Trial Forge, PRECIS-2 and how to design an efficient trial

Shaun Treweek

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University of Aberdeen

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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 Failure Review 2014; 19:135-52.

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 is an efficient trial?

- **Scientific efficiency: right question, right design**
- **Process efficiency: do what is needed to answer question, keeps focused, results made public in a way people can understand**

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

Choosing the right research question

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]

[1]Department of Radiology, Geneva University Hospitals, 4 rue Gabrielle-Perret-Gentil, CH-1211 Geneva 14, Switzerland; [2]Division of Anaesthesiology, Geneva University Hospitals, Geneva, Switzerland; [3]Faculty of Medicine, University of Geneva, Geneva, Switzerland; [4]Department of Anaesthesiology and Intensive Care, University Hospital Münster, Münster, Germany; [5]Institute of Global Health, Faculty of Medicine, University of Geneva, Geneva, Switzerland

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 research question

thebmj

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

RESEARCH

Number of clinically irrelevant trials:

87 of 136 (64%)

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Process: what helps recruitment?

Strategies to improve recruitment to randomised controlled trials (Review)

Treweek S, Mitchell E, Pitkethly M, Cook J, Kjeldstrøm M, Johansen M, Taskila TK, Sullivan F, Wilson S, Jackson C, Jones R, Lockhart P

THE COCHRANE COLLABORATION®

Process: what helps recruitment?

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Process: what helps recruitment?

We're almost done with the update of this review. We now have 66 included studies and we've sharpened up how we present the results.

GRADE **High**

GRADE **Moderate**

Process: what helps recruitment?

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GRADE **High**

GRADE **Moderate**

Process: what helps recruitment?

We're almost done with the update of this review. We now have 66 included studies and we've sharpened up how we present the results.

GRADE **High** — 2 things

GRADE **Moderate** — 8 things

Process: what helps recruitment?

[Both GRADE High; caveat: statistician hasn't signed off these numbers..]

1. An open design compared to a blinded, placebo-controlled design increases recruitment: RD = 10% (95% CI 7% to 13%)

[two studies: both 2004]

2. Using a telephone reminder to contact non-responders to a postal invitation increases recruitment. RD = 6% (95% CI 3% to 9%)

[two studies: 2004 & 2013]

The cost of poor recruitment

The Prevalence and Economic Impact of Low-Enrolling Clinical Studies at an Academic Medical Center

Darlene R. Kitterman, MBA, Steven K. Cheng, PhD, David M. Dilts, PhD, MBA, and Eric S. Orwoll, MD

Abstract

Purpose
The authors assessed the prevalence and associated economic impact of low-enrolling clinical studies at a single academic medical center.

Method
The authors examined all clinical studies receiving institutional review board (IRB) review between FY2006 and FY2009 at Oregon Health & Science University (OHSU) for recruitment performance and analyzed them by type of IRB review (full-board, exempt, expedited), funding mechanism, and academic unit. A low-enrolling study included those with zero or one participant at the time of study termination. The authors calculated the costs associated with IRB review, financial setup, contract negotiation, and department study start-up activities and the total economic impact on OHSU of low-enrolling studies for FY2009.

Results
A total of 837 clinical studies were terminated during the study period, 260 (31.1%) of which were low-enrolling. A greater proportion of low-enrolling studies were government funded than industry funded ($P = .006$). The authors found significant differences among the various academic units with respect to percentages of low-enrolling studies (from 10% to 67%). The uncompensated economic impact of low-enrolling studies was conservatively estimated to be nearly $1 million for FY2009.

Conclusions
A substantial proportion of clinical studies incurred high institutional and departmental expense but resulted in little scientific benefit. Although a certain percentage of low-enrolling studies can be expected in any research organization, the overall number of such studies must be managed to reduce the aggregate costs of conducting research and to maximize research opportunities. Effective, proactive interventions are needed to address the prevalence and impact of low enrollment.

Editor's Note: A commentary on this article appears on page 1334.

Academic medical centers (AMCs), or institutions with the core mission of conducting clinical research, play a vital

communities.[1] One critical role of an AMC is to conduct research that advances basic scientific observations to applications in medical practice. The National Institutes of Health (NIH) has made translational research a priority, in

recruited less than 75% of their planned enrollment goals.[4] A sampling of 13 studies sponsored by the National Heart, Lung, and Blood Institute found that planned enrollment was completed for only two of the studies (15.4%),[5] and

Academic Medicine, Vol. 86, No. 11 / November 2011

The cost of poor recruitment

Institutional Issues

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Cost of 260 studies with zero or 1 participant at trial termination in 2011: almost $1 million

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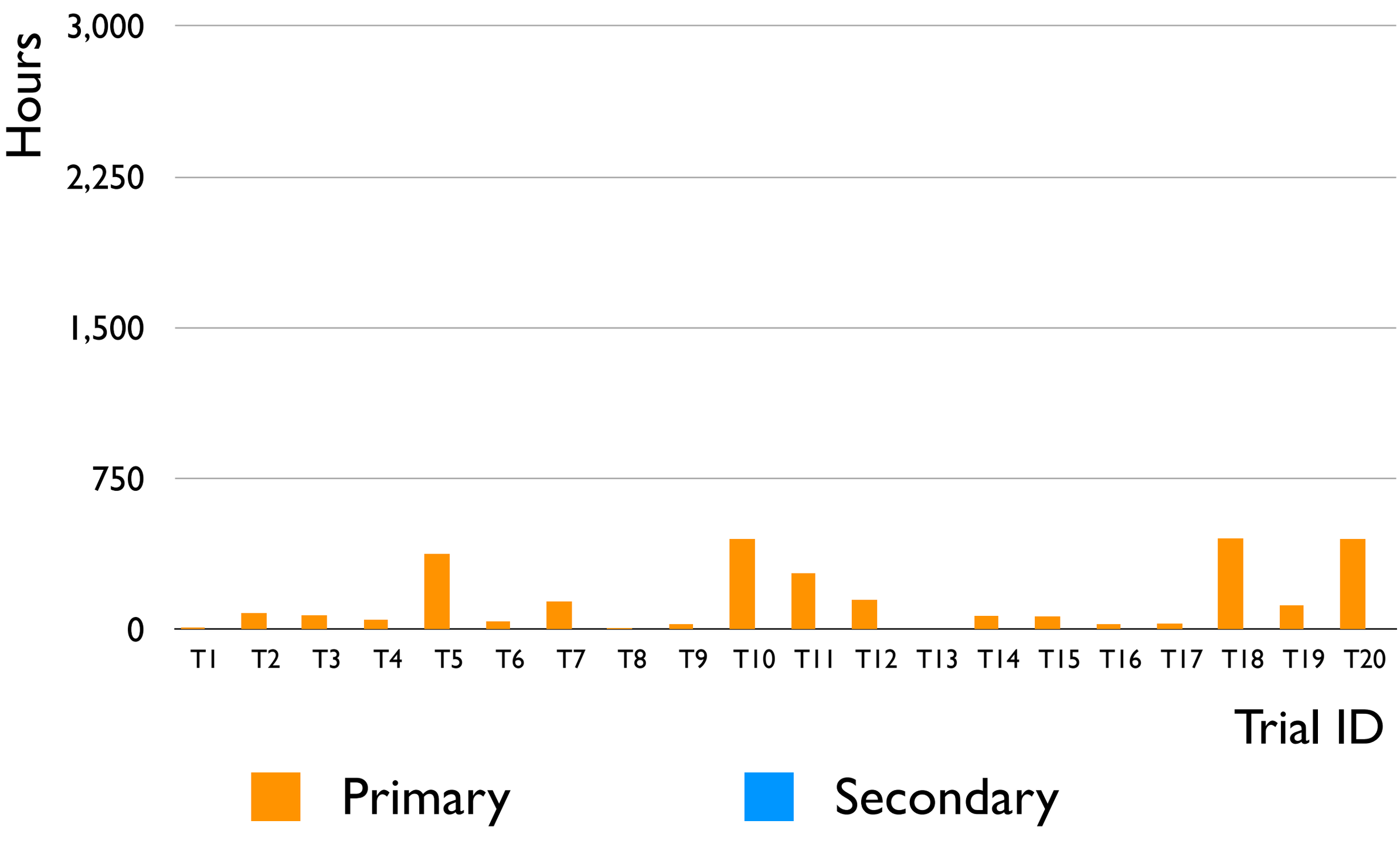
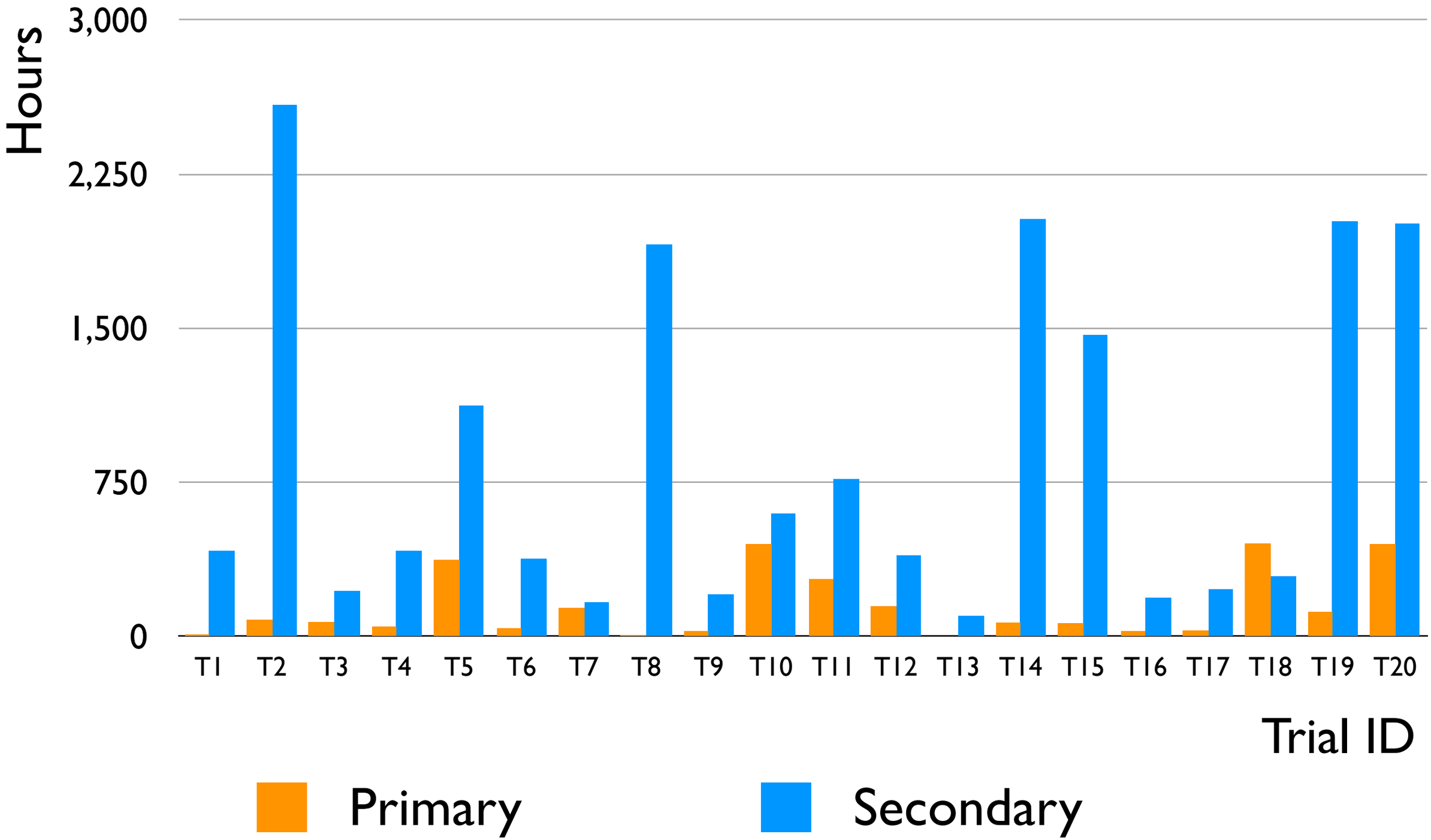
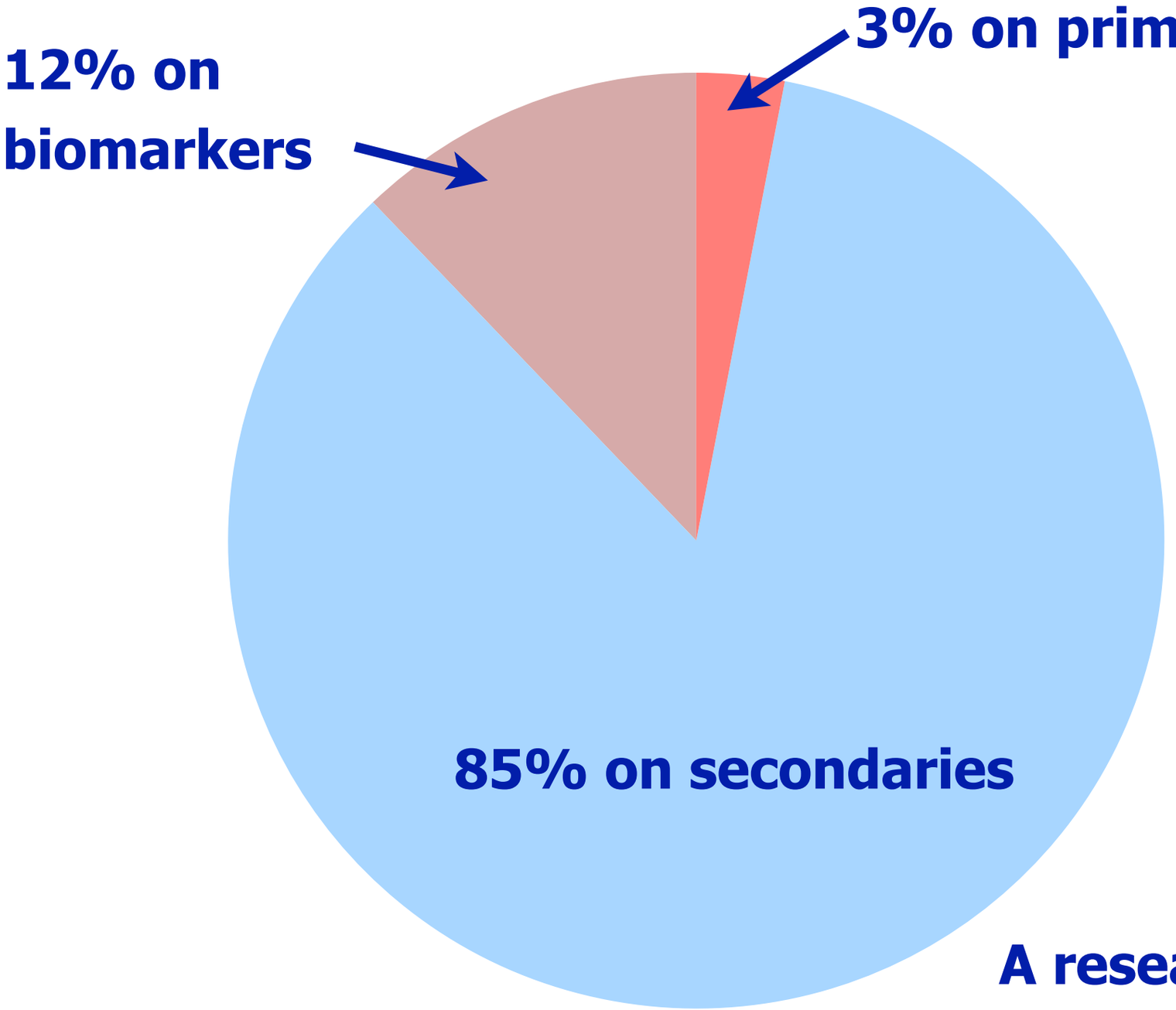
Process: outcomes for 20 trials..



..and now with secondary outcomes



Trial T2: data collection



Primary = £2,106

Biomarker = £8,424

Secondaries = £58,890

Total = £69,420

A research nurse in Grampian costs around £26 per hour

The cost of extra outcome data

American Journal of Therapeutics 22, 117–124 (2015)

Quantifying the Magnitude and Cost of Collecting Extraneous Protocol Data

Kenneth A. Getz, MBA,[1]* Stella Stergiopoulos, BA,[1] Michelle Marlborough, BS,[2]
Jane Whitehill, BS,[3] Marla Curran, PhD,[4] and Kenneth I. Kaitin, PhD[1]

Although most research professionals believe that protocol designs contain a growing number of unnecessary and redundant procedures generating unused data, incurring high cost, and jeopardizing study success, there are no published studies systematically examining this issue. Between November 2011 and May 2012, Tufts Center for the Study of Drug Development conducted a study among a working group of 15 pharmaceutical companies in which a total of 25,103 individual protocol procedures were evaluated and classified using clinical study reports and analysis plans. The results show that the typical later-stage protocol had an average of 7 objectives and 13 end points of which 53.8% are supplementary. One (24.7%) of every 4 procedures performed per phase-III protocol and 17.7% of all phase-II procedures per protocol were classified as "Noncore" in that they supported supplemental secondary, tertiary, and exploratory end points. For phase-III protocols, 23.6% of all procedures supported regulatory compliance requirements and 15.9% supported those for phase-II protocols. The study also found that on average, $1.7 million (18.5% of the total) is spent in direct costs to administer Noncore procedures per phase-III protocol and $0.3 million (13.1% of the total) in direct costs are spent on Noncore procedures for each phase-II protocol. Based on the results of this study, the total direct cost to perform Noncore procedures for all active annual phase-II and phase-III protocols is conservatively estimated at $3.7 billion annually, not including the indirect costs associated with collecting and managing Noncore procedure data and the ethical costs of exposing study volunteers to unnecessary risks associated with conducting extraneous procedures.

Keywords: protocol design, protocol complexity, clinical data, excessive clinical data, extraneous clinical data

American Journal of Therapeutics, Vol. 22, 2015

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In pharma trials more than 20% of procedures are 'non-core'. Estimated annual cost: $3.7 billion

American Journal of Therapeutics, Vol. 22, 2015

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?

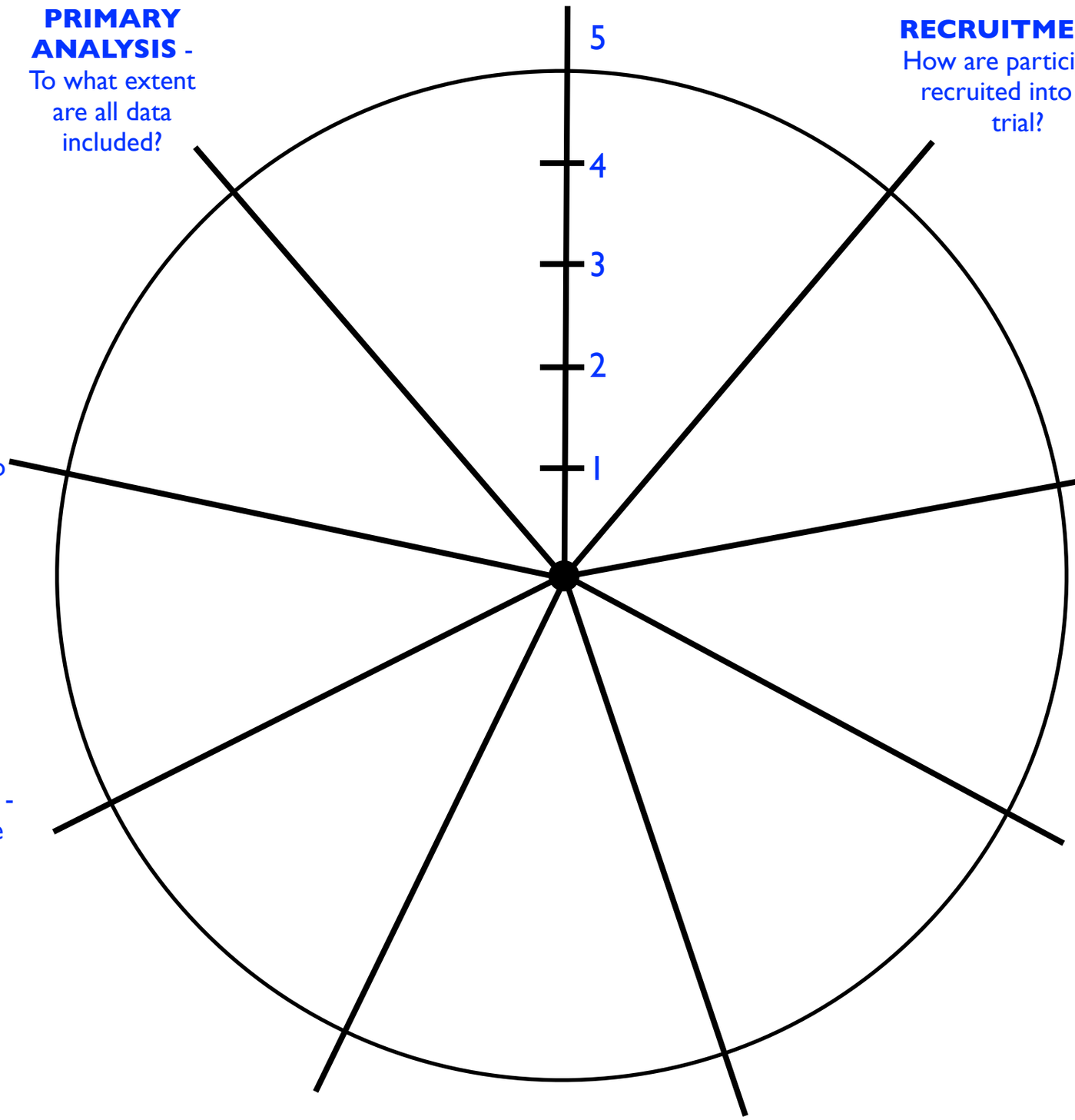
FLEXIBILITY: DELIVERY -
How should the intervention be delivered?

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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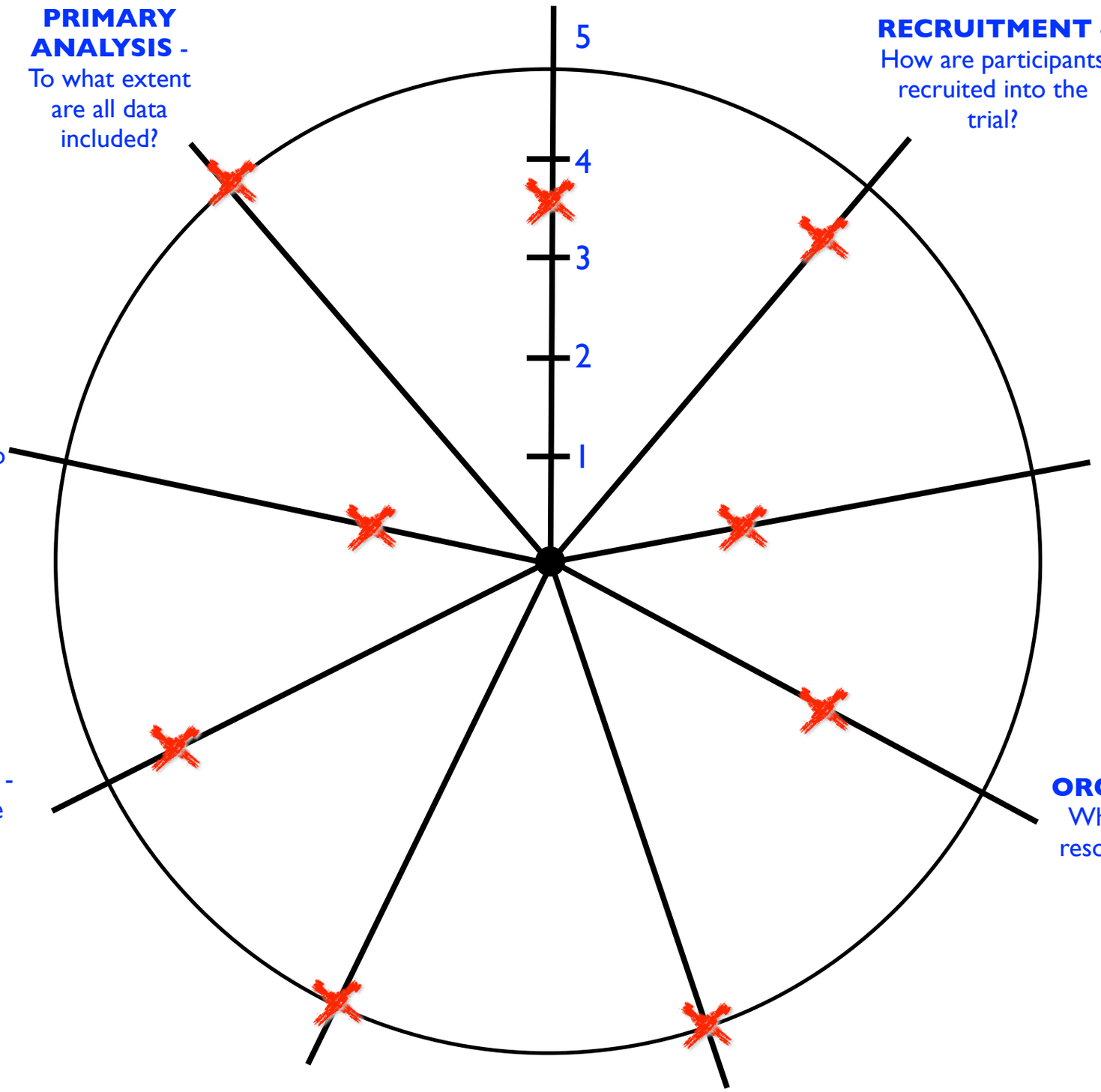

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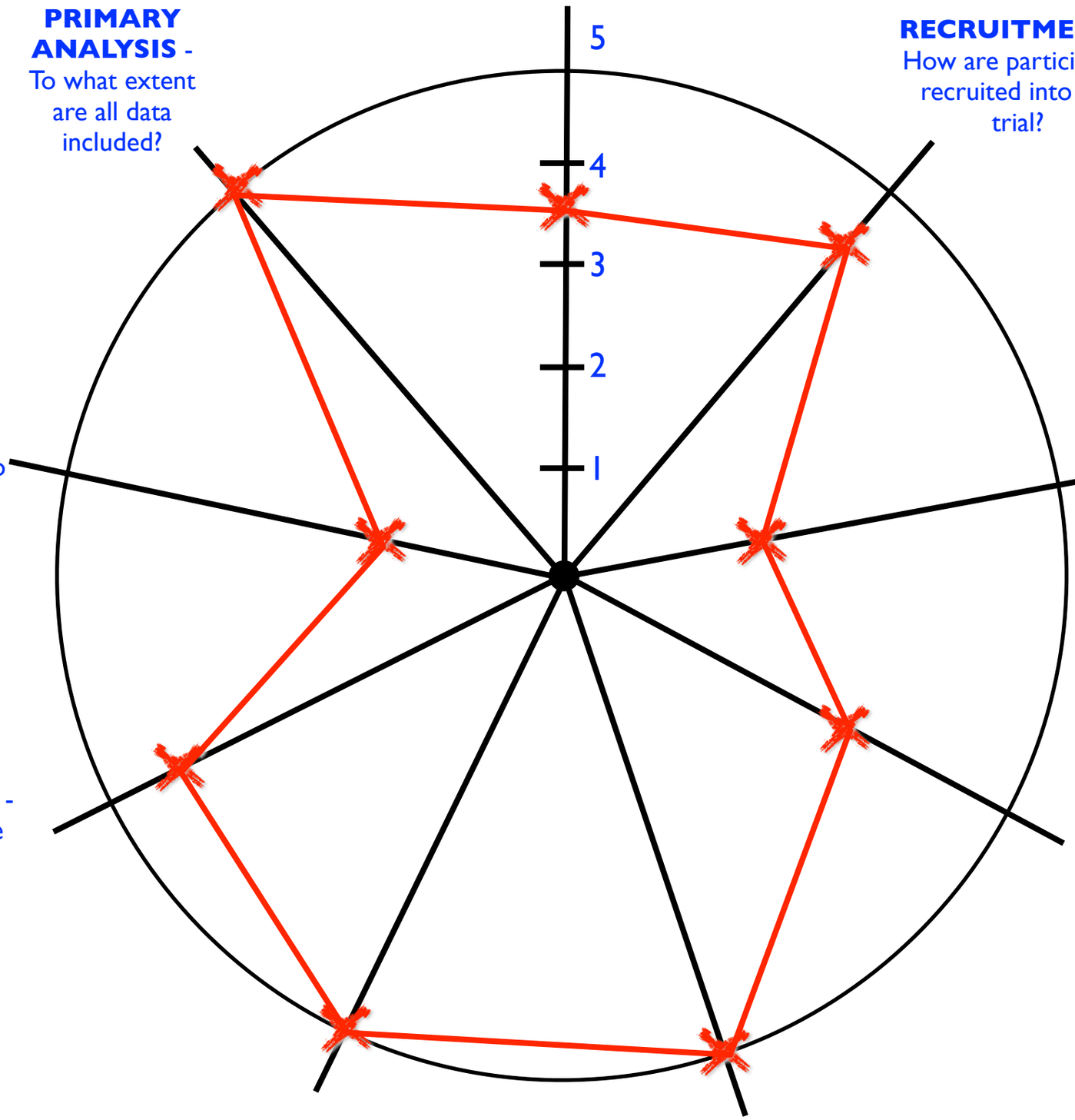

TRIAL FORGE


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HOME
ABOUT
WHATS NEW
COLLABORATORS
GET INVOLVED
PATHWAY
OBTAIN FUNDING
LOGISTICAL PLANNING FOR TRIAL DELIVERY
DATA MANAGEMENT
WRITING AND PUBLISHING THE TRIAL PROTOCOL
TRAINING TRIAL STAFF
MOTIVATING TRIAL STAFF
IDENTIFYING TRIAL SITES
CHOOSING THE RESEARCH QUESTION
CHOOSING THE RIGHT DESIGN
FEASIBILITY AND PLOT WORK
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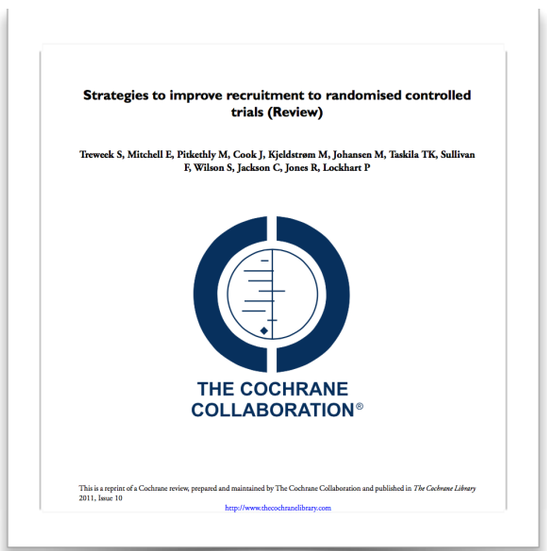
MANAGING AND MONITORING TRIAL SITES
RECRUITMENT
DATA COLLECTION
RETENTION
ANALYSIS
DISSEMINATION OF FINDINGS
CLOSE DOWN

Trial Forge: the big recruitment reviews

Barriers & facilitators

Catherine Houghton, Galway

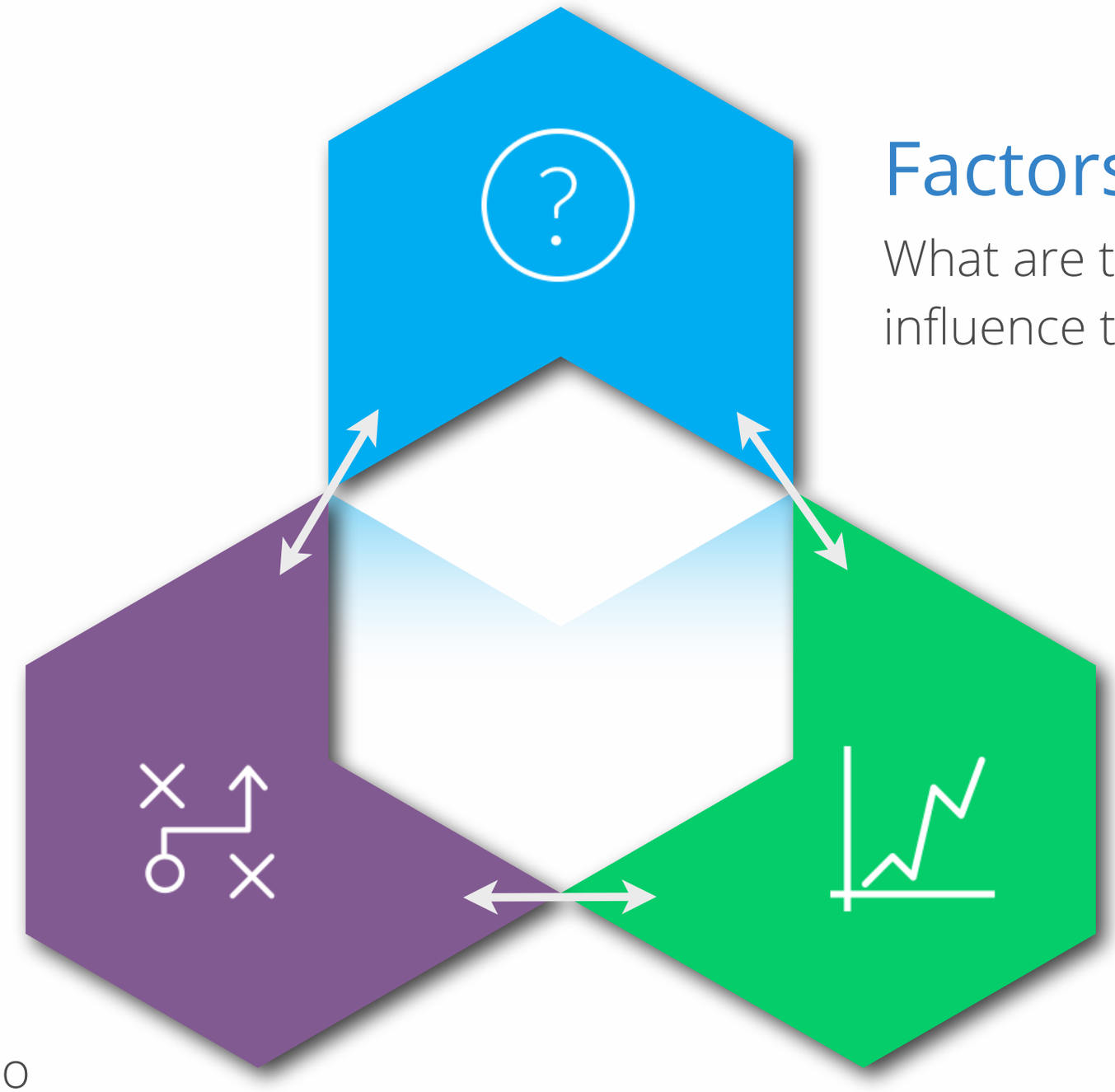
Randomised evaluations



Non-randomised evaluations

Heidi Gardner, Aberdeen

TRINITY packages: recruitment



Factors

What are the factors that influence the process?

Non-randomised evaluations

Non-randomised evaluations of initiatives that aim to improve the process.

Randomised evaluations

Randomised evaluations of initiatives that aim to improve the process.

Filling evidence gaps: SWAT 24

Using a theory-based cover letter to improve questionnaire response rates in trials

Craig Ramsay, Anne Duncan, Aberdeen; Jan Clarkson, Debbie Bonetti, Dundee

Dear <<Title>> <<Family Name>>

Please find enclosed the annual *[Trial Name]* questionnaire and a reply-paid envelope. It would be greatly appreciated if you could complete and return as soon as possible. If you have any questions, please get in touch with the *[Trial Contact Office]* on *[Trial Contact Phone Number]*.

Why we have sent <u>you</u> this questionnaire

Your *[e.g. dentist]* is participating in this UK-wide study looking at the very best way they can help their patients improve their *[e.g. oral health]*. This is an important study with the potential to impact on the treatment of all *[e.g. dental]* patients, and involves academic and research groups from *[Trial Centres e.g. Aberdeen, Dundee, Edinburgh, Newcastle, Manchester and London Universities]*.

This is a *[e.g. 3]* year study, as it will take this long to collect meaningful information about how *[e.g. oral health treatments]* can affect *[e.g. a person's quality of life, general health and teeth]*. Such long-term studies require a strong commitment from your *[e.g. dentist]* to stay in the study until the end. This means your *[e.g. dentist]* has placed considerable trust in the patients they asked to join them in this research. Your *[e.g. dentist]* will not be able to fulfil their part in this study without the continued co-operation and participation of their patients.

As one of these patients, you consented to complete this annual questionnaire at the start of the study, asking about *[e.g. a wide range of actions and beliefs]*. This is to provide a broad view of the

SWAT 24: who wants to get involved?

CTEU Bristol

Clinical Trials and Evaluation Unit Bristol

PCTU

MANCHESTER 1824
The University of Manchester

CHaRT
Centre for Healthcare Randomised Trials

NOTTINGHAM CLINICAL TRIALS UNIT

tctu
TAYSIDE CLINICAL TRIALS UNIT

NHS
National Institute for Health Research
Oxford Biomedical Research Centre
Enabling translational research through partnership

Y T U
York Trials Unit

Health Research Board
TMRN
Trials Methodology Research Network

nmahp-ru
Nursing, Midwifery and Allied Health Professions Research Unit
Improving health through research
Chief Scientist Office

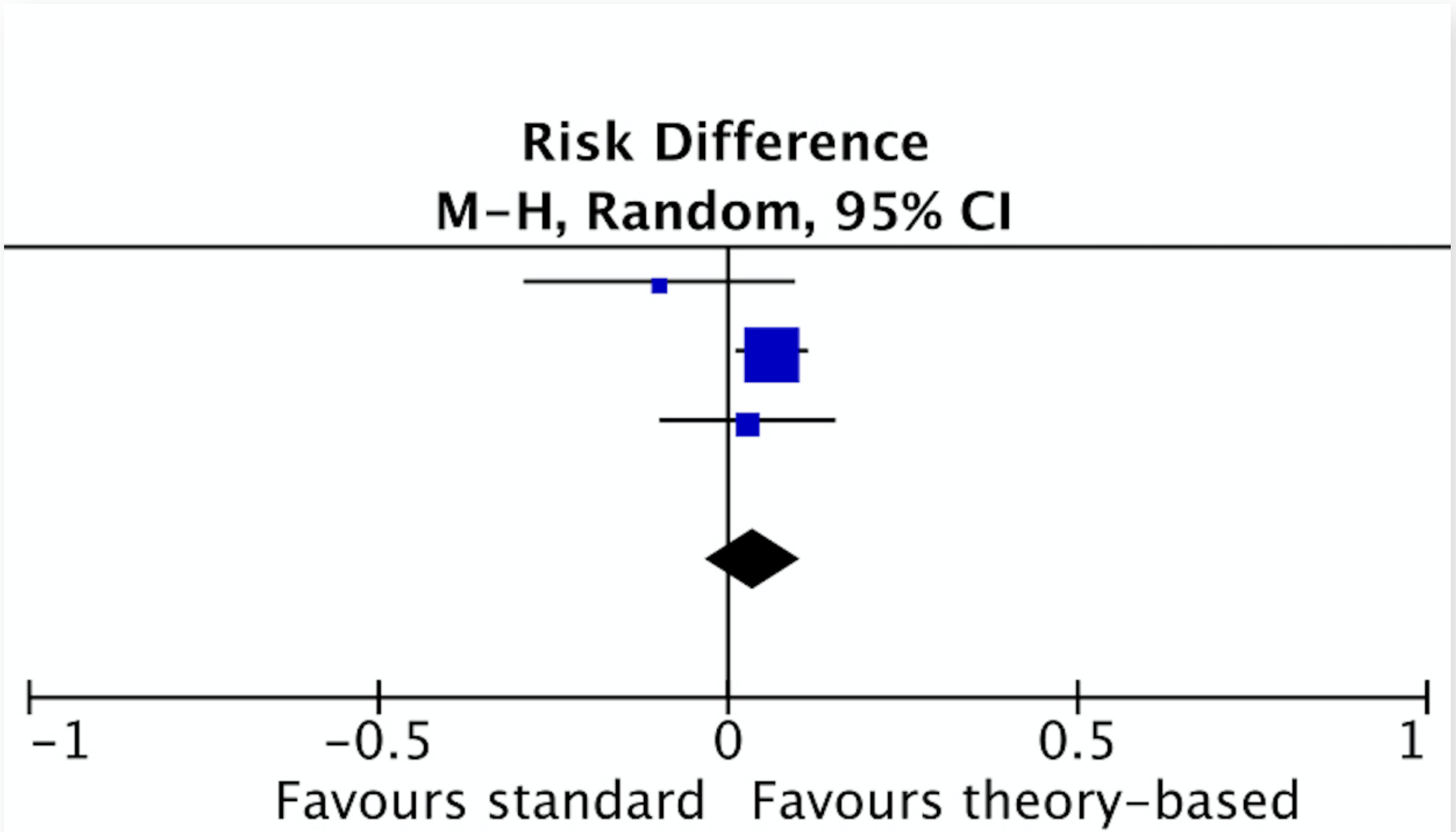
SOUTHAMPTON CLINICAL TRIALS UNIT

VUmc
VU University Medical Center Amsterdam

Four trials (at least) have now looked at SWAT24

- Two dental trials (2014 and 2016)
- A trial in MS (2017)
- A trial in urinary incontinence (2017)

Four trials (at least) have now looked at SWAT24

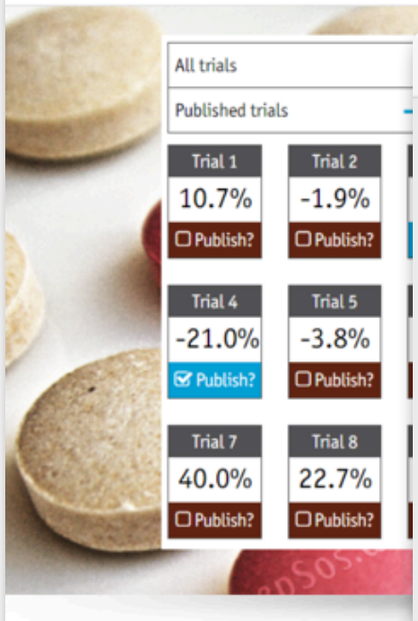


alltrials.net

Español

+AllTrials

Home Find out more Get involved



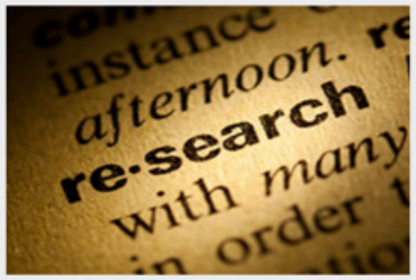
moretrials.net

MoreTrials
to do more trials better

thelancet.com

REWARD

Priorities | Design conduct analysis | Regulation & management | Accessibility | Complete & usable reporting | Action & recommendations | Statement



The *Lancet* REWARD (REduce research Waste And Reward Diligence) Campaign invites everyone involved in biomedical research to critically examine the way they work to reduce waste and maximise efficiency.
Read the REWARD statement and join the campaign

Updates

REWARD Alliance Update April 2016, by Professor Paul Glasziou

The 2015 REWARD/EQUATOR conference in Edinburgh abstracts are downloadable at http://rewardalliance.net/research-wasteequator-conference/. The first video in a series from the conference is an 8-minute video providing a great overview of the main issues of research waste: https://youtu.be/K0wyc5w6bQE. Several other short videos from the conference on different themes are in preparation and will be available in the next few weeks. Please watch, enjoy and tweet.

More…

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Increasing value and reducing waste in biomedical research: librarians are listening and are part of the answer

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University of Oxford
Athena SWAN Bronze Award

BioMed Central
The Open Access Publisher

NHS
Health Research Authority

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equator network

SPIRIT
Standard Protocol Items: Recommendations for Interventional Trials

AWMF

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TRIALFORGE

CEBM

University of Oxford

Wessex Institute
University of Southampton

European

Summary

- **Much of the business of doing trials is not very efficient.**
- **Trial Forge aims to improve this through more coordination and collaboration.**
- **Join up – go to ‘Get involved’ on Trial Forge website**

Thank you!

TRIAL FORGE

Twitter: @Trial_Forge

http://trialforge.org

UNIVERSITY OF ABERDEEN

HEALTH SERVICES RESEARCH UNIT

HSRU is funded by the Chief Scientist Office of the Scottish Government Health and Social Care Directorates. The author accepts full responsibility for this talk.