Making trials matter: using PRECIS-2 to match trial design to trial intent

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TRIAL FORGE

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MRC | Hubs for Trials Methodology Research

OK TO ASK about clinical research

NHS National Institute for Health Research

Trials Change Lives

"Clinical trials are the backbone of primary research that informs clinical practice in the NHS in the UK"

Prof Hywel Williams, Director, Health Technology Assessment Programme (NIHR)

Listen to the podcast

Clinical Trials for the NHS

www.methodologyhubs.mrc.ac.uk/trials-change-lives/

Photo reference,
Queen's University Belfast

Let’s do what we did last time..

‘There is a peculiar paradox that exists in trial execution - we perform clinical trials to generate evidence to improve patient outcomes; however, we conduct clinical trials like anecdotal medicine:

- **we do what we think works**
- **we rely on experience and judgement and..**
- **limited data to support best practices.’**

Monica Shah in ‘Site selection in global clinical trials in patients hospitalized for heart failure: perceived problems and potential solutions’. Heart Fail Rev. 2012; Oct 26. [Epub ahead of print]

trialforge.org

TRIAL FORGE

HOME ABOUT WHATS NEW COLLABORATORS GET INVOLVED PATHWAY

A systematic approach to making trials more efficient

The evidence base for how to make the trials process efficient is remarkably thin. Trial Forge aims to change this.

EXPLORE PATHWAY LEARN MORE

Trials

Randomised controlled trials are the gold standard for evaluating healthcare

Essential

Randomised trials are the cornerstone of evidence-based healthcare because they

Inefficient

The evidence base for how to make the trials process efficient is remarkably thin.

What are we trying to do with our trial?

- **Who am I designing my trial for?**
- **What do they need?**

What are we trying to do with our trial?

- **Who am I designing my trial for?**
- **What do they need?**

This is what they need

Now let’s think about design..

Work

Now let’s think about design..

Work

Now let’s think about design..

Work

Now let’s think about design..

Work

What you have produced is irrelevant

Do we think enough about design?

'…most therapeutic trials are inadequately formulated, and this from the earliest stages of their conception. Their inadequacy is basic..

Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutical trials. Journal of chronic diseases 1967; 20: 637–48.

Choosing the right design

BMJ 2014;349:g5219 doi: 10.1136/bmj.g5219

RESEARCH

Ability of a meta-analysis to prevent redundant research: systematic review of studies on pain from propofol injection

Céline Habre *research fellow*[1], Martin R Tramèr *professor in anaesthesia*[2 3], Daniel M Pöpping *anaesthetist*[4], Nadia Elia *public health epidemiologist*[2 5]

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Abstract

Objective To examine whether, according to the conclusions of a 2000 systematic review with meta-analysis on interventions to prevent pain

of the new trials were considered clinically relevant since they used the most efficacious intervention as comparator or included a paediatric population.

Choosing the right design

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Number of clinically irrelevant trials:

87 of 136 (64%)

PRECIS, something to help trialists think through their decision decisions

ELSEVIER

Journal of Clinical Epidemiology 62 (2009) 464–475

Journal of Clinical Epidemiology

ORIGINAL ARTICLE

A pragmatic–explanatory continuum indicator summary (PRECIS): a tool to help trial designers

Kevin E. Thorpe[a,*], Merrick Zwarenstein[b], Andrew D. Oxman[c], Shaun Treweek[d], Curt D. Furberg[e], Douglas G. Altman[f], Sean Tunis[g], Eduardo Bergel[h], Ian Harvey[i], David J. Magid[j], Kalipso Chalkidou[k]

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[c]*Preventive and International Health Care Unit, Norwegian Knowledge Centre for the Health Services, Oslo, Norway*
[d]*Division of Clinical & Population Sciences and Education, University of Dundee, Dundee, UK; Norwegian Knowledge Centre for the Health Services, Oslo, Norway*
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[f]*Centre for Statistics in Medicine, University of Oxford, Oxford, UK*
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[h]*UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction, Department of Reproductive Health and Research, World Health Organization, Geneva, Switzerland*
[i]*Faculty of Health, University of East Anglia, Norwich, UK*
[j]*Institute for Health Research, Kaiser Permanente Colorado; Departments of Preventive Medicine and Biometrics and Emergency Medicine, University of Colorado Health Sciences Center, Denver, CO, USA*
[k]*National Institute for Health and Clinical Excellence, London, UK*

Accepted 13 December 2008

Abstract

Objective: To propose a tool to assist trialists in making design decisions that are consistent with their trial's stated purpose.

Study Design and Setting: Randomized trials have been broadly categorized as either having a pragmatic or explanatory attitude. Pragmatic trials seek to answer the question, "Does this intervention work under usual conditions?," whereas explanatory trials are focused on the question, "Can this intervention work under ideal conditions?" Design decisions make a trial more (or less) pragmatic or explanatory, but no tool currently exists to help researchers make the best decisions possible in accordance with their trial's primary goal. During the course of two international meetings, participants with experience in clinical care, research commissioning, health care financing, trial methodology, and reporting defined and refined aspects of trial design that distinguish pragmatic attitudes from explanatory.

Results: We have developed a tool (called PRECIS) with 10 key domains and which identifies criteria to help researchers determine how pragmatic or explanatory their trial is. The assessment is summarized graphically.

Conclusion: We believe that PRECIS is a useful first step toward a tool that can help trialists to ensure that their design decisions are consistent with the stated purpose of the trial.

PRECIS, something to help trialists think through their decision decisions

ELSEVIER

A pragmatic–explan
a

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[c]Preventive and International
[d]Division of Clinical & Population Sci
[e]Division of Public Heal
[f]Cent
[g]
[h]UNDP/UNFPA/WHO/World Bank Special
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[i]
[j]Institute for Health Research, Kaiser Per
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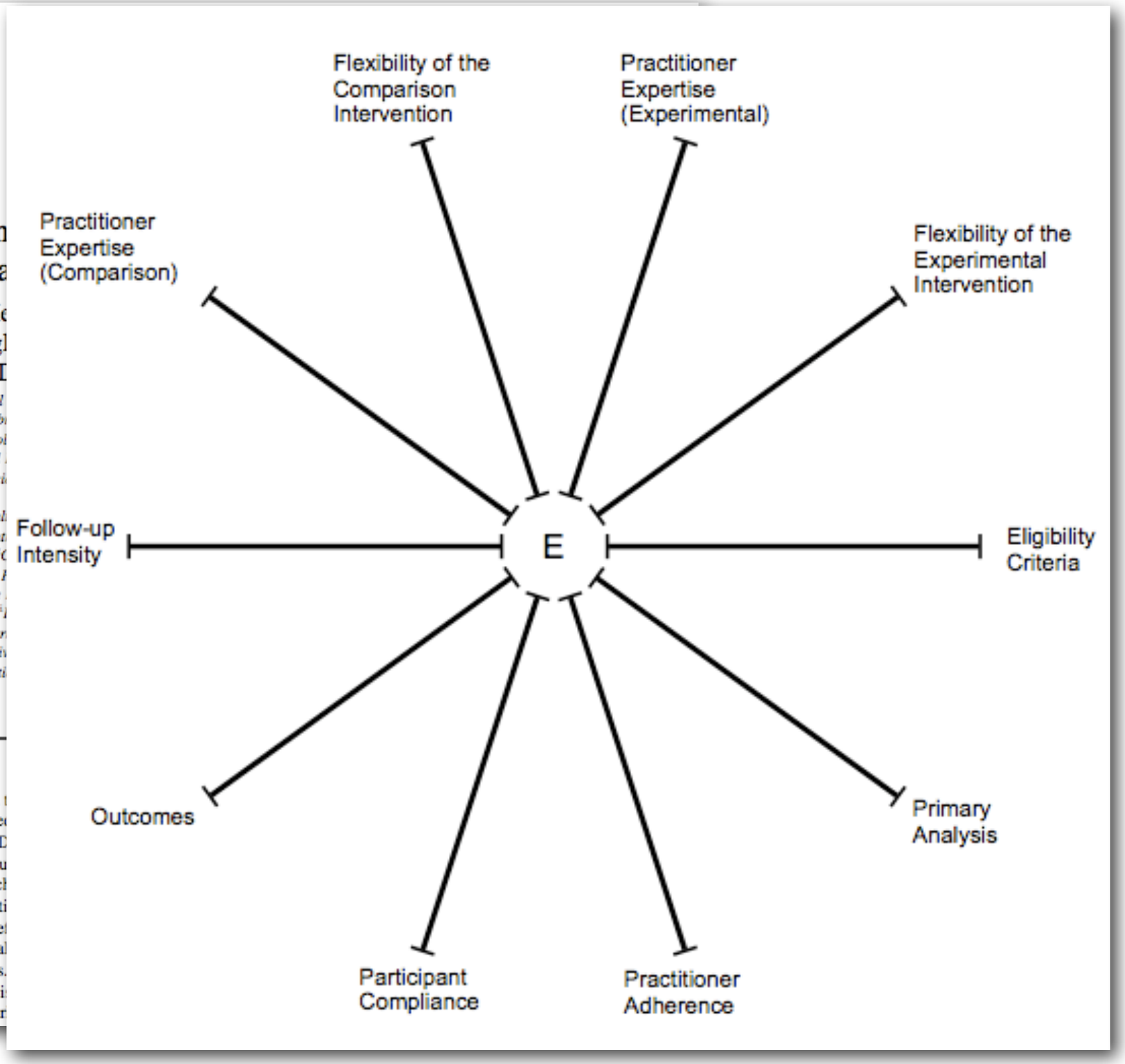


Design: PRECIS-2

Who am I designing my trial for and what have I done to make sure they don't have to dismiss my trial as irrelevant?

Kirsty Loudon, Stirling

Who are your users and what do they want?

Loudon K, Zwarenstein M, Sullivan F, Donnan P, Treweek S. Making clinical trials more relevant: improving and validating the PRECIS tool for matching trial design decisions to trial purpose. Trials 2013, 14: 115.

PRECIS 2

BMJ 2015;350:h2147

ELIGIBILITY -
Who is selected to participate in the trial?

RECRUITMENT -
How are participants recruited into the trial?

SETTING -
Where is the trial being done?

ORGANISATION -
What expertise and resources are needed to deliver the intervention?

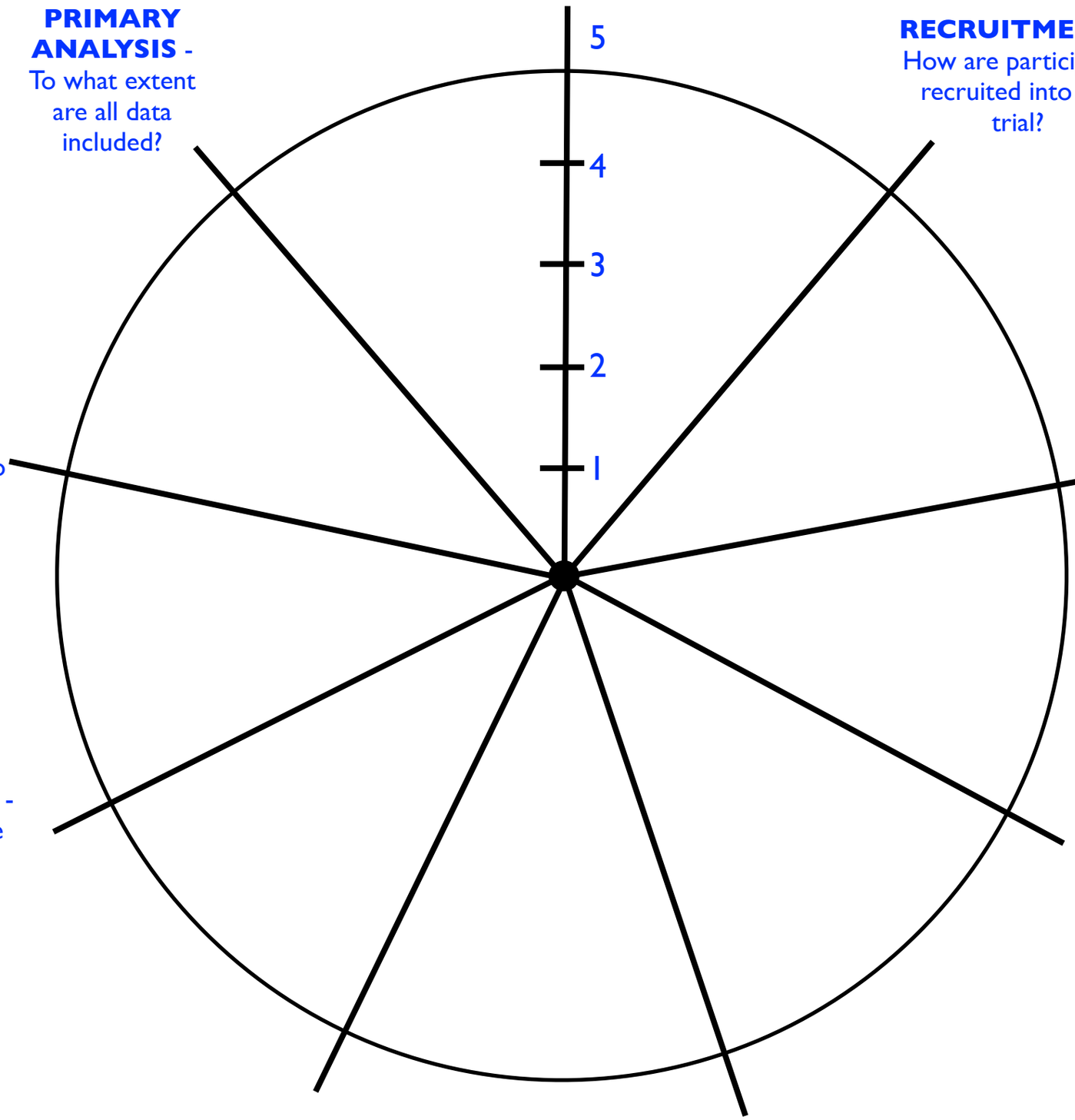
FLEXIBILITY: DELIVERY -
How should the intervention be delivered?

FLEXIBILITY: ADHERENCE -
What measures are in place to make sure participants adhere to the intervention?

FOLLOW-UP -
How closely are participants followed-up?

PRIMARY OUTCOME -
How relevant is it to participants?

PRIMARY ANALYSIS -
To what extent are all data included?



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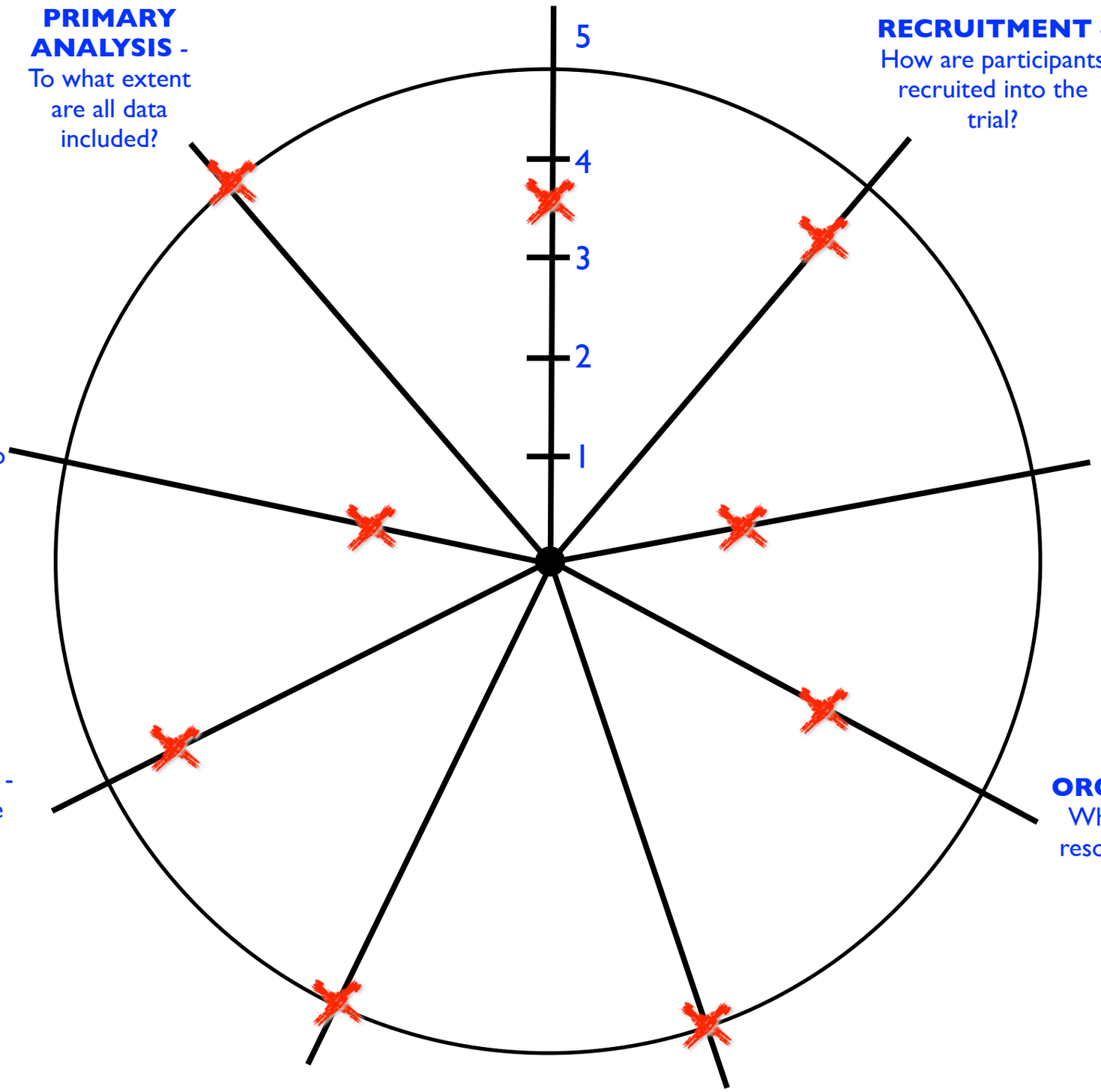

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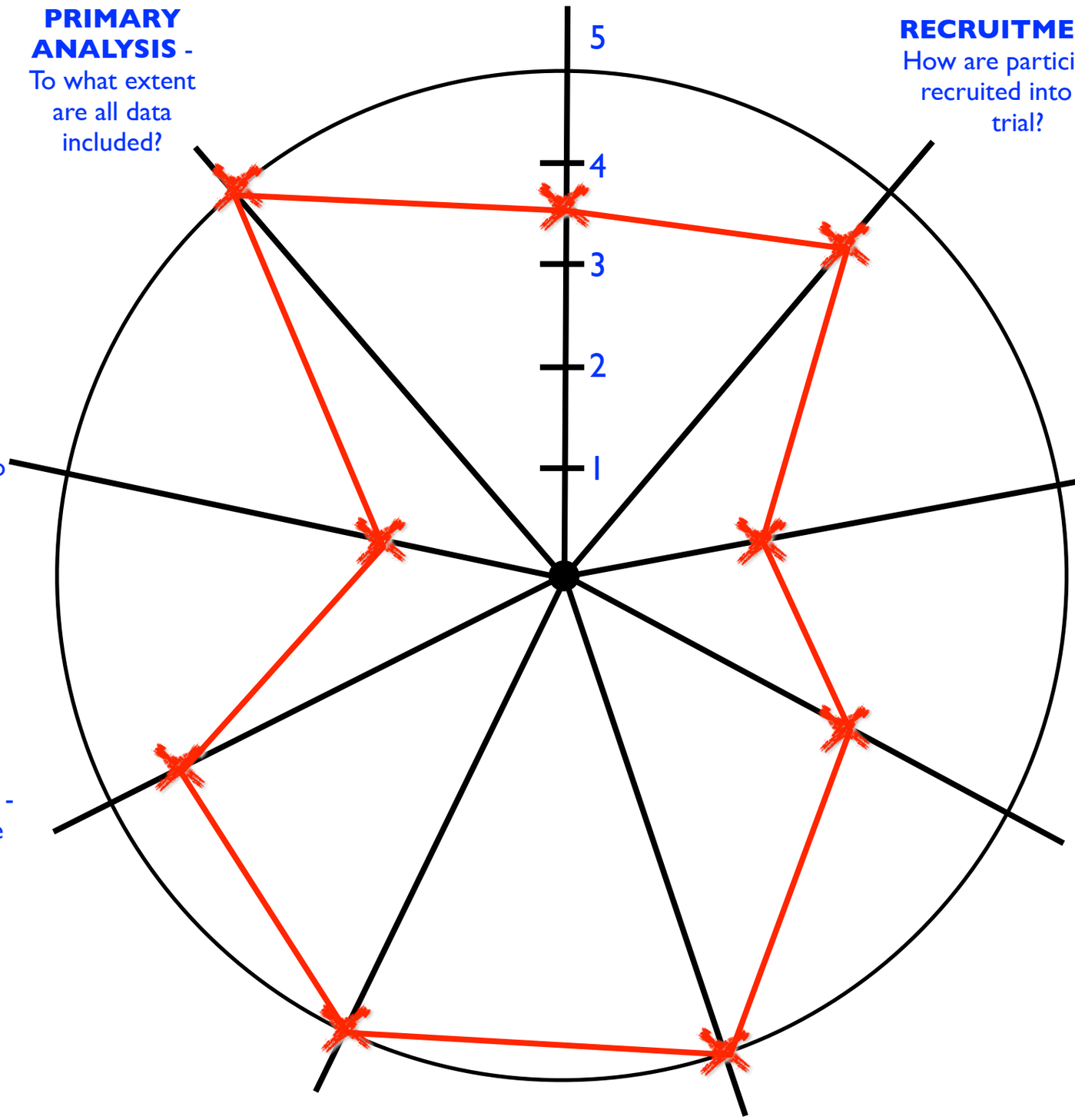
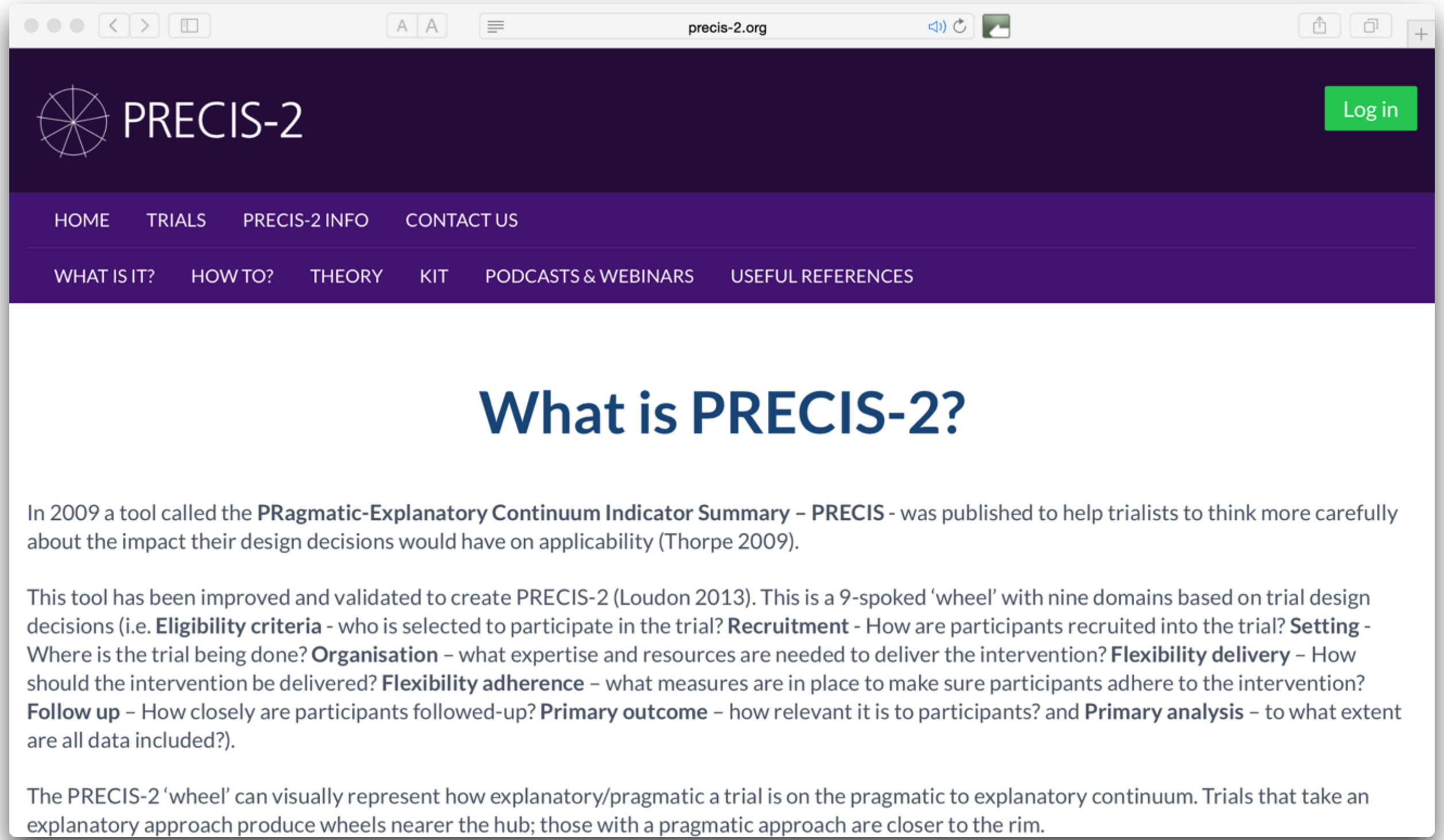


Website: www.precis-2.org



So, why should you use PRECIS-2?

Who am I designing my trial for and what have I done to make sure they don't have to dismiss my trial as irrelevant?

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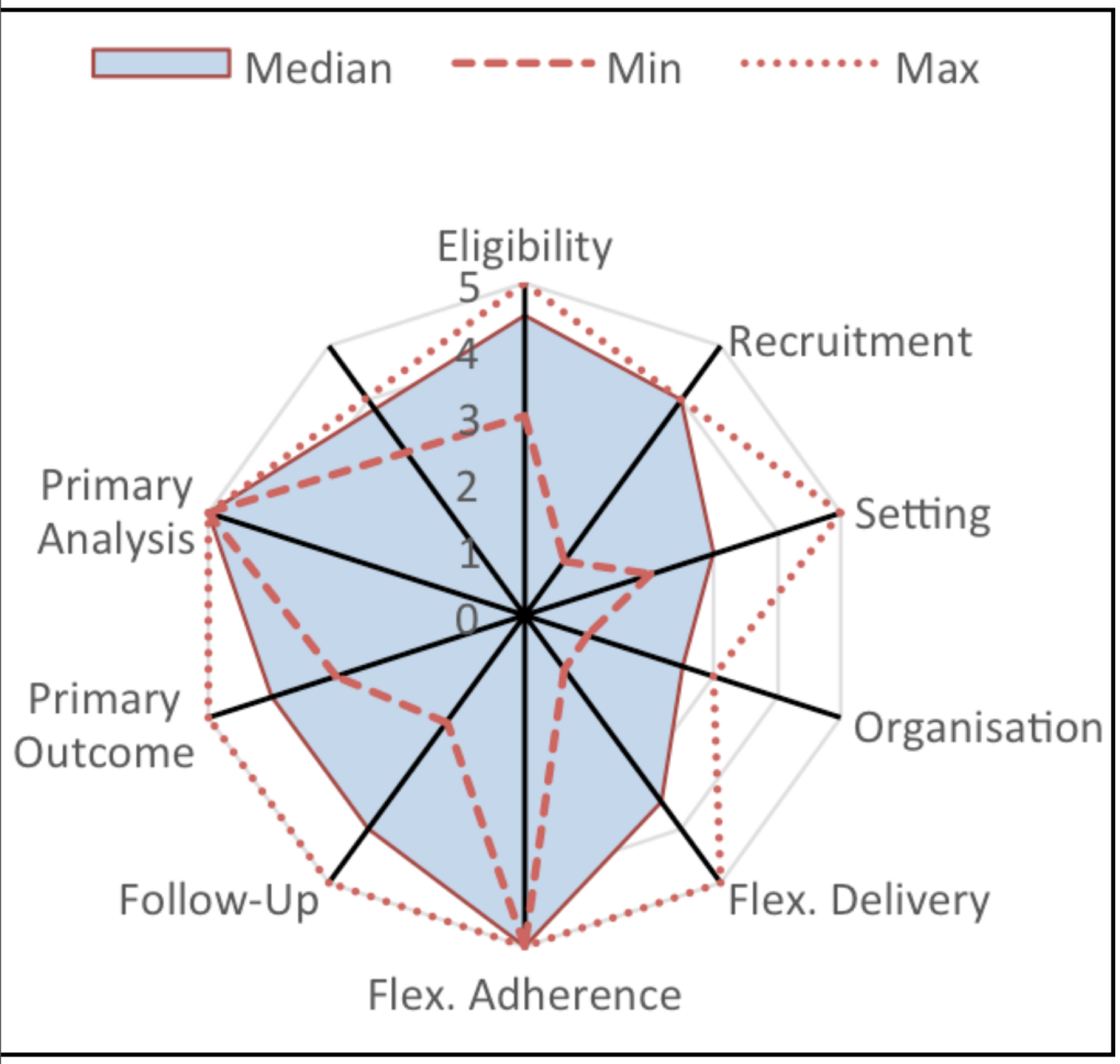
Who am I designing my trial for and what have I done to make sure they don't have to dismiss my trial as irrelevant?

Work

#1– PRECIS-2: before and after



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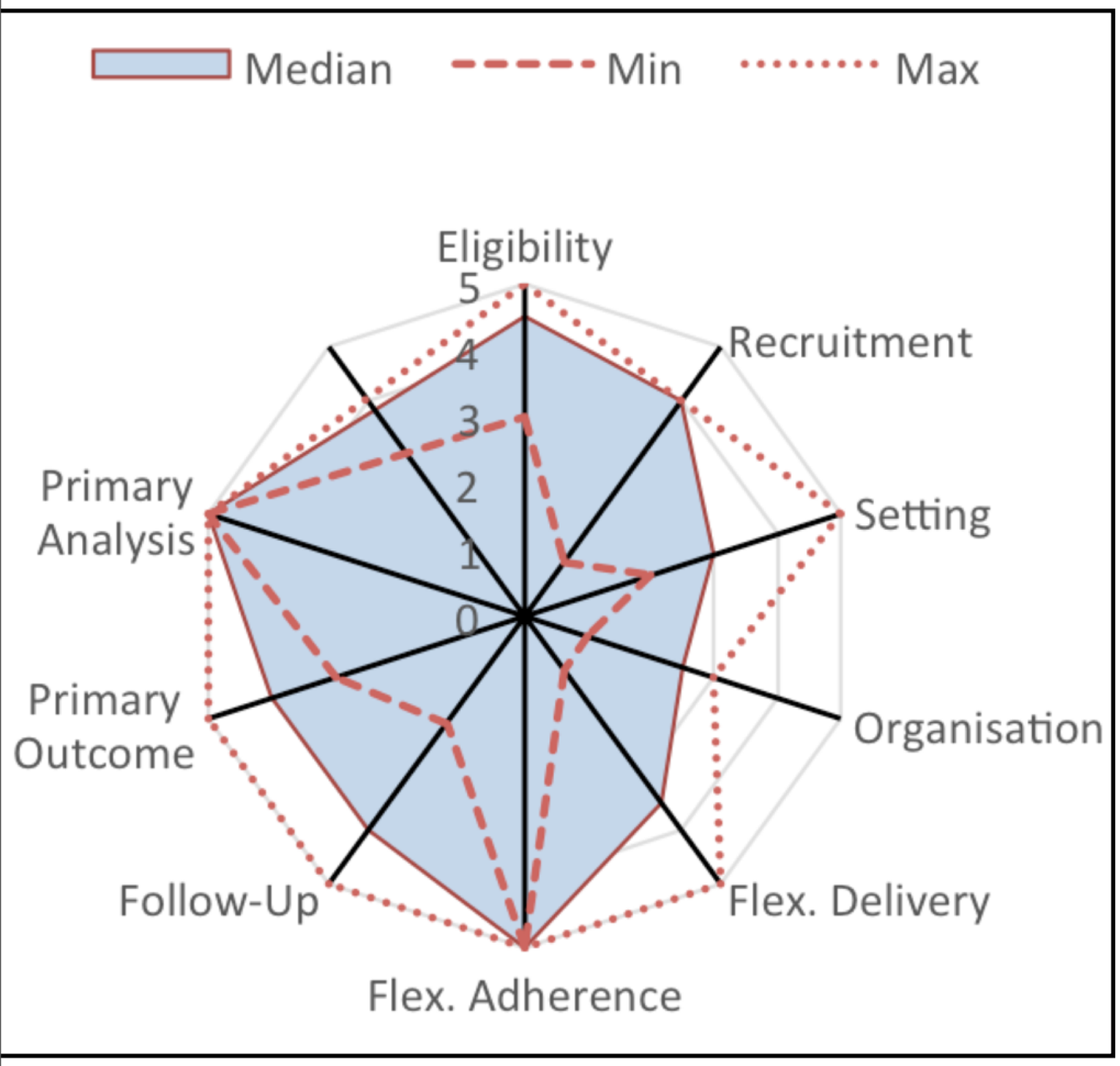

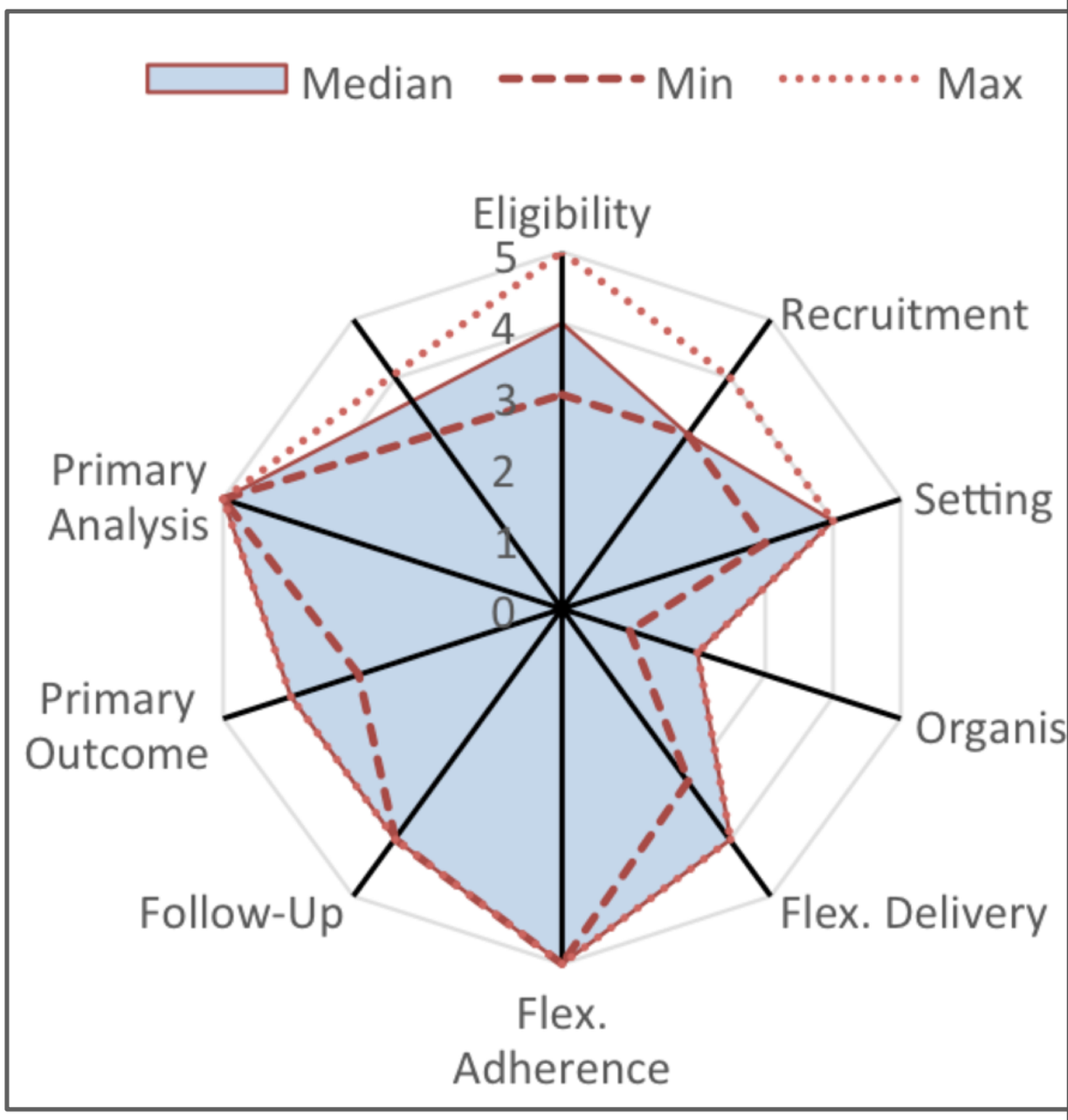

#2– 23 included trials in a Cochrane review

Carter [4] **High-dose thiazide**	pragmatic	Total mortality:0.58 (0.33-1.01)	Unclear	Thiazide, 76%, Methyldopa (0.75-2 g), bethanidine or debrisoquine	Stroke, mortality, CHD, CHF	
Dutch TIA [5] **Beta blocker**	pragmatic	Total mortality 1.12 (0.79-1.57)	Low	Atenolol 50 mg daily Identical placebo tablet	Mortality, CHD, stroke, total CV events,	
EWPHBPE [6, 7]	explanatory	Total mortality 0.92 (0.76-1.12)	Low	HCTZ/triamterene, 25/50 mg. 1 to 2 tabs, methyldopa 0.5-2 g.	Mortality, stroke, CHD, CHF, systolic BP and diastolic BP	
HOPE HYP[8] **ACE inhibitors**	explanatory	Total mortality 0.79 (0.67-0.93)	Low	Ramipril 2.5 mg titrating up to 10 mg or placebo. Other factor was Vitamin E 400 IU/day.	Primary: composite of myocardial infarction, stroke, or cardiovascular death (total CV events). Total mortality, total stroke, total CHD.	
HSCSG[9] **High-dose thiazide**	explanatory	Total mortality: 1.01 (0.6-1.72)	Low	Deserpidine 1 mg plus methyclothiazide 10 mg.	Mortality, stroke, CHD, CHF, systolic BP and diastolic BP	
HYVET[10] **Low-dose thiazide**	explanatory	Total mortality 0.82 (0.69-0.99)	Low	Step 1 indapamide 1.5 mg daily. Step 2 perindopril 2 mg daily.	Total stroke, total coronary artery disease, total mortality, total cardiovascular events	

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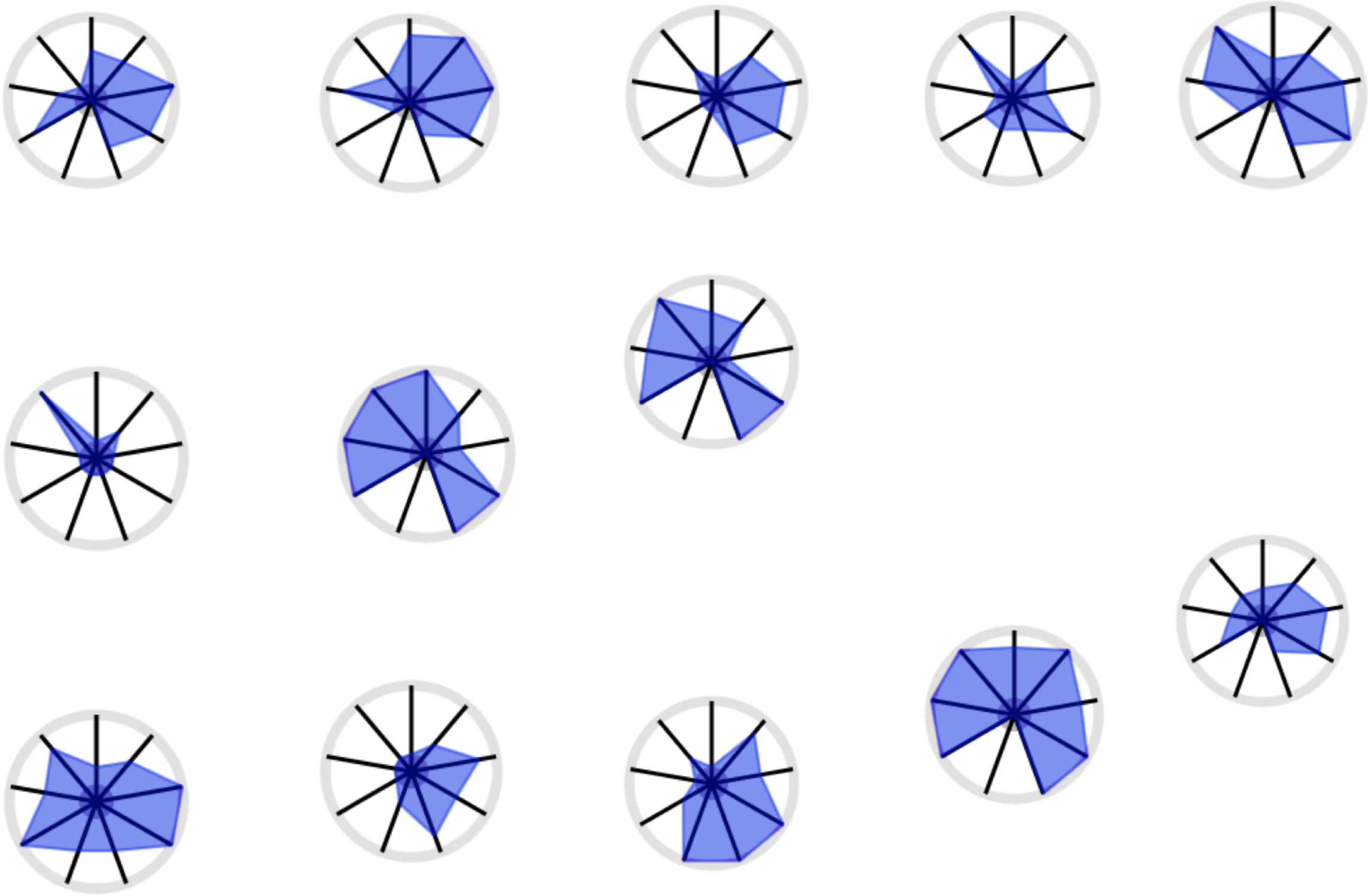

#3– Internal vs external validity

	Risk of bias		
	High risk	Low risk	Unclear risk
Explanatory trials n = 19			
Pragmatic trials n = 22			
Neither one nor the other n = 8			

#3– Internal vs external validity

	Risk of bias		
	High risk	Low risk	Unclear risk
Explanatory trials n = 19	1 (5%)	10 (53%)	8 (42%)
Pragmatic trials n = 22	2 (9%)	13 (59%)	7 (32%)
Neither one nor the other n = 8	2 (25%)	4 (50%)	2 (25%)

Future developments

- **Nothing for a while..**
- **It would be good to catalog the sorts of changes that using the tool leads to.**
- **How can the tool be used in funding decisions?**
- **How can the tool be used in systematic reviews?**
- **Could the PRECIS-2 'format' have a role in intervention development?**

Summary

- **Poor design decisions can render a trial irrelevant**
- **Some decisions are made almost accidentally**
- **We think PRECIS-2 can help improve how design decisions are made (and perhaps funding decisions too)**
- **Have a look at www.PRECIS-2.org**

Thank you!

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http://trialforge.org

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