Planning a biomarker-guided trial: points to consider

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MRC Hubs for Trials Methodology Research

Just one of a team !

- Work presented today represents significant efforts of a team of individuals…
  - Miranta Antoniou (Hub PhD student 2014-2017)
  - Danielle Johnson (Current Hub PhD student)
  - Ruwanthi Kolamunnage-Dona (co-supervisor for Miranta; co-applicant on network grants)
  - Duncan Appelbe (IS lead for BiGTeD project)
  - James Cook (Current Hub postdoctoral researcher)
  - The MRC HTMR Network's Stratified Medicine Working Group (co-lead with James Wason, Cambridge)

What is a biomarker-guided trial

- **Biomarker-guided trial**: A trial incorporating one or more biomarkers in its design e.g. to determine eligibility to the trial or a particular trial arm, or to guide treatment
- **Biomarker**: Not just those traditionally thought of as biomarkers (liver function, blood count etc.), but also:
  - genetic markers
  - other measurements (e.g. example imaging data, sensor data etc.)

Why are they needed ?

- Shift towards personalised approach to treatment
- As for any intervention, RCT gold standard to demonstrate clinical utility

- Lack of well designed randomised controlled trials cited as key reason for delay in uptake of biomarker-guided treatment strategies

Aims of programme of work

- Provide guidance on design and analysis of biomarker-guided trials (BM-guided trials)
- Evaluate how evidence of biomarker validity should be compiled to inform BM-guided trials
- Consider whether BM-guided trials are always necessary and ethical
- Identify practical challenges faced when conducting BM-guided trials

Guidance on BM-guided trials: BiGTeD

- Literature on BM-guided trials plentiful…but navigating it to understand the various designs and identify the most appropriate in a given context is difficult
- Lack of clear guidance on how the trials should be planned, conducted and analysed
- To address these issues, we:

  a) undertook a systematic review[1,2] of the literature to identify all BM-guided trial designs previously proposed

  b) developed an online tool to provide guidance on the design and analysis of BM-guided trials (**www.bigted.org**)

1. Antoniou M, Jorgensen AL, Kolamunnage-Dona R (2016) Biomarker-Guided Adaptive Trial Designs in Phase II and Phase III: A Methodological Review. PLoS ONE 11(2): e0149803.

2. Antoniou, M.; Kolamunnage-Dona, R.; Jorgensen, A.L. Biomarker-Guided Non-Adaptive Trial Designs in Phase II and Phase III: A Methodological Review. J. Pers. Med. ***2017****, 7, 1.*

www.bigted.org

Bi omarker

G uided

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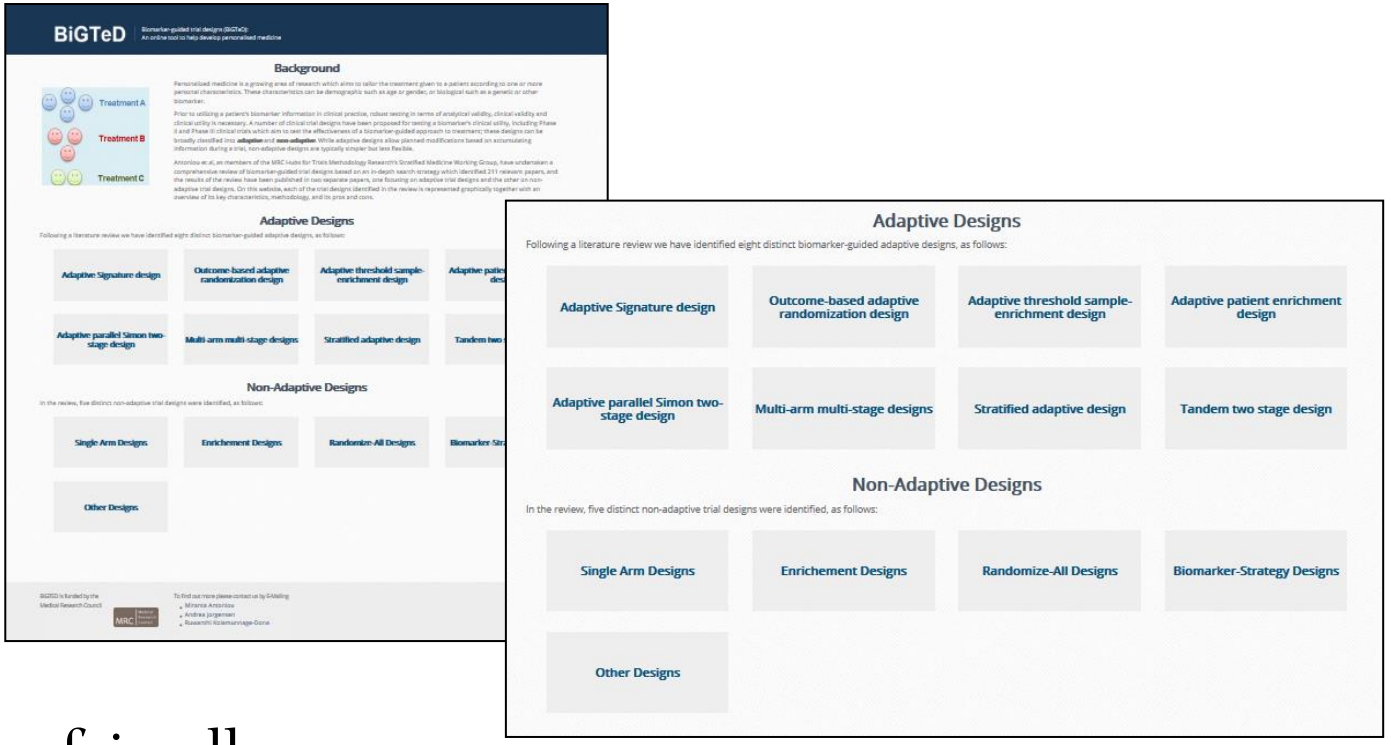
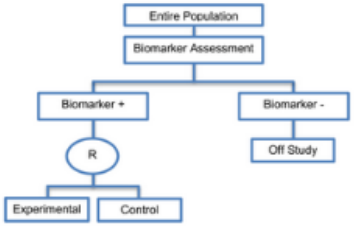
D esigns



- Free and <u>user-friendly</u>
- Overview of each design's <u>key characteristics</u>, methodology and <u>pro's and con's</u>
- <u>Clear, interactive graphics</u> standardised across all trials to help guide and aid comparison

Enrichment Designs

View more details by clicking on image to fully expand. Then hover over boxes for info.



Enrichment designs are described either in Phase II or Phase III clinical trials, and involve randomizing only the biomarker-positive patients and comparing the experimental treatment versus the standard treatment only in this particular biomarker-defined subgroup.

Alternative names: Targeted designs, Selection designs, Efficient Targeted designs, Biomarker-Enrichment designs, Marker-enrichment designs, Gene enrichment designs, Enriched designs, Clinically enriched Phase III study designs, Clinically Enriched Trial designs, Biomarker-Enriched designs, Biomarker Enriched designs, Biomarker Selected trial designs, Screening enrichment designs, Randomized Controlled Trial (RCT) of test positive designs, Population enrichment designs

Details

Utility

1. Useful when we aim to test the treatment effect only in biomarker-positive subgroup for which there is prior evidence that the novel treatment is beneficial, but the candidate biomarker requires prospective validation.
2. Useful when it is not ethical to assign biomarker-negative patients to the novel treatment for which there is prior evidence that it will not be beneficial for this subpopulation, or that it will harm them.
3. Recommended when both the cut-off point for determination of biomarker-status of patients and the analytical validity of a biomarker are well established.

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Key reference...

Variations:

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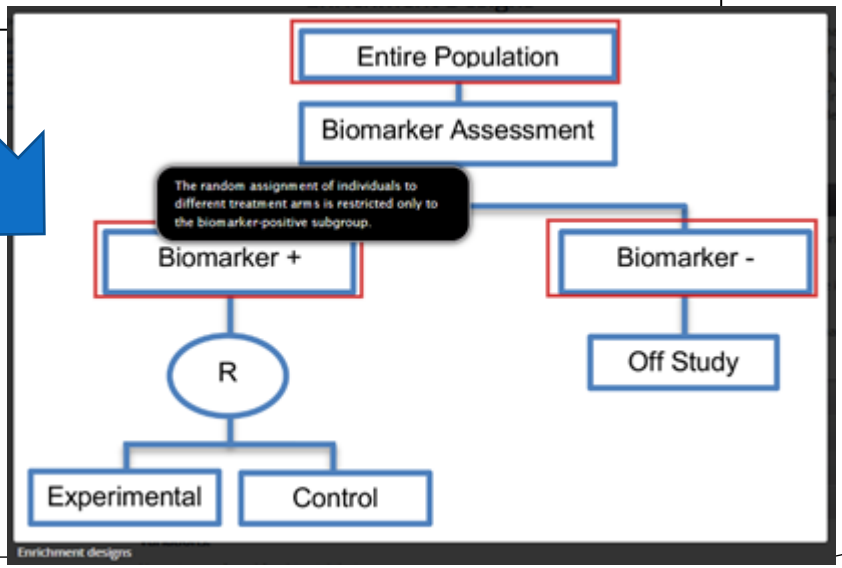

Adaptive threshold sample-enrichment design

View more details by clicking on image to fully expand. Then hover over boxes for info.

It is a two-stage design in a Phase III setting which was proposed by Liu et al. (2010) to adaptively modify accrual in order to broaden the targeted patient population.

Alternative names: Threshold sample enrichment approach, Two-stage Sample Enrichment, Two-stage sample-enrichment design strategy

Adaptations: Change in the inclusion criteria of the study population after the initial stage of the study in order to broaden the targeted patient population.

Details

Methodology

Statistical/Practical considerations

Advantages

- More cost-effective as it avoids further recruitment of patients when there is no difference in treatment outcome among the biomarker-defined subgroups.
- Researchers can use the data which was accumulated during the first stage of the study to proceed with further investigation of any other potential assumption made at the start of the trial.

Disadvantages

- If there is no information about a subset of patients for whom the novel treatment is more effective than other[s] at the beginning of the trial.

Key references

Variations:

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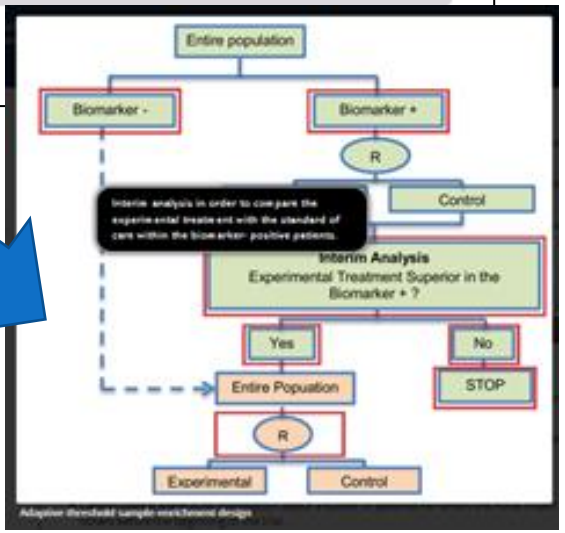
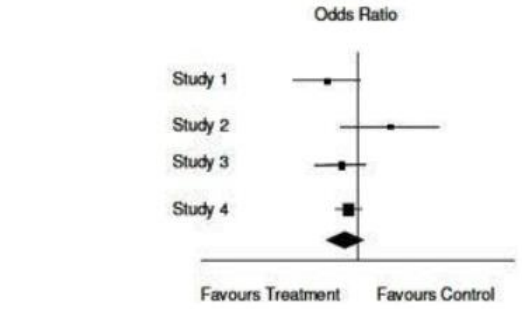


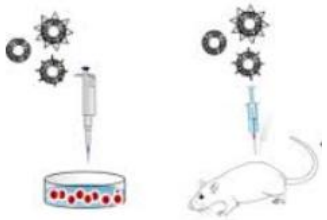
Biomarker validity: justifying a trial

- BM-guided trials require substantial investment
- Expect certain level of confidence in biomarker at outset - evidence of biomarker validity
- Unclear what this evidence should look like
- Literature review to explore:
  - what approach is used to compile evidence ?
  - what is strength of evidence ?
  - what is recommended approach ?

Justifying inclusion of biomarker

- Literature review (2013-present) included 90 trials
- No standard approach to compiling evidence – combination of one or more of:
  - Systematic review/Meta-analysis
  - Previous RCT
  - Observational study
  - Sub-analysis of previous trial
  - In-vitro/in-vivo studies





Guidelines for compiling evidence

- Clear from review no standard approach
- No suggestion of strength of evidence required
- 'Pyramid of Evidence' provides some guidance, but quality is of key importance
- Next steps:
  - review guidance on demonstrating biomarker validity
  - consider whether guidelines required (incorporating quality assessment)

Necessary and ethical

- RCT sometimes impractical e.g. rare ADR outcome
- Need to be mindful of loss of clinical equipose – evidence synthesis may suggest overwhelming evidence of benefit
- Unethical to assess approach in a trial
- Ongoing work:
  - Study to compare precision of effect estimates from combining observational biomarker studies of ADRs vs simulated RCT (in collaboration with GSK)
  - Investigating patient/clinician's perspective on level of evidence regarding biomarker-guided treatment

Practical challenges

- Many BM-trial designs proposed, but what about their practical application ?
- Workshop held 2017 to explore practical challenges
- 25 attendees: statisticians, methodologists, clinicians, trial managers, information systems specialists
- Series of talks by those experienced in conducting BM-guided trials
- Group discussion sessions to identify key challenges
- Report to be published shortly

Key practical challenges

- Funders perceive as expensive – but can be more efficient in demonstrating patient benefit
- Total cost difficult to estimate due to uncertainties
- Additional administrative burden – approval paperwork for each new arm, multiple CRFs etc.
- Who funds the biomarker test ? NHS vs trial
- Regulatory issues when adding new arm
- Ethical issues when adding new arm

Key practical challenges [2]

- Consenting patients on day of diagnosis
- Patient perception of 'personalised' medicine – particularly if denied a treatment
- Incidental findings
- Recruitment rate uncertainty – unknown biomarker prevalence
- High dropout due to slow genetic profiling

Continuous biomarkers

- BM-trial designs identified in systematic review assumed binary biomarkers
- Assumption works for genetic variants e.g. SNPs
- Often continuous – e.g. blood biomarkers
- Dichotomising to 'fit' design loses information
- Network grant for review of methods used to demonstrate clinical utility of continuous biomarker (alone and in combination), including:
  - trial designs for development/validation
  - optimal methods for choosing threshold
  - timing of setting threshold

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  - MRC HTMR Network