TMRP PhD Student Cohort

Rapid-fire two minute presentations

Afternoon Session

OPTIMISING THE IMPLEMENTATION OF A COMPLEX INTERVENTION WITHIN A TRIAL INVOLVING OLDER PEOPLE

Sadia Ahmed

University of Leeds

A Systematic Methods Overview → **Mixed methods SWAT** → **Review**

STUDY WITHIN A TRIAL

Mixed methods SWAT - nested RCT & qualitative interview study

ENGAGEMENT

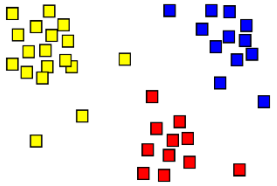
Trial Case Report Forms

Interviews

A unified approach for the statistical analysis of post-randomisation variables in Clinical Trials

Anca Chis Ster, KCL

Clustering effects | **Non-compliance** | **Mediation** | **Missing data**



Challenges in analysing post-randomisation variables

In Clinical Trials, we aim to estimate valid treatment effects defined by some estimand. For example, the ITT effect will provide unbiased estimates in trials with complete compliance with medication. However, in real data, we are faced with a number of challenges, including non-compliance, mediation, missing data and clustering effects. If unaddressed, these issues will compromise the validity of the treatment effect estimates. Although these issues often occur simultaneously, they are currently considered separately and there is little overlap on how to approach these issues at once.

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Behavioral approaches to recruitment and retention in clinical trials

Taylor Coffey, MS

Health Services Research Unit

TMRP Annual Meeting 2020

My project

What

- Clinical trials are at the core of evidence-based medicine
- Recruitment and retention (completion of study data) have been identified as major impediments to scientifically rigorous trials when goals are not met
- Recruitment and retention involve a number of behaviours, such as returning a survey, and so can be examined through the lens of behavioural science

Why

- Major consequences of inadequate recruitment or retention are:
  - Financial
  - Ethical
  - Scientific
- Framing recruitment and retention as behaviours to change, we can systematically identify issues and develop interventions in a way that is rigorous and reproducible

How

- A systematic mapping review will allow a narrative synthesis of the current application of behavioural theories to aspects of recruitment and retention
- Qualitative interviews with clinical trial recruiters embedded in an ongoing trial along with analysis of recruitment discussions and documents
- An intervention will be developed based on the results of these interviews and analysis

The cost effectiveness of Studies Within A Trial (SWATs) for improving recruitment and retention in RCTs

Nassos Gkekas, PhD Health Sciences, University of York

- Recruitment and retention is a major challenge in RCTs
- Poor recruitment leads to underpowered trials and poor retention can lead to biased trials
- There are huge direct economic costs arising from poor recruitment and retention.
- A study within a trial (SWAT) is an evidenced based approach to evaluating techniques to improve recruitment and reduce attrition.

PhD Plan

- SWATs usually do not have an economic framework.
- This PhD aims to clarify the ways through which economic evaluations of SWATs could be conducted, mainly on the basis of cost-effectiveness/cost-utility analysis.
- Plan of the first year of the PhD:

1. Systematic Review of existing economic evaluations in SWATs
2. Computation of incremental costs and net QALYs gained had the recruitment rate in the RECOVERY trial been higher

A discrete choice experiment for measuring public opinion of genetic testing

Danielle Johnson, University of Liverpool

Scenarios

	Option A	Option B
Cost	£20	£100
Time taken	1 month	1 week
Type of sample	Urine sample	Biopsy

Attributes

Levels

Qualitative work

Focus group priorities

HCP priorities

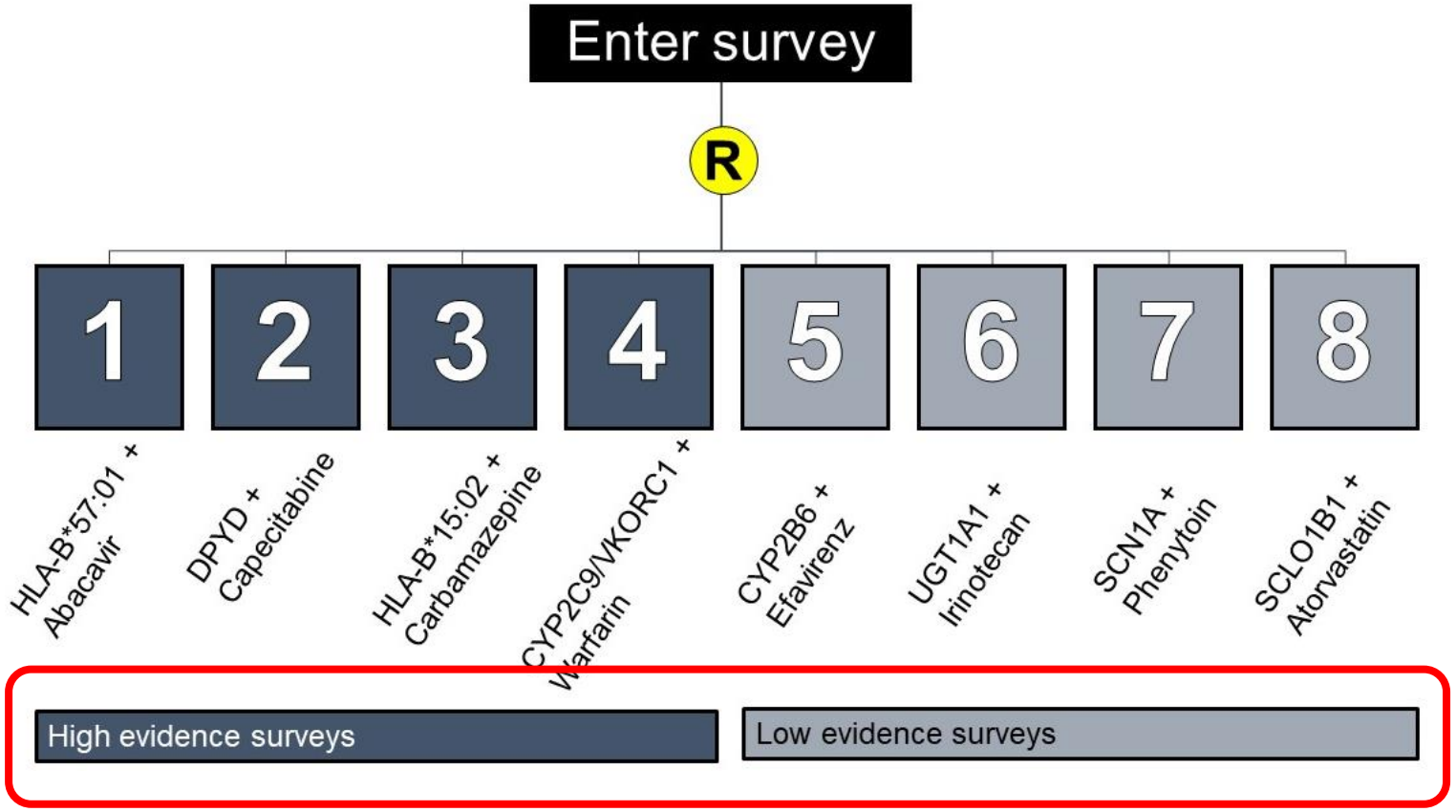
PPV, NPV, etc, are of little value if the evidence is poor

Levels of evidence required will be different in each scenario but robust independently verified evidence is key to ensure starting point for robust implementation

Final DCE plan

Attributes will be:

- Cost of the test to the NHS
- Use of your data for further research
- Number of drugs the test can be used to inform
- Chance of serious side-effect from the drug treatment



Acknowledgements

Thanks to Professor Sir Munir Pirmohamed for advice.
Thanks to Emily Holmes for DCE design advice.
And also to my supervisors, Professors Andrea Jorgensen and Dyfrig Hughes

Involvement of participants from LMICs in COS development

Jamlick Karumbi – University of Liverpool

Development and use of Core Outcome Set (COS) could ensure all future research in a field reports a common subset of outcomes and reduces research waste by enhancing comparability thereby improving research translation and use. COS are agreed-on minimum standardized outcome sets that should be measured and reported in all research in a given health area. Most COS have been developed from the perspectives of high-income countries.

To describe the differences in COS with LMIC participants compared HIC participants

Data were extracted from COS study. Comparisons are made on the scope of the study, participant characteristics and methods used in COS development

- Only **20%** of published COS involved LMIC Participants
- **53%** COS with LMIC participants developed in last 5 years
- 83% of COS with LMIC were specifically for COS as opposed to as part of wider trial design
- More of LMIC participants were likely to be clinical experts compared to HIC participants
- LMIC participants were more likely to be from Brazil, China and South Africa
- Across the two settings a mixture of methods were used often being literature review, Delphi and Semi structured discussions.

Centre for Trials Research

Canolfan Ymchwil Treialon

Project title: The use of modern modelling methods for the statistical analysis of microbiological data in clinical trials of antimicrobial stewardship interventions

Research gaps:

- The current statistical methods for analysis the microbiological data are too simplistic.
- Several guidance given to report antimicrobial stewardship studies, but no specific recommendations on analysing/reporting microbiological outcomes.

Mandy Lau – 1st year PhD student
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TMRP Annual meeting PhD rapid presentations 17 November 2020

CARDIFF UNIVERSITY
PRIFYSGOL CAERDYDD

Centre for Trials Research
Canolfan Ymchwil Treialon

Research objectives:

1. Review the literatures to see what existing statistical methods are used to analyse and report microbiological findings in antimicrobial stewardship (AMS) studies.
2. Methodological literature review to investigate statistical approaches for modelling the treatment effects on high-dimensional data (e.g. Factor analysis, machine learning)
3. Convene a stakeholder group to gain consensus on important hypotheses and consensus on the gaps in the representation of microbiology findings in AMS interventions, and potential statistical approaches.
4. Apply analytical methods which can maximise the information contained within microbiological datasets in order to address key hypotheses agreed during the stakeholder group.
    - What is a person's microbiological "profile"?
    - How does a person's microbiological "profile" change over time?
    - How does an intervention work in changing a person's microbiological "profile"?

The Maintenance of Trials Methodology Research Document Databases Using Machine Learning

Iqra Muhammad[1], Frans Coenen[1], Paula Williamson[2] , Carrol Gamble[2] and Anna Kearney[2]

1. Department of Computer Science, University of Liverpool

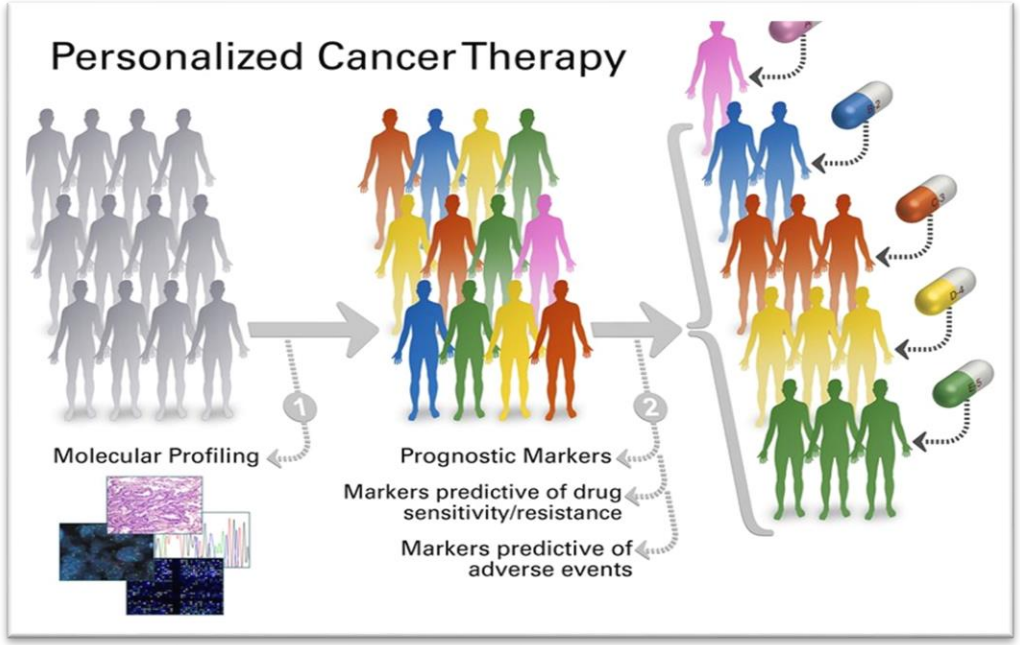
2. Department of Biostatistics, University of Liverpool

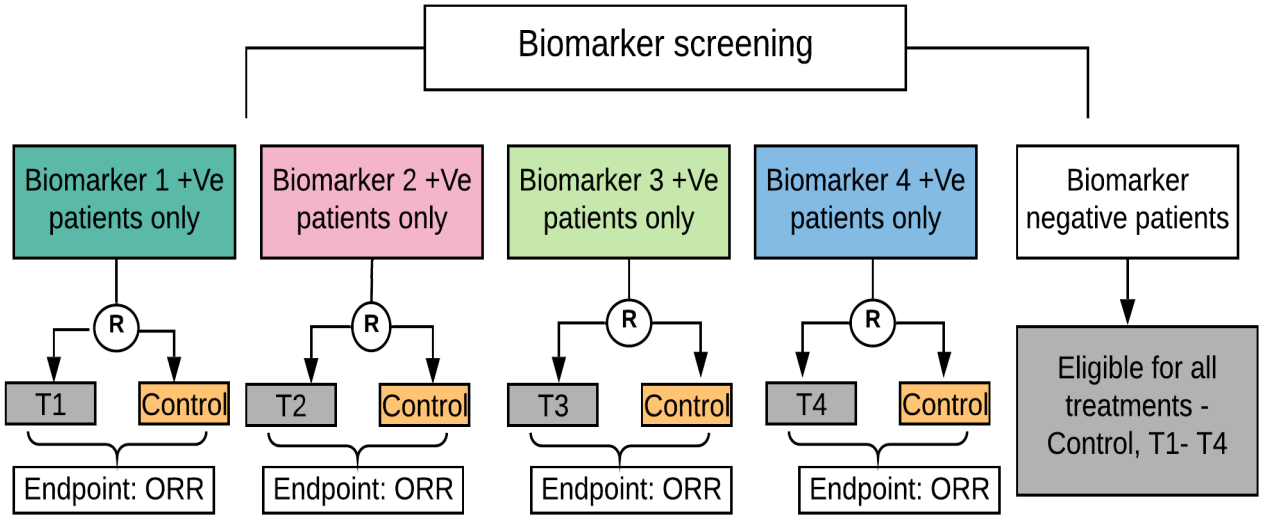
Application of machine learning to the maintenance of curated databases

- Curated databases play a critical role in helping researchers find relevant articles in the available literature. One such curated database is the ORRCA (Online Resource for Recruitment research in Clinical trials) document collection.

- Machine learning techniques can help to automate the update process and reduce the workload needed for screening articles for inclusion.

Treatment allocation strategies for umbrella trials in the presence of multiple biomarkers: A comparison of methods





Q: Which subgroups of patients benefit from a given treatment & to what extent?

Methods:

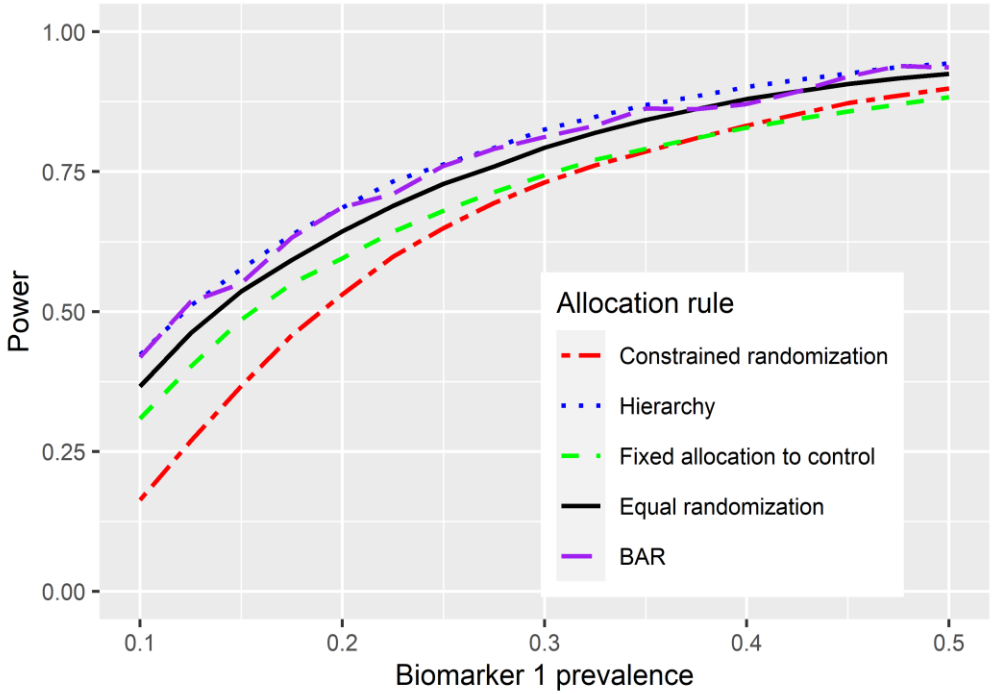
- Equal randomization
- Hierarchy of biomarkers
- RFAC
- Constrained randomization
- Bayesian adaptive randomization

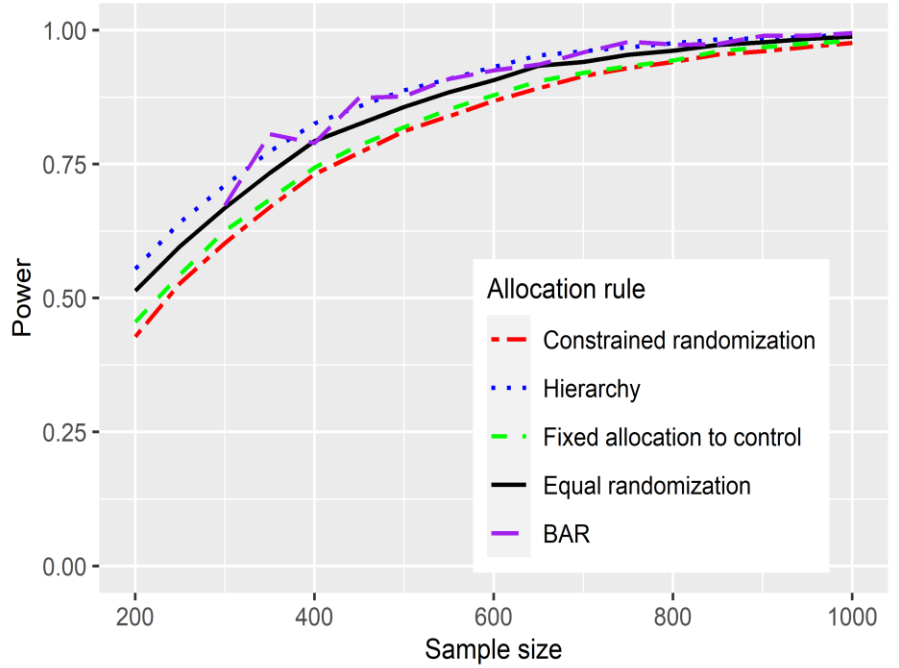
Simulation study – 10,000 sims; Methods evaluated on five operational characteristics

Luke Ouma | Prof. James Wason | Dr. Michael Grayling | Dr. Haiyan Zheng

Average proportion of patients on experimental treatment

		Proportion (Range)
Equal Randomisation		63.9% (52.7 – 72.5)
Randomisation with fixed allocation probability to control	θ = 0.2	80.0% (71.2 – 87.5)
	θ = 0.25	75.0% (66 – 83)
	θ = 0.3	70.0% (60.5 – 78.8)
Hierarchy	ρ = 0.5	64.5% (54.8 – 72.7)
	ρ = 0.75	57.3% (47 – 66.3)
	ρ = 0.9	52.9% (43.7 – 62.5)
Constrained randomisation	ϕ = 0.5	79.0% (72 – 80.5)
	ϕ = 0.75	79.8% (78.8 – 80.2)
	ϕ = 0.9	79.9% (79.3 – 80.2)
BAR		62.6% (54 – 70.3)





- Not all approaches are optimal in all settings:
  - When recruitment to certain treatment(s) is low, CR approach best balances allocation to treatment arms.
  - Hierarchy of biomarkers and BAR have the highest power to detect a linked interaction.
  - When a treatment delivers an unanticipated detrimental effect, BAR allocates highest proportion on the best treatment available to them.
- Approaches should be considered in the context trial sample size, biomarker prevalence, and prevalence of individual overlaps within the patient population.

HETEROGENEITY IN OUTCOME ASSESSMENT FOR INFLAMMATORY BOWEL DISEASE IN ROUTINE CLINICAL PRACTICE

- **Violeta Razanskaite, Clinical Research Fellow**
- Department of Health Data Science, University of Liverpool
- Supervisors: Dr K Bodger Prof P Williamson, Prof B Young

- **MIXED METHODS STUDY IN ENGLISH HOSPITALS:**
  - Observations of real-life clinical consultations (n=102)
  - Interviews with clinicians (n=27)
  - Retrospective analysis of electronic health records (n=909)

Main findings:

- There is substantial clinician variation in capturing clinical outcomes in routine practice in inflammatory bowel disease
- Limited evidence for standardisation

Implications:

- Unwarranted variation may lead to inequalities in care
- Challenges in leveraging clinician-recorded outcomes from routine data sources
- Patient-reported outcomes may be a practical alternative
- Design of clinical trials does not reflect real-world decision-making

Analysis of binary outcomes with covariate adjustment in cluster randomised trials

Jacqueline Thompson
University of Birmingham

Covariate adjustment increases power. Mostly implemented via logistic regression. But:

- Potential for misinterpretation
- Non-collapsibility with covariate adjustment

Complementary estimates of interest:

i. Relative risk
ii. Risk difference
iii. Odds ratio

Methods for estimation:

i. M-H, Indirect method, GLM (Binomial / Modified Poisson)
ii. GLM (Binomial with identity link)
iii. Logistic regression

PLAN

***Step 1 (what's known)*:**
Simulations for RCTs

- RR + covariates = ↑
- RD + covariates = ?
- OR + covariates = ↑

***Step 2 (what's unknown)*:**
Simulation study for cluster RCTs

***Step 3 (recommendations)*:**
How to adjust for covariates with binary outcomes in cluster RCTs

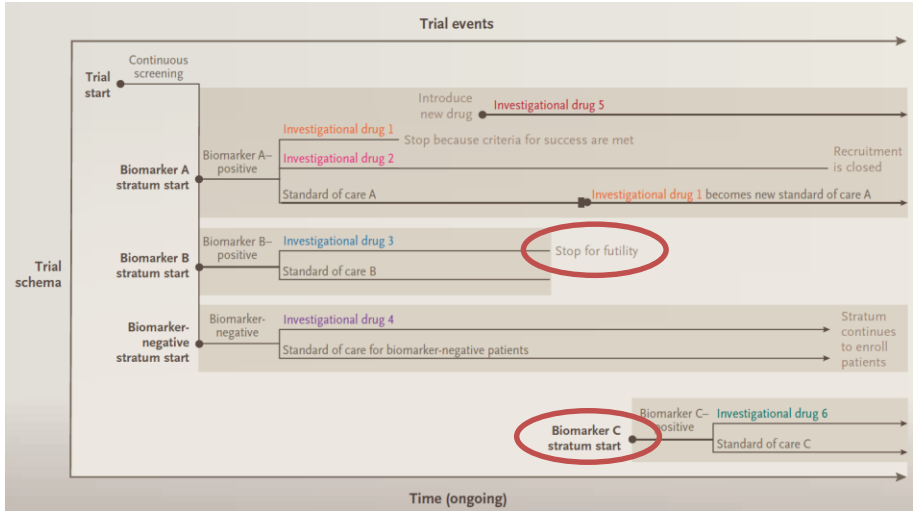
The evolving terminology of master protocols

Randomized controlled trial – designed to test a *single hypothesis in a single disease*

Master protocol trial – designed to test *multiple questions*

Table 1. Types of Master Protocols.

Type of Trial	Objective
Umbrella	To study multiple targeted therapies in the context of a single disease
Basket	To study a single targeted therapy in the context of multiple diseases or disease subtypes
Platform	To study multiple targeted therapies in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm



Attractive features of master protocols

- Reduce sample sizes
- Reduce time
- Increased ability to detect efficacy

STAMPEDE, ongoing (2005) prostate cancer

ISPY-2, ongoing (2010) breast cancer

GBM AGILE, ongoing (2019) glioblastoma

Woodcock and LaVange. *Master Protocol to Study Multiple Therapies, Multiple Diseases, or Both. NEJM 2017.*

The evolving terminology of master protocols

Defining master protocols

Addressing issues in design and conduct

→ **No consensus!**

*How has the concept and definition of master protocols changed **over time**?*

*How are the concept and issues of master protocols **understood by stakeholders**?*

***What terminology is used** in trial protocols, registration pages, and publications? How does this affect our understanding of the master protocol trial landscape?*

1. Examine concepts and terminologies given in the literature over time
2. Survey various stakeholders (clinicians, statisticians, sponsors, regulators) about their understanding of master protocols
3. Explore how the use of different terminologies affects our understanding of the landscape of master protocols; i.e. ability to identify and track registered such trials

Development of Bayesian Adaptive Designs with Late-onset Outcomes in Early Phase Oncology Trials

Zhulin Yin
First-year PhD student in ICR

DI-Keyboard Design

- The monotonic assumption on efficacy is not required
- Phase I-II design paradigm

- Dose - toxicity: Keyboard Design
- Dose – efficacy: Double-Sided Isotonic Regression
- Easy to implement

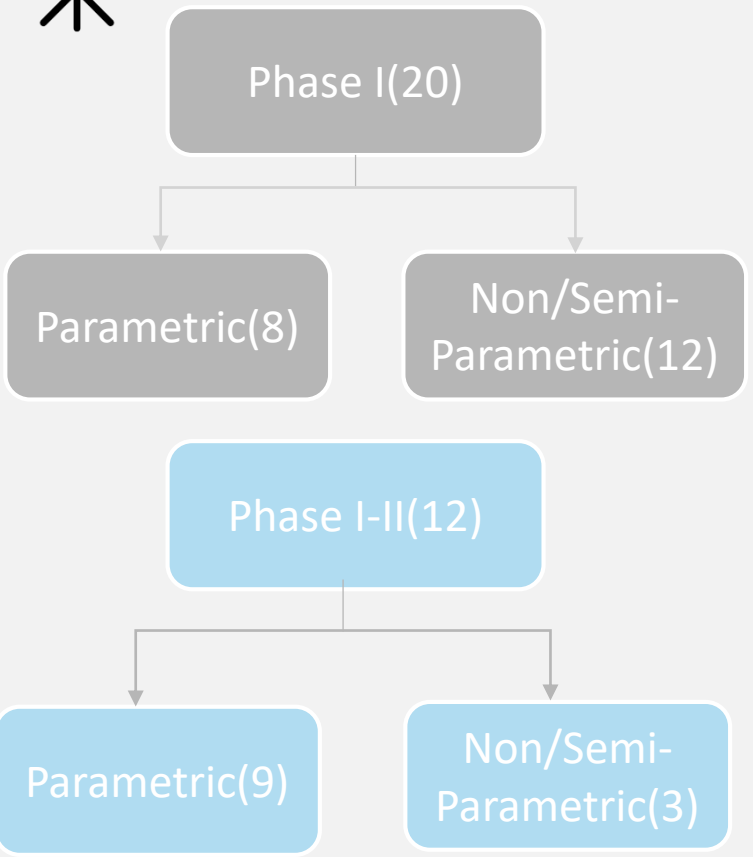
Late-onset outcomes

Oncology Trials

How to give patients timely and appropriate treatment while previous patients' outcomes are still unobserved?

Development of Bayesian Adaptive Designs with Late-onset Outcomes in Early Phase Oncology Trials

Literature Review



Common ways to deal with delayed outcomes

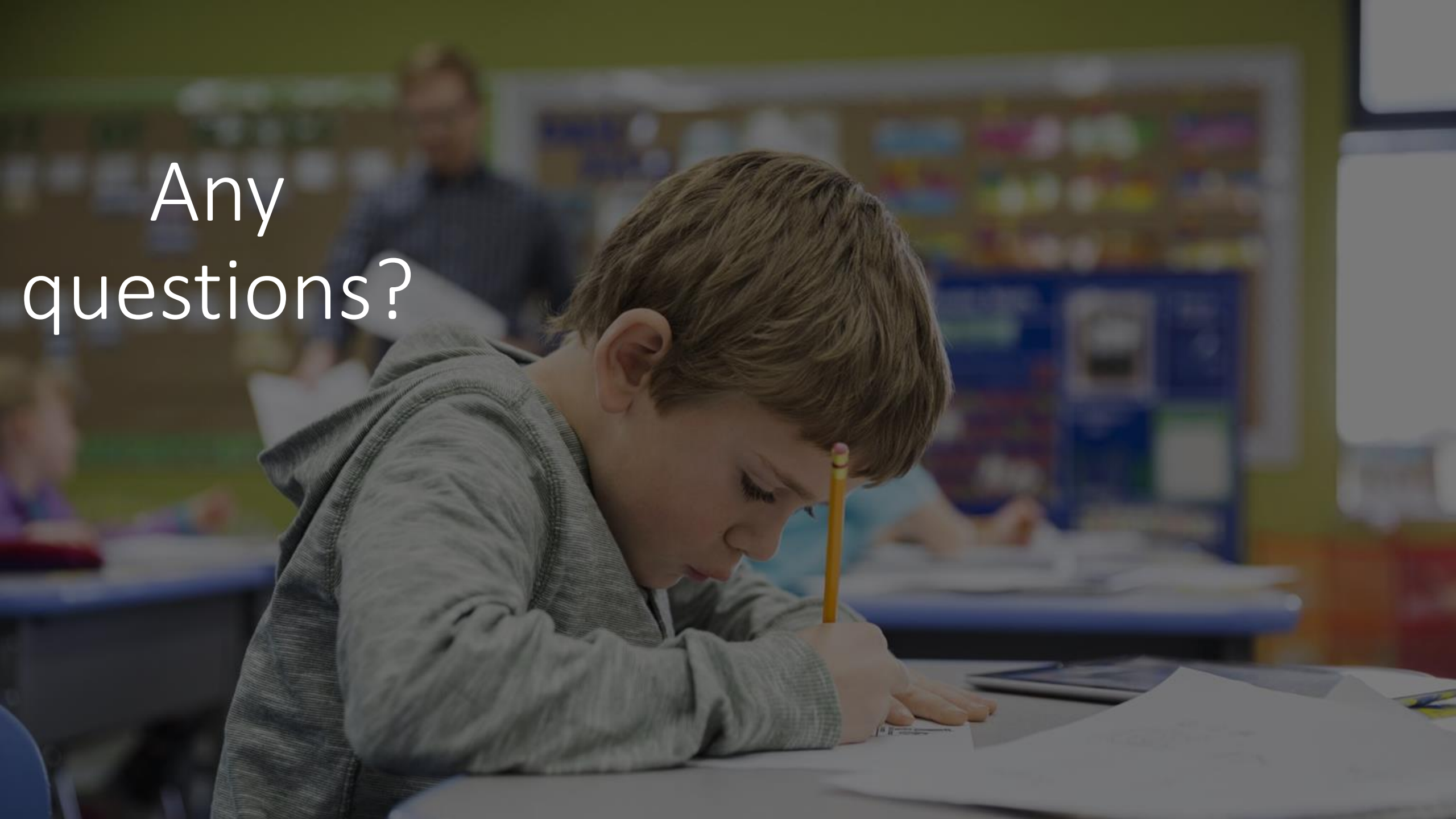
- Treat unobserved outcomes as **missing data** and **use model to predict those outcomes** for pending patients
- Weight pending patients by their **follow-up time** and **use weighted likelihood to guide further decision**
- Use the **likelihood approach** so that only the information before a patient is censored is included to guide further decision

The value of blinding in complex intervention RCTs

Abdullah Yonis
TMRP PhD studentship in Clinical Trial Methodology (Year 1)
College of Medicine and Health, University of Exeter

The components of the project

a. Online survey of the UK researchers (UKCRC)
b. scoping review
c. empirical study to assess the value outcome blinding complex interventions RCTs
d. consultation about the value of outcome assessment blinding in complex interventions (Delphi exercise)


Any
questions?