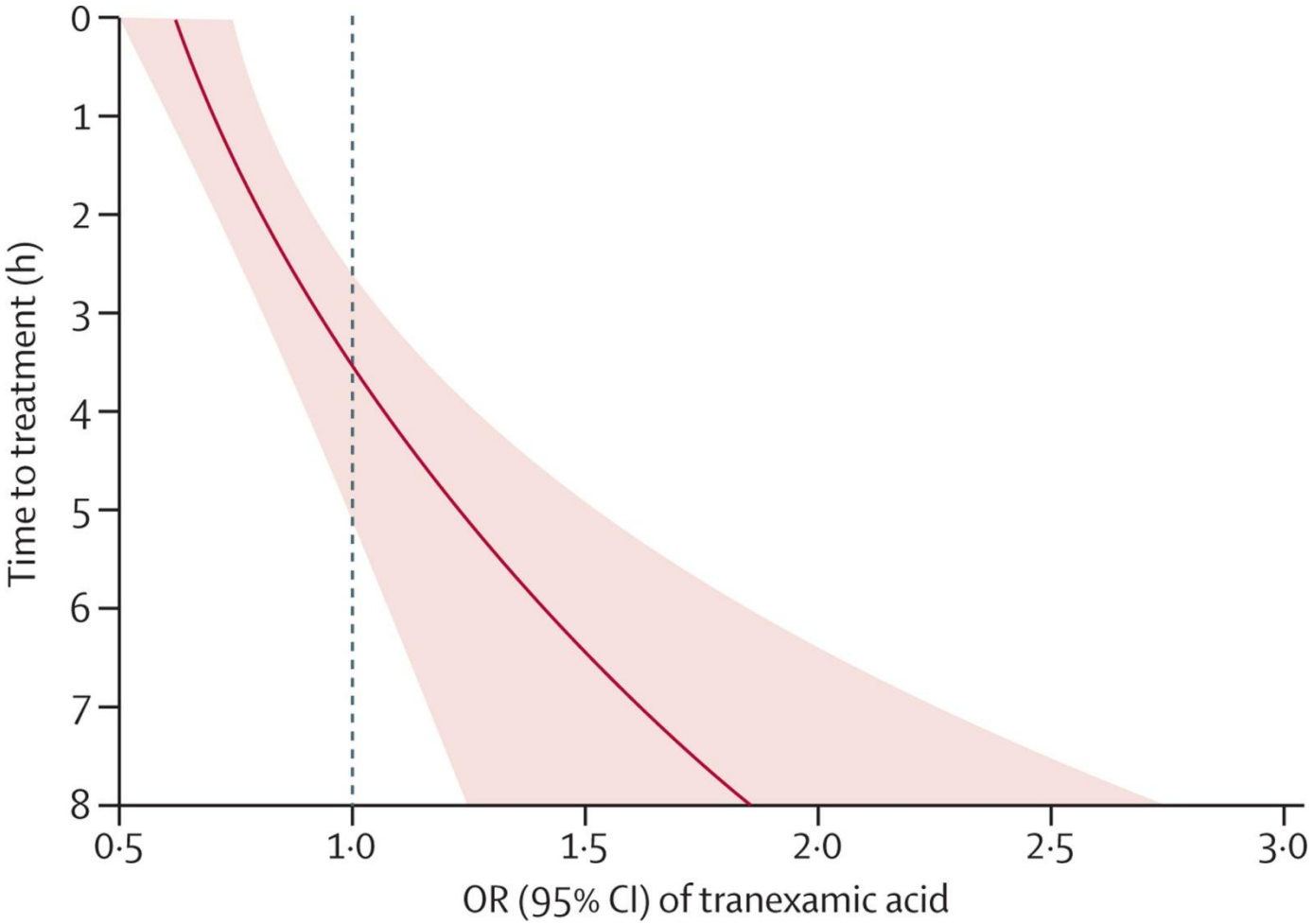
Does this compromise effectiveness?

CRASH-2

- RCT of tranexamic acid (TXA) in bleeding trauma in ED
- Recruited and randomised 20,211 patients from 40 countries
- Led by Ian Roberts from LSHTM
  - Risk of all cause death reduced by 9%
  - Risk of death due to bleeding by 15%

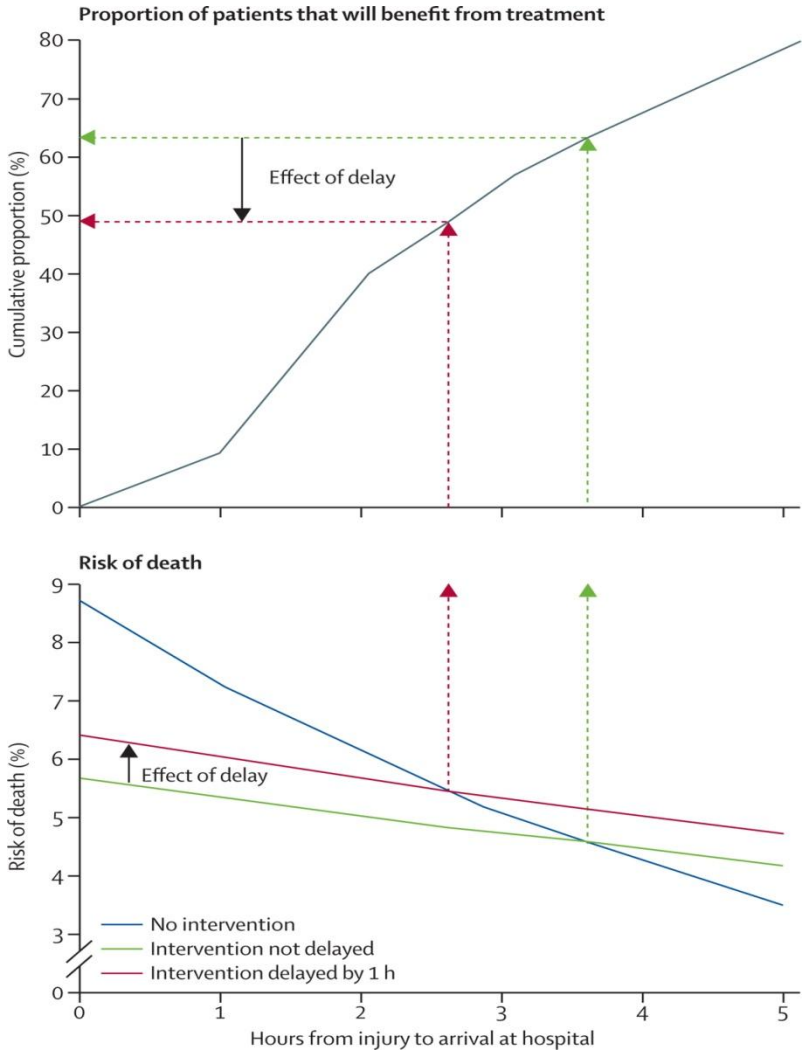
But recruited just 135 patients from UK mainly due to consent and governance restrictions

Effect of TXA by time to treatment in CRASH2

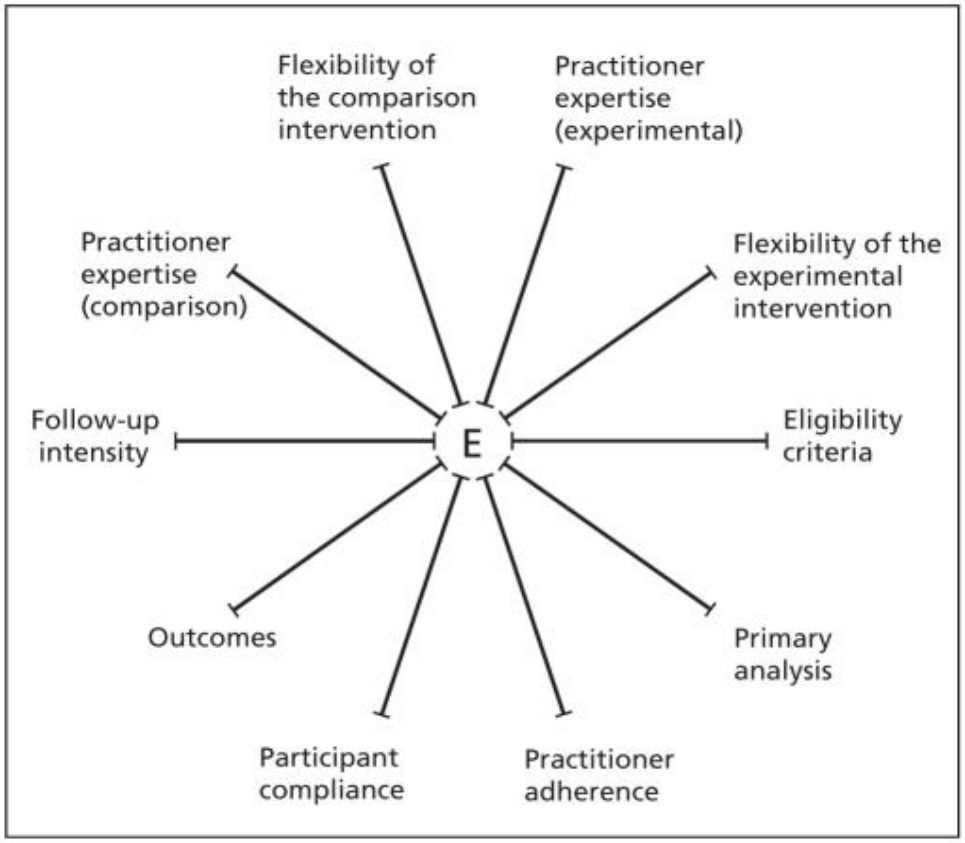


- The relative risk of death from bleeding with tranexamic acid was estimated in the CRASH-2 trial as 0·85 (95% CI 0·76–0·96),
- the corresponding relative risk in the presence of an extra 1hr delay is 0·96 (0·86–1·08).

Delay due to trial recruitment compromises effectiveness



Missing spokes: 2. treatment in the usual way



But missing a spoke. eg for emergency and critical care trials: is the treatment given at the usual time? For all trials: is the treatment given in the way it would be in routine care?

Is it inevitable that trials of emergency care are not pragmatic?

- Is it possible to randomise and treat in the usual time frame by not seeking informed consent?

Pre-consent ??

NHS pre-consent approval

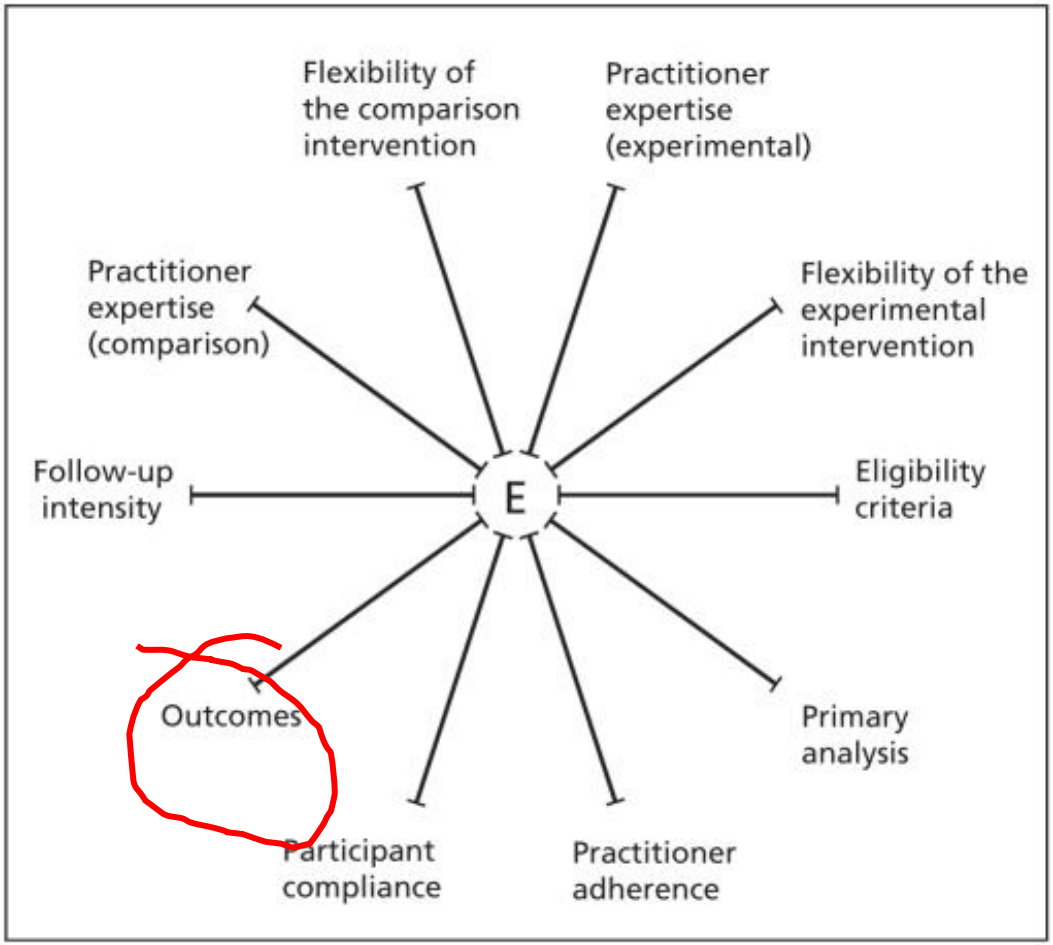
I consent to be randomised to care in any randomised controlled trial approved by an NHS Ethics Committee for which I am eligible

Signed: 

Declaration of Helsinki

“....if the research cannot be delayed, the study may proceed without informed consent....”

Limitations on pragmatism: 1. Patient outcomes

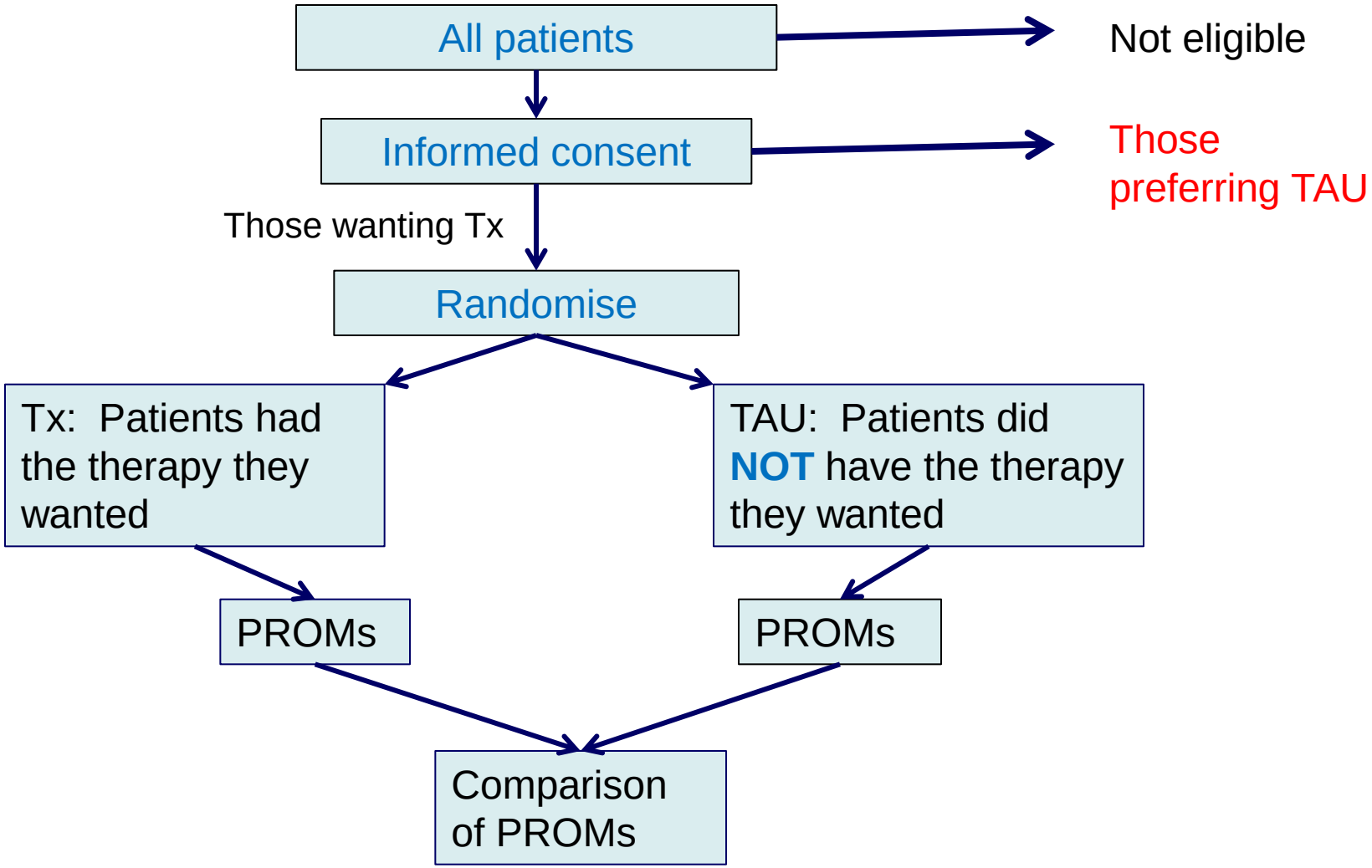


More pragmatic is interpreted as more patient focused

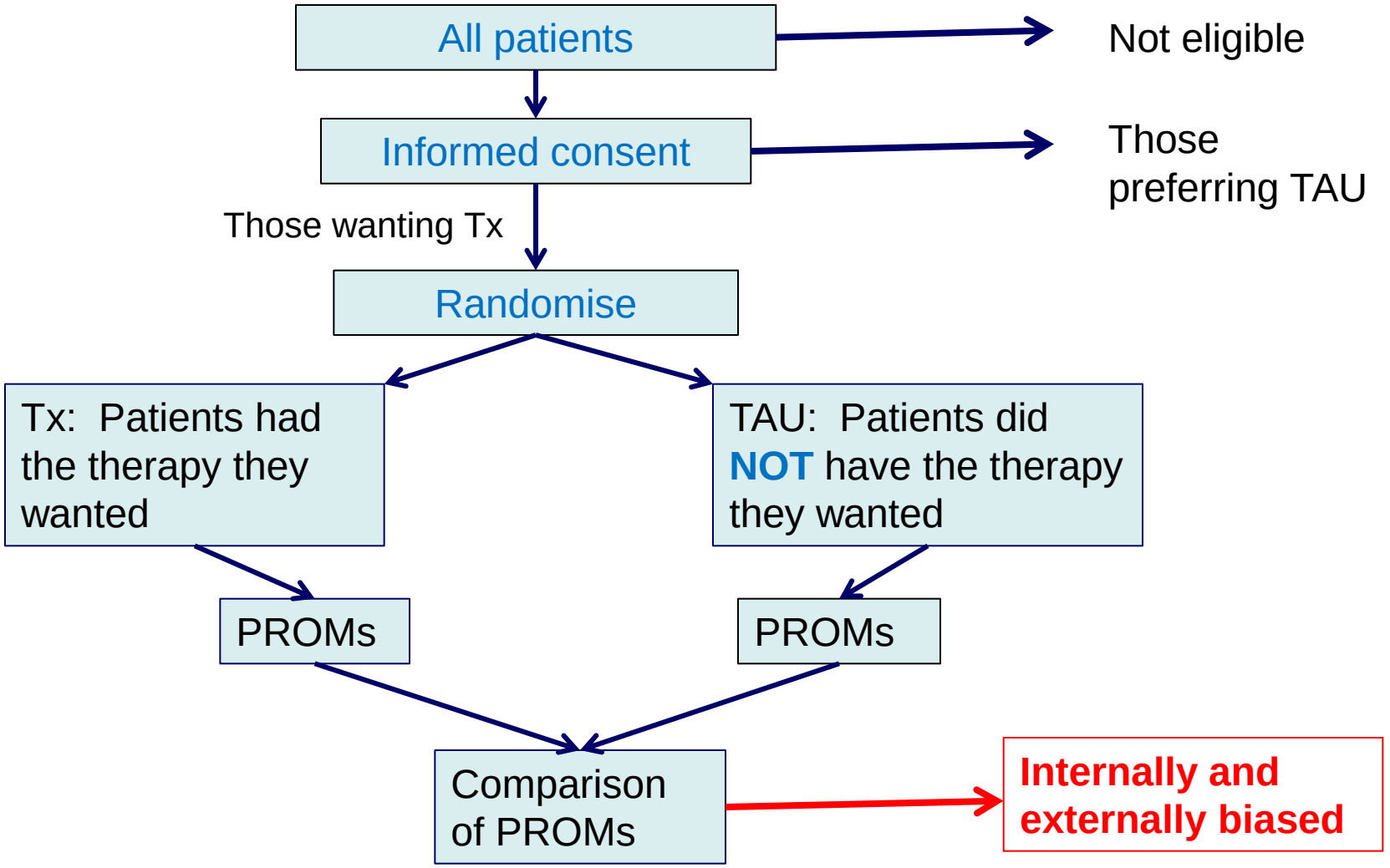
Can we design pragmatic trials with PROMs?

- Open TAU trials and patient preferences

Open trials of Tx vs TAU



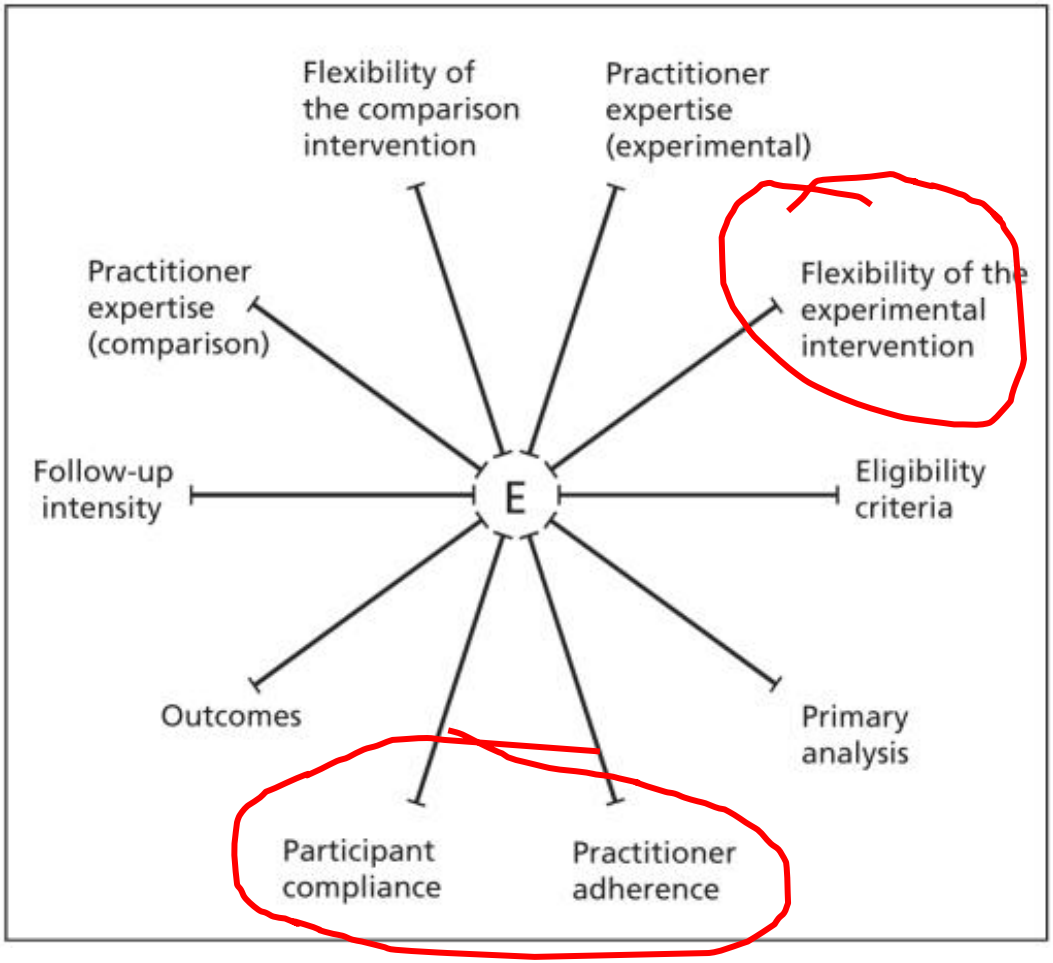
Open trials of Tx vs TAU



Solution to the patient preference problem

- Zelen designs in which you randomise before consent. Eg ‘Cohort trials’ (Relton et al BMJ 2010; 340, 963-)
- Don’t use PROMs, use objective measures of physiological response which can’t be influenced by preferences or expectations
  - So in open TAU trials the pragmatic limit is not the PRECIS rim

Limitations on pragmatism: 2. Flexibility in treatment delivery



Thorpe et al. J Clin Epi 2009; 464-

Flexibility and Interpretability

- In the real world treatments are flexible and patients have many interventions which may affect outcomes (treatments, timings, carers, settings, etc)

- These treatments also change in response to emerging outcomes

- Detecting the signal from one treatment from the noise of all the care is difficult

Treatment effects and non-inferiority

- One well known example is detecting equivalence or non-inferiority in pragmatic trials
- These designs are necessary for testing reductions in treatment, eg drug holidays or not doing pre-op assessments
- X-overs or multiple additional treatments in both arms ‘dilute’ the treatment effect and may make non-inferiority inevitable
- Especially if additional ‘rescue’ treatments can be given in response to emerging outcomes

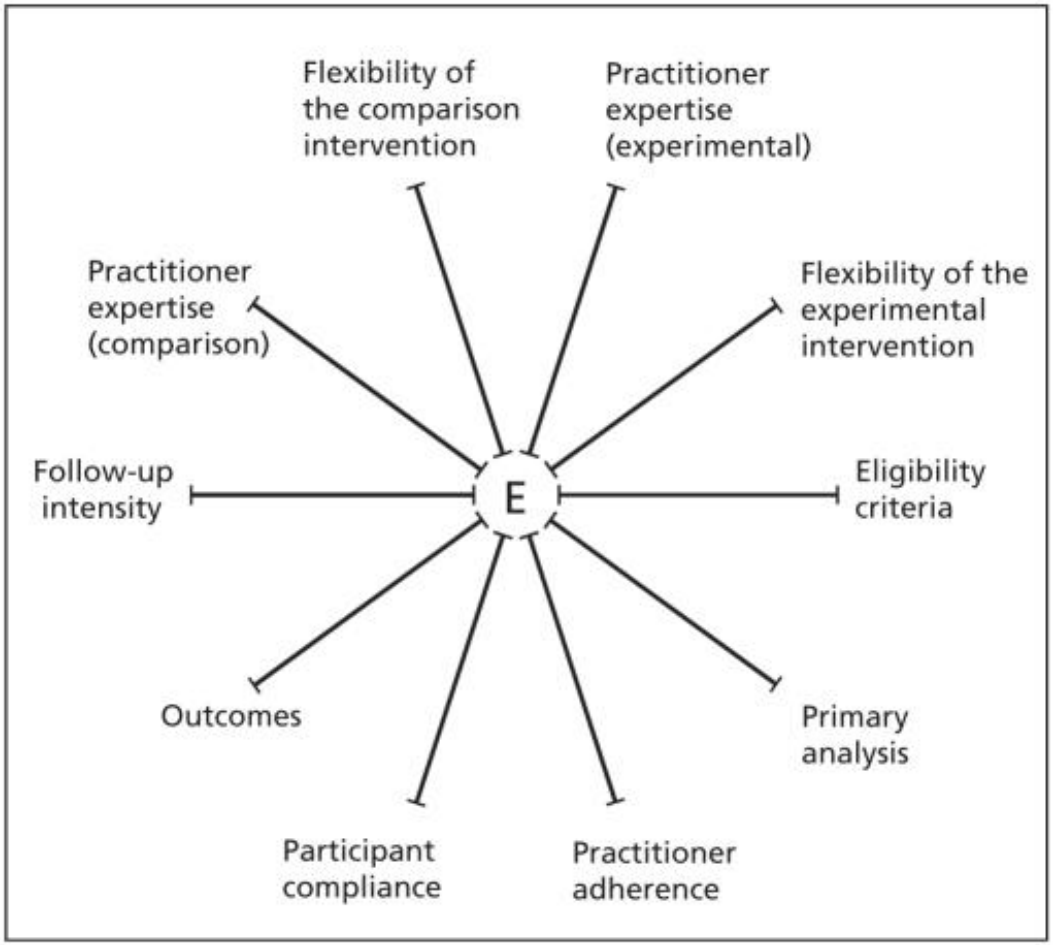
So in equivalence or non-inferiority trials the pragmatic limit is not complete flexibility

Solution?

- One possible solution to the problem of flexibility in equivalence trials is to do a cost-effectiveness analysis
- In which the whole treatment pathways are costed – from a societal perspective
- Now, if equivalence is achieved by different routes that's fine, unless the 'cost' is different

So cost-effectiveness analysis is necessary in pragmatic trials with real world care

Missing spokes: 3. cost effectiveness



Where's the cost-effectiveness measurement spoke?

Summary

- ‘Real world’ randomised trials are not strictly possible
- PRECIS is a helpful tool in the design of pragmatic trials
- But needs care regarding interpretation (outcomes and flexibility) and omissions (treatments, costs, and settings)

Thank you