Platform Studies in Drug Development

James Matcham, Head ECD Biometrics, IMED Biotech Unit

PSI Webinar

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Disclaimer

The speaker is an employee of Astrazeneca, a pharmaceutical company. The opinions of the speaker do not necessarily reflect the company's official position and should be taken as their personal opinion only.

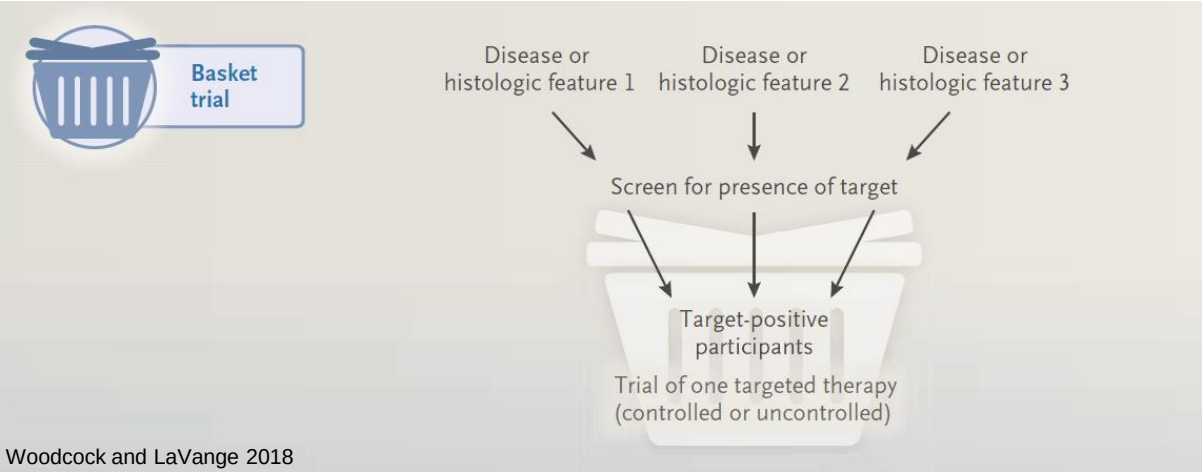
Background

- Adaptive design is now common in pharmaceutical drug development, particularly in phase 1 and phase 2 trials. Pharma is now looking for the next innovation.
- The platform trial is popular in collaborative groups with pharma companies contributing treatments
- The design of single-sponsor platform trials is being explored

Agenda

- Some definitions
- Early phase platform trial concept
- Practicalities
- Implications for drug development

Basket Design

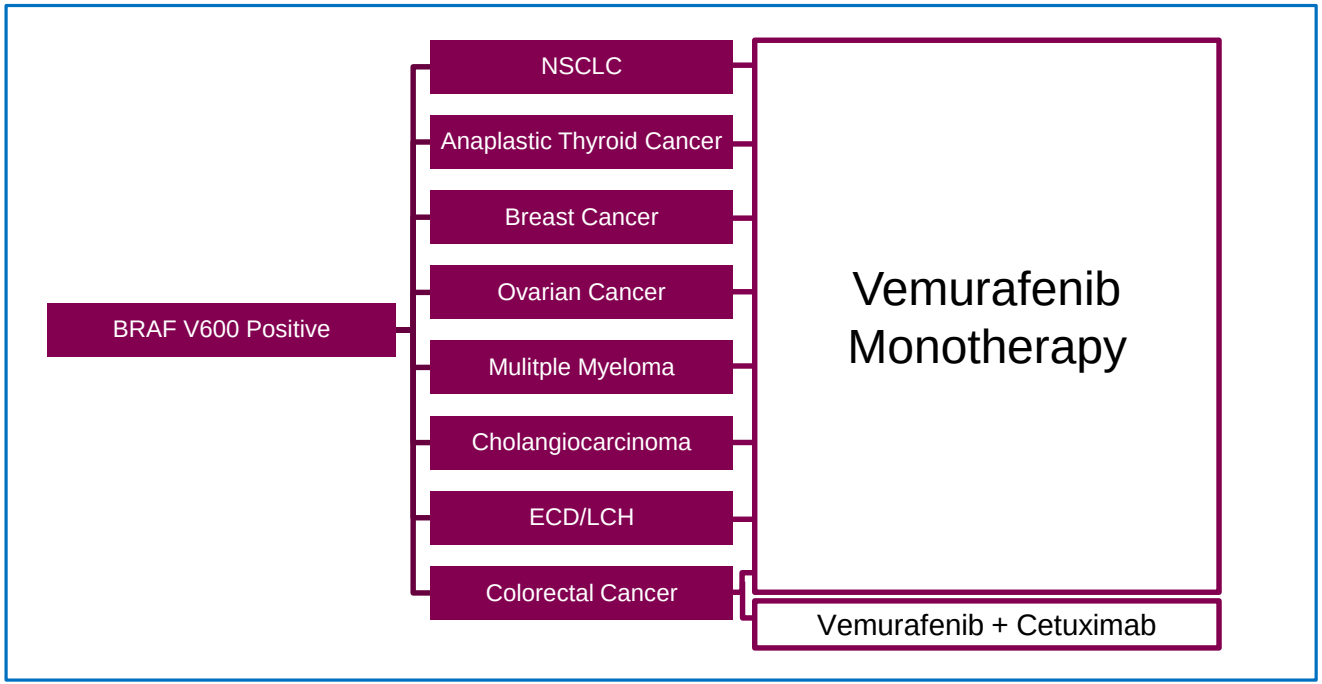


Woodcock and LaVange 2018

- Used where there is a single biomarker signature seen in different diseases
- Single treatment examined for all diseases with the same signature
- Use of control group considered for each disease

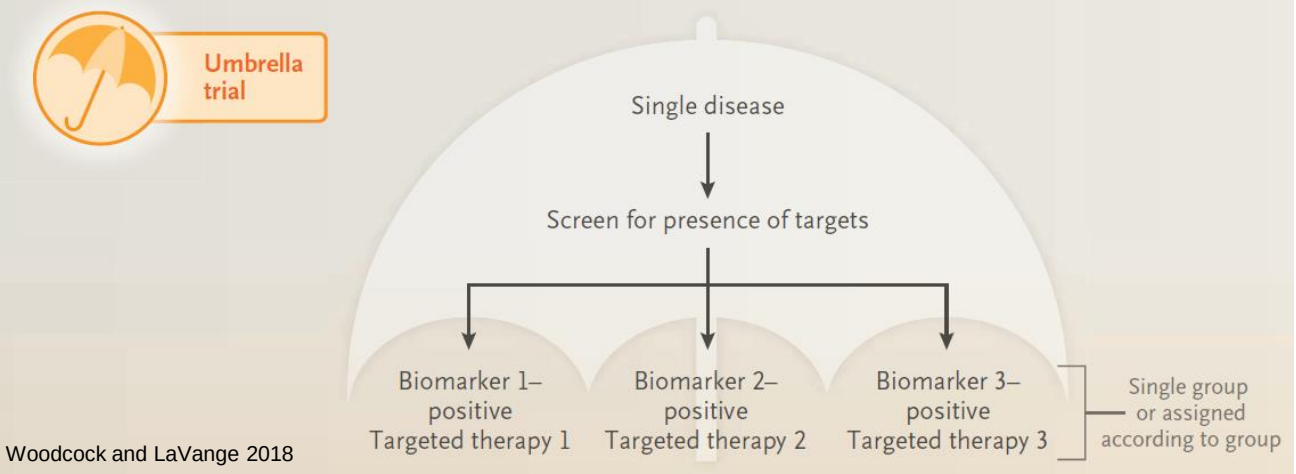
Basket Example

Vemurafenib in BRAF V600^{+} Nonmyeloma



Hyman et al 2015

Umbrella Design

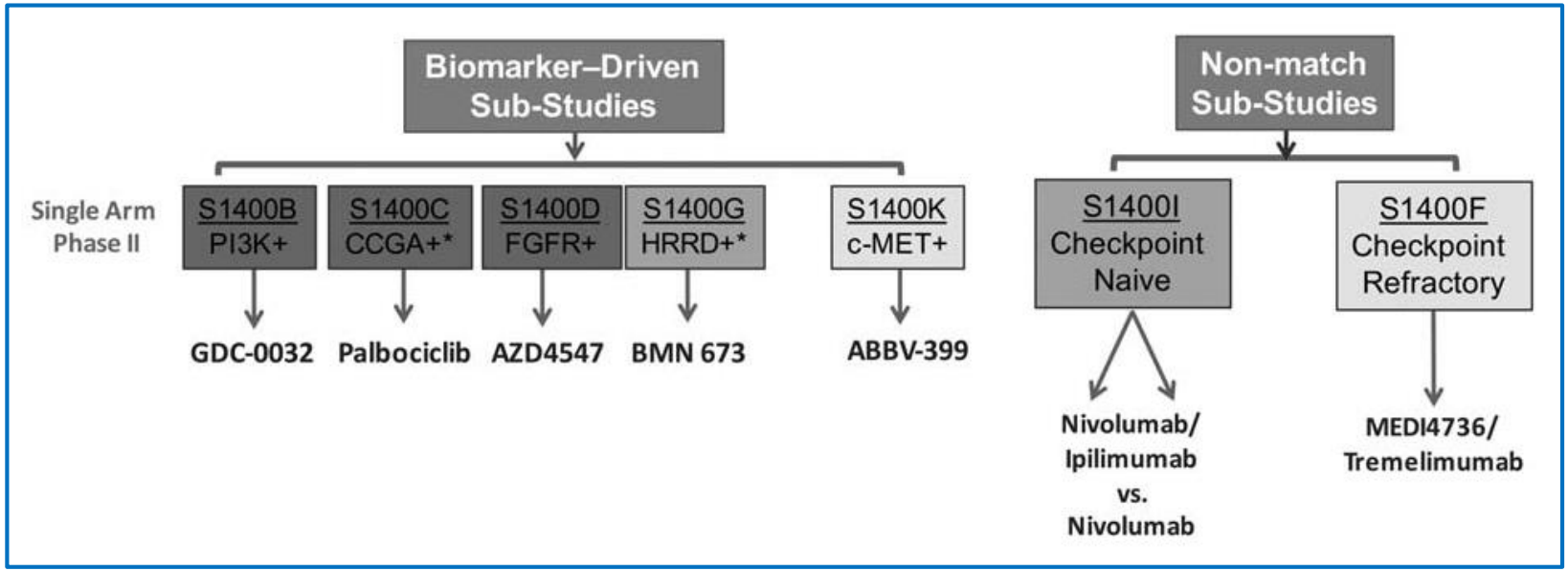


Woodcock and LaVange 2018

- Used in a single disease
- Patient assigned to biomarker groups using a Biomarker Allocation Algorithm
- Different treatment examined in each biomarker group
- Biomarker groups enrol at different rates
- Biomarker tests may be new
- A ‘Miscellaneous’ biomarker group is common
- Use of control group considered for each biomarker group
- Trial stops when each biomarker group is complete

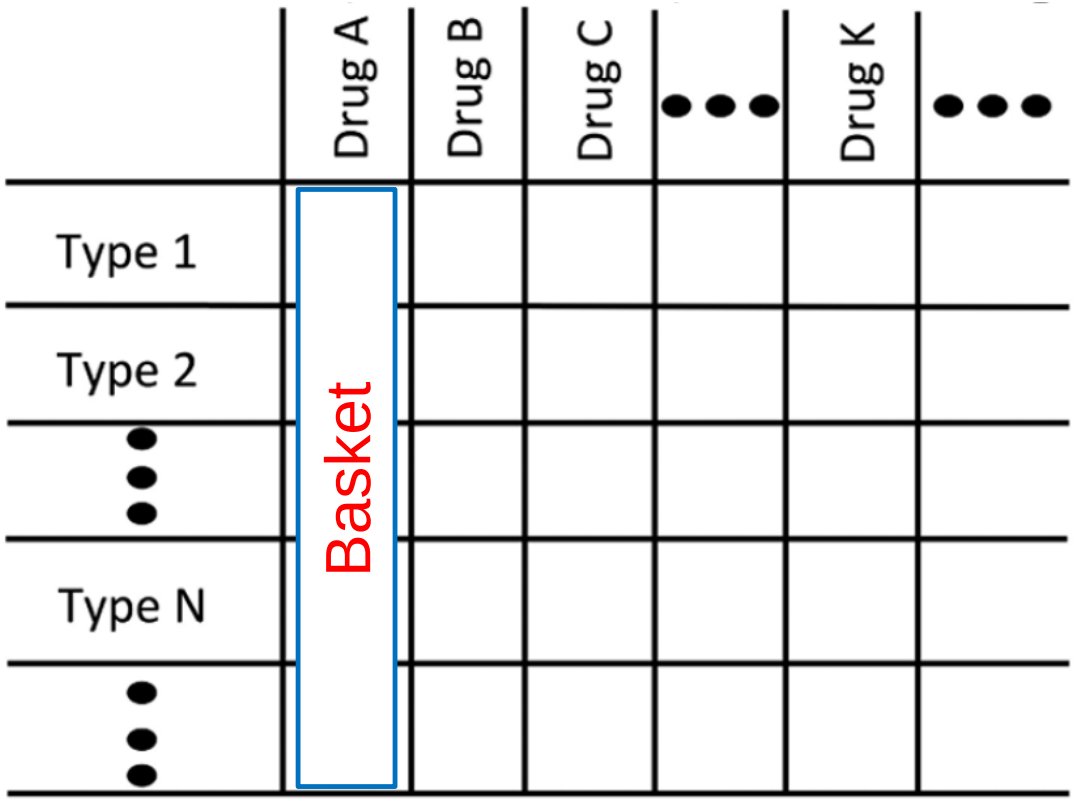
Umbrella Example

Lung-MAP Protocol

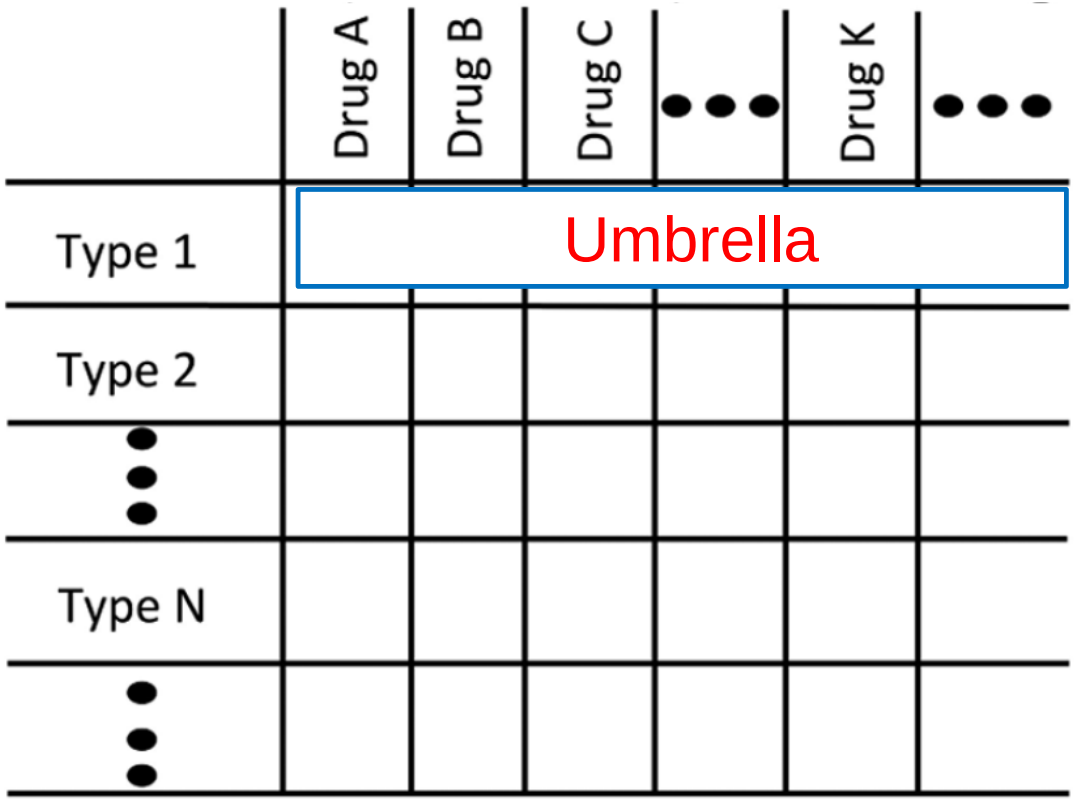


Lam and Papadimitrakopoulou (2018)

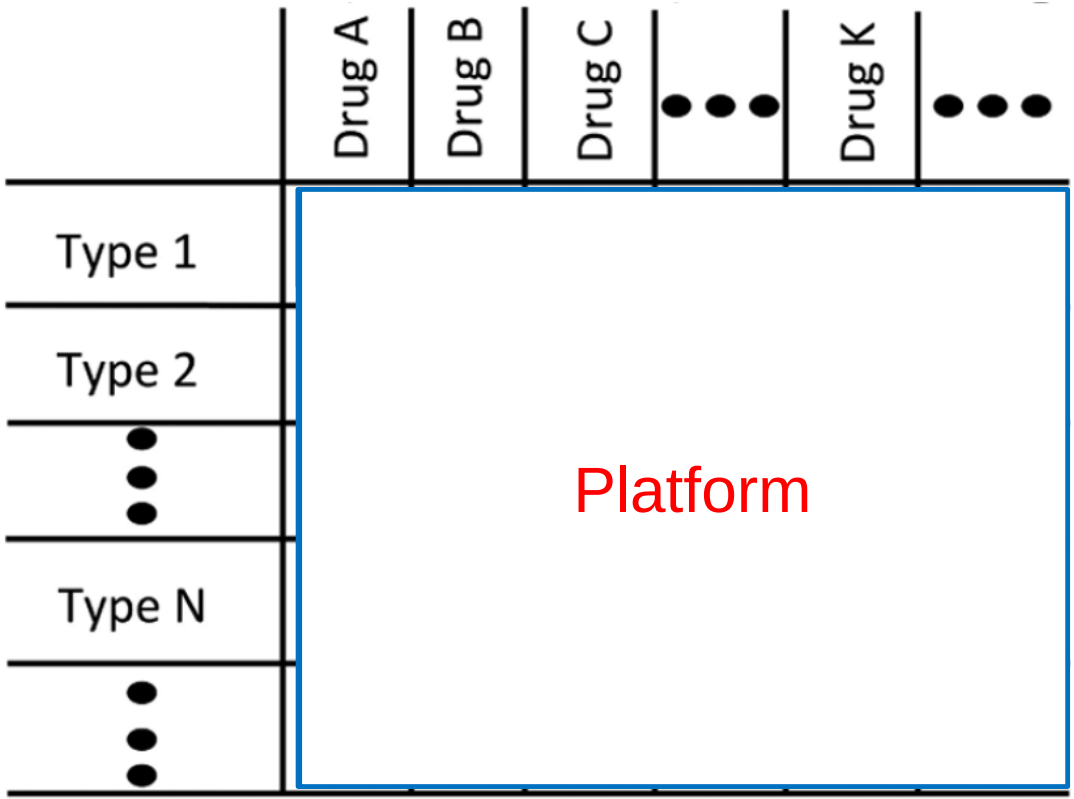
Platform Design



Platform Design



Platform Design



Platform Design

- Objective is to promote or relegate a new treatment to the next phase
- A biomarker algorithms is required
- Studies tend to be cooperative group and multi-sponsor
- Studies can learn about the disease as well as the treatments
- Data office and trial steering committee organisation is essential
- A ‘waitlist’ of replacement treatments is needed
- Biomarker groups complete at different times due to the biomarker prevalence

Platform Design

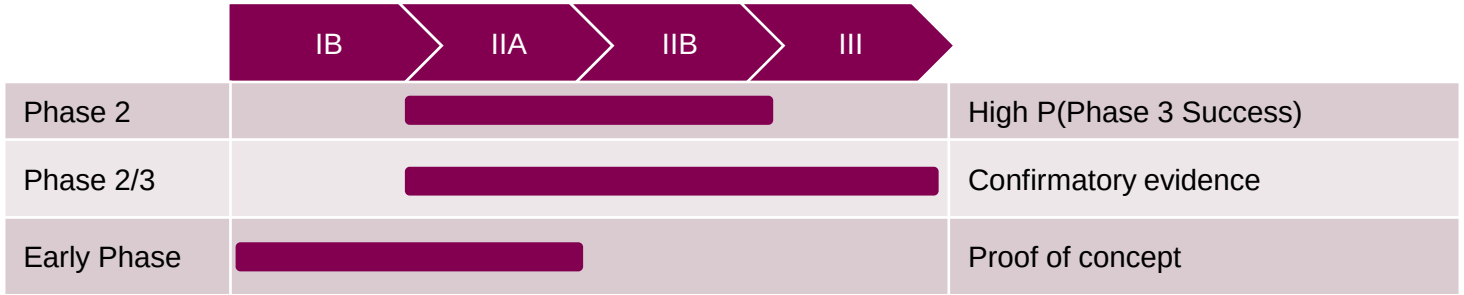
Biomarker Group	Year of Study					
	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
BM1	Treatment A		Treatment E		Treatment J	
BM2	Treatment B			Treatment F		Treatment L
BM3	Treatment C				Treatment G	
Misc	Treatment D		Treatment H		Treatment K	

Fixed vs Platform Trial Characteristics

Characteristic	Traditional Trial	Platform Trial
Scope	Single agent in a homogeneous population	Multiple agents in a heterogeneous population
Duration	Finite	Long-term
Treatment groups	Pre-specified and limited	Multiple and may change over time
Stopping rules	Entire trial may be stopped early	Arms may be removed from the trial, but the trial continues with new arms
Allocation strategy	Fixed randomisation	Response adaptive randomisation
Sponsor support	Single federal or industry sponsor	Multiple federal or industry sponsors, or a combination

Berry et al 2015

Position in Development Program

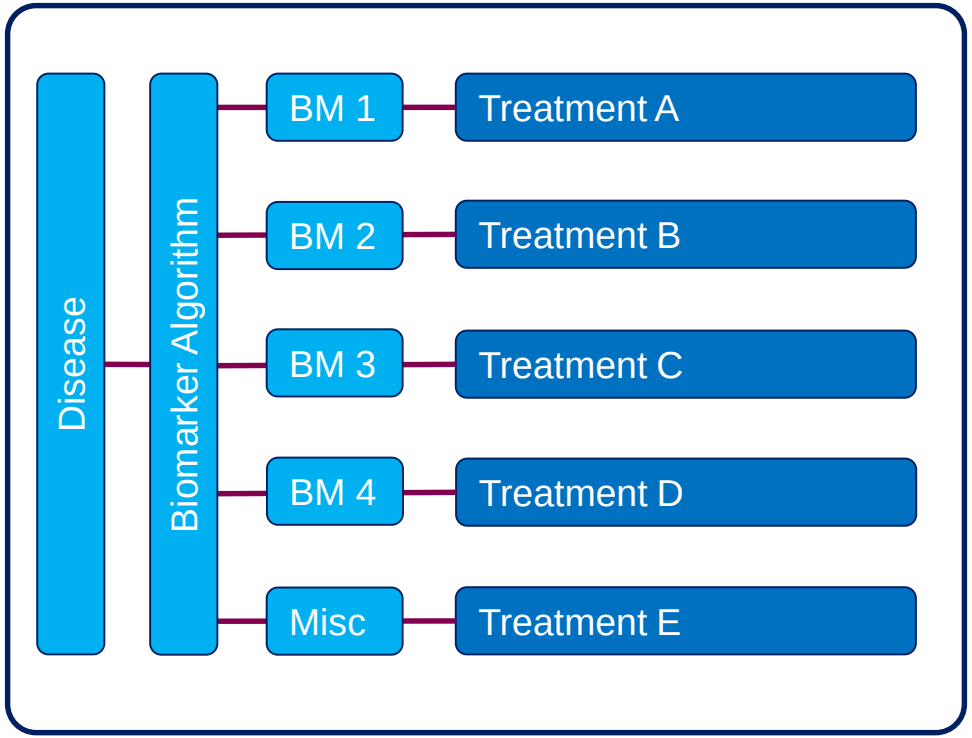


Early Phase Platform Trial

Objectives

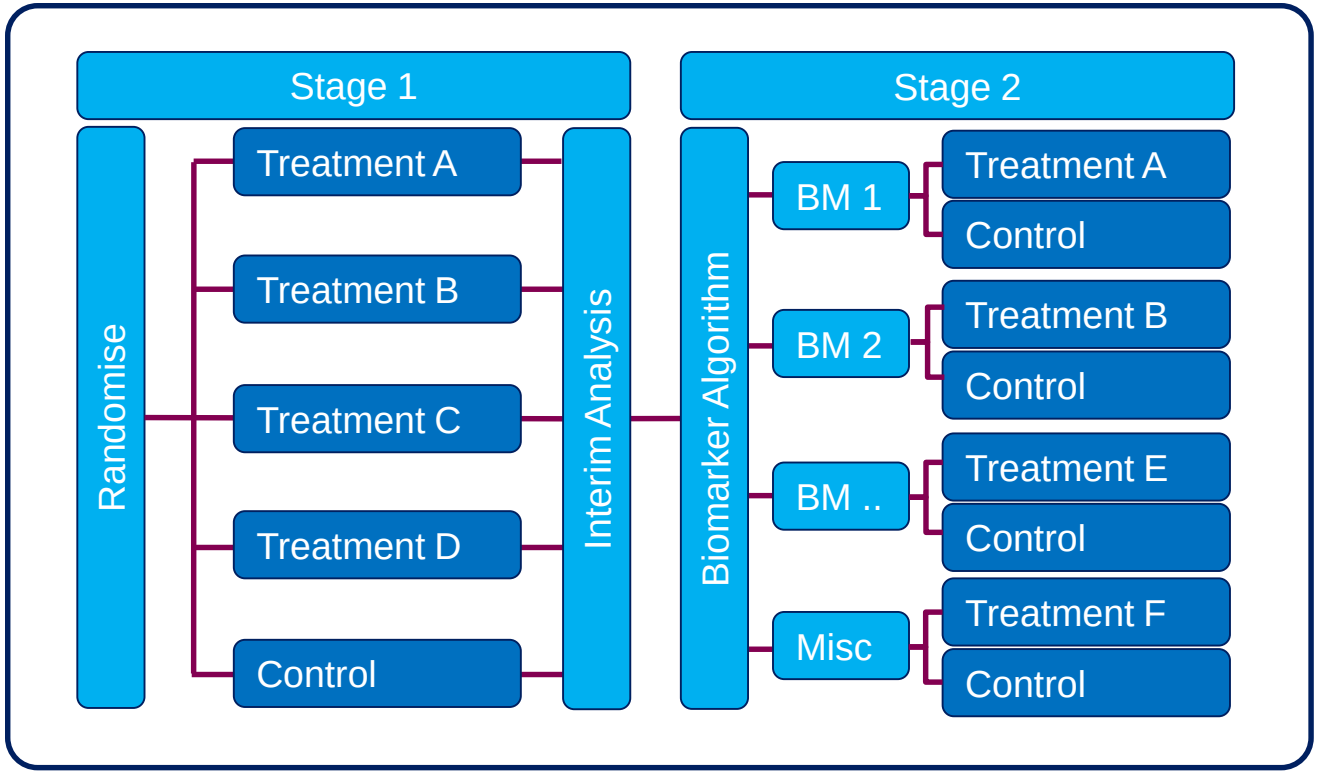
- Current assessing the phase 2A platform trial concept
- Objective to provide phase 2B ready candidates
  - Graduate drugs with activity using early phase endpoints
  - Relegate drugs quickly (fast fail)
  - Accelerate exceptional treatments
- Study acts as ‘early phase filter’
- Use current AZ decision-making framework (Frewer et al 2016)
- Over time the trial learns about disease, new endpoints, stratification biomarkers, prognostic vs predictive effects

Early Phase Oncology Platform Design

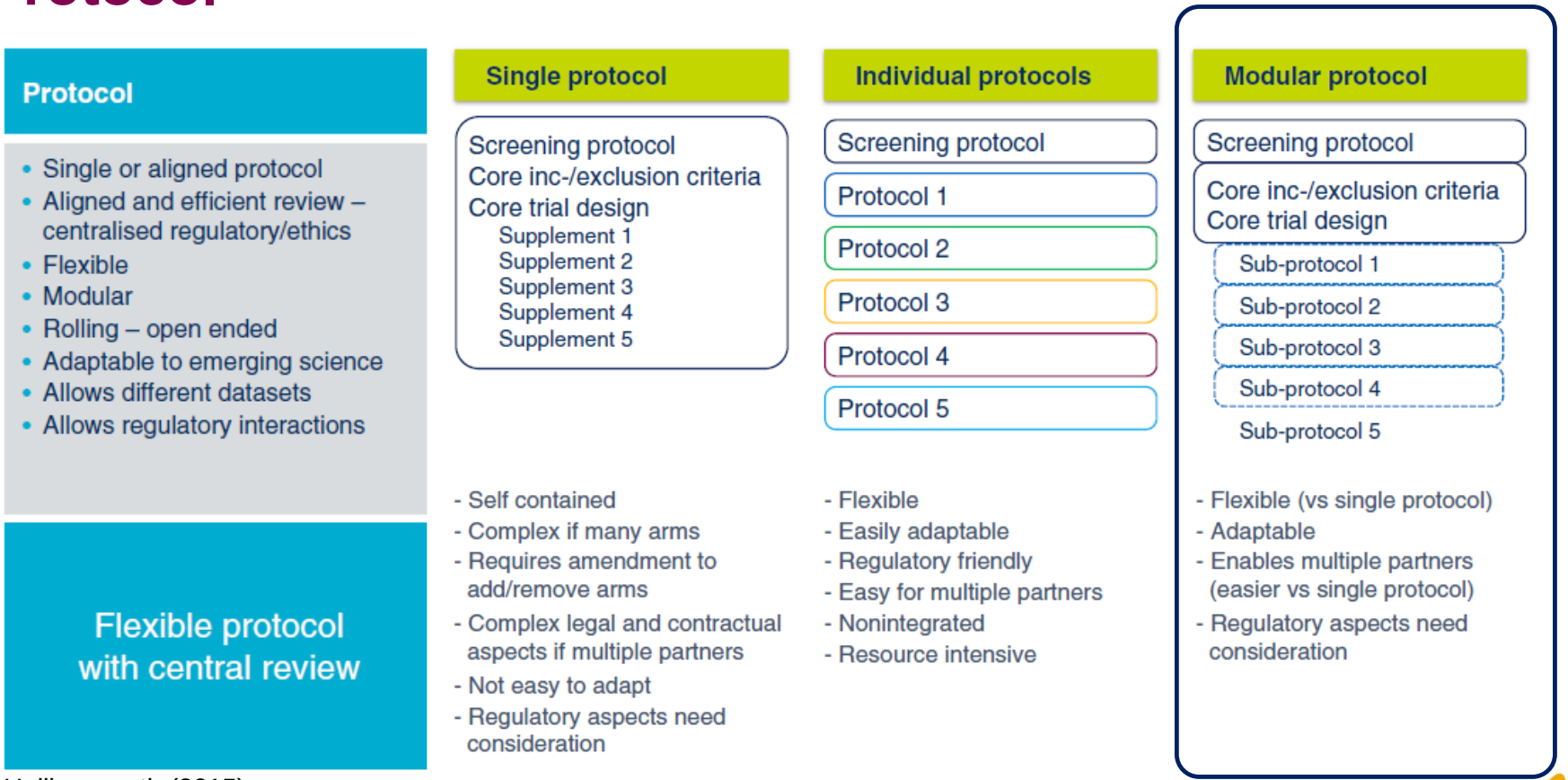


- Oncology Indication
- Response rate endpoint
- Clear interim and final decision criteria with historical response rates
- N in each treatment arm
- Interim at N/2
- Biomarkers fixed
- Can relegate, continue, graduate or accelerate at interim
- Relegate or Graduate at final
- Five modules
- Treatments can be combinations
- Waitlist for new treatments

Biomarker-Finding Platform Design

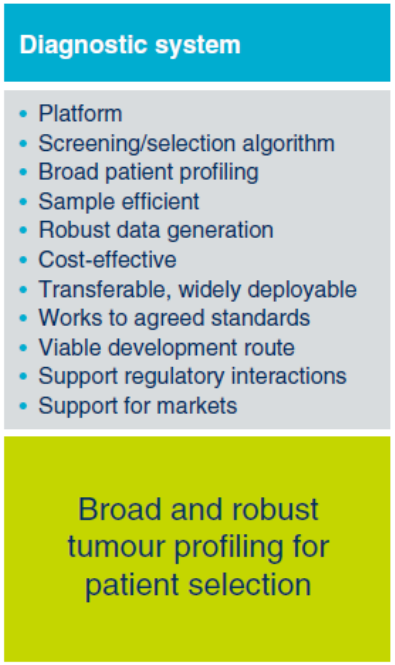


Protocol



Hollingsworth (2015)

Biomarker Algorithm



Hollingsworth (2015)

Framework for incorporating biomarker stratification in a platform trial
1. Can the biomarker of interest be reliably measured using a validated assay?
2. What is test-performance in clinically available samples representative of the population of interest?
3. Is the biomarker prognostic necessitating a separate control in order to distinguish a prognostic from a predictive effect?
4. What is the biomarker prevalence in the population of interest?
5. What is the strength of evidence of a predictive effect, i.e. the specificity of the biomarker?
6. What is the strength of evidence to support the rationale and clinical efficacy of the targeted therapy in the biomarker-defined group?
7. What is the overlap between this biomarker-defined group and others of interest?
8. What are the implications for other overlapping accruing comparisons?

Gilson et al 2018

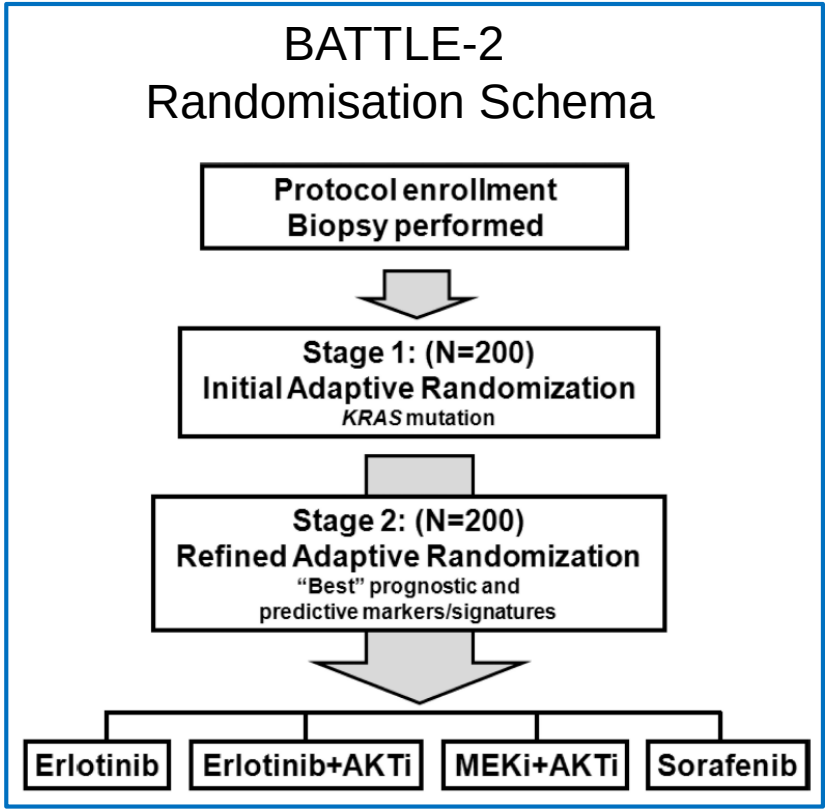
- Defined in the protocol
- Prognostic v Predictive
- Categorise biomarkers
  - Clinical evidence
  - Pre-clinical evidence
  - Scientific hypothesis

Interim Analyses

- Frequency of interim analyses should be pre-determined and simulated
- Short term endpoints are preferred
- Efficient data process
- Data monitoring committee
- Automated as much as possible
- Timing
  - Regular times (e.g. once per month, quarter)
  - Data driven

Randomisation

- Control group selection
- Fixed randomisation
- Catch-up randomisation
- Adaptive randomisation
- Two-stage adaptive randomisation



Gu et al 2016

Decision Making

- Linked to the trial objective
- Defined in the protocol
- Decision-making for treatments
  - Graduation decisions
  - Relegation decisions
  - Accelerate decision
- Decision-making for biomarkers
  - Initial biomarker algorithm
  - Updating the algorithm
- Decisions at the beginning of the trial should be as good as decisions at the end of the trial (decision consistency)

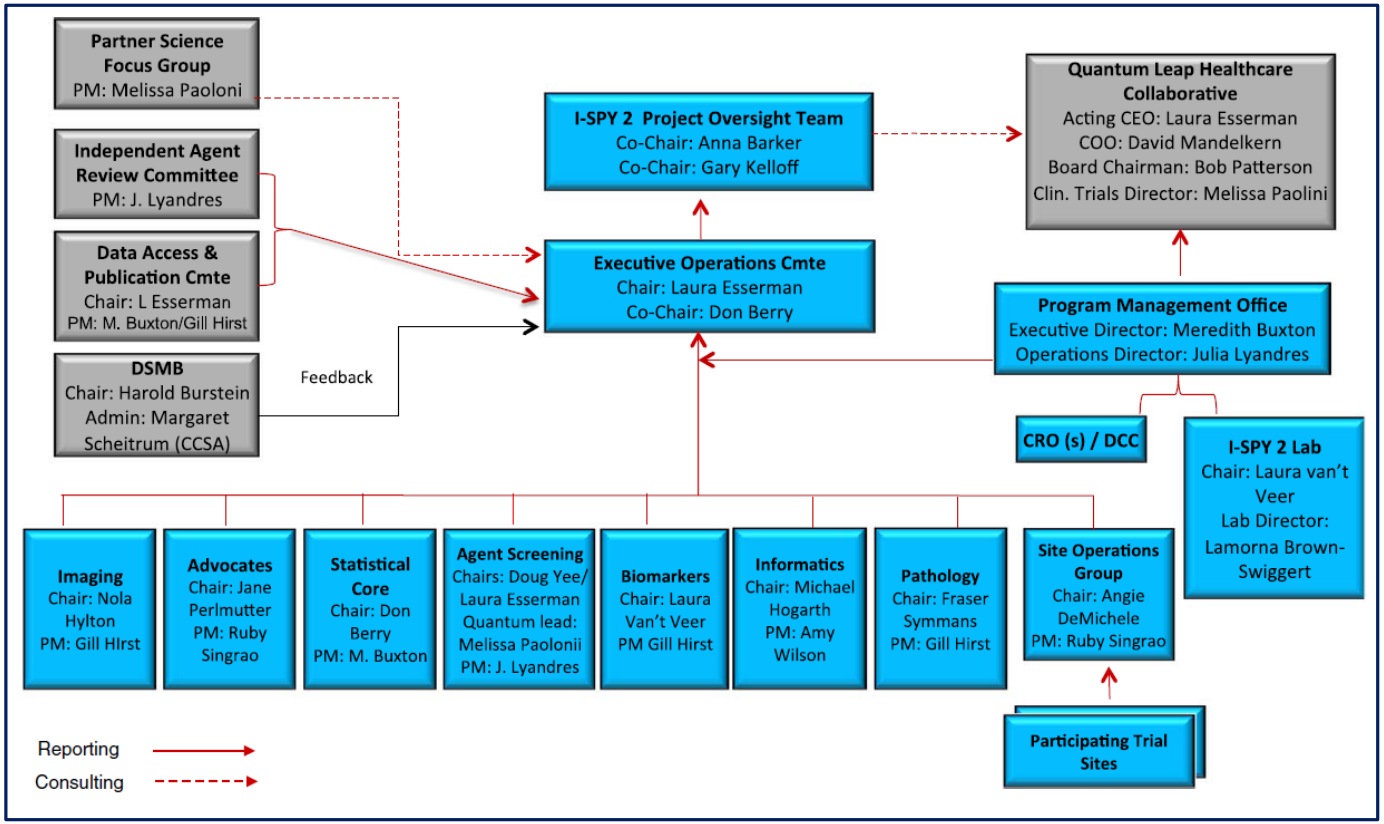
Trial Simulation

- All platform trials should be thoroughly simulated and simulations should be used to decide among design options
- Simulations documented in a Simulation Plan and Report
- Simulation report is expected to be presented to ethics/regulatory bodies
- Simulation should comprise
  - Many scenarios, including null scenario to establish overall type I error
  - Decision operating characteristics
  - Estimation bias evaluation
  - Sensitivity to patient withdrawals, missing data, enrolment rates/patterns, IA timings, data access delays, data cleanliness, analysis delays

Statistical Challenges

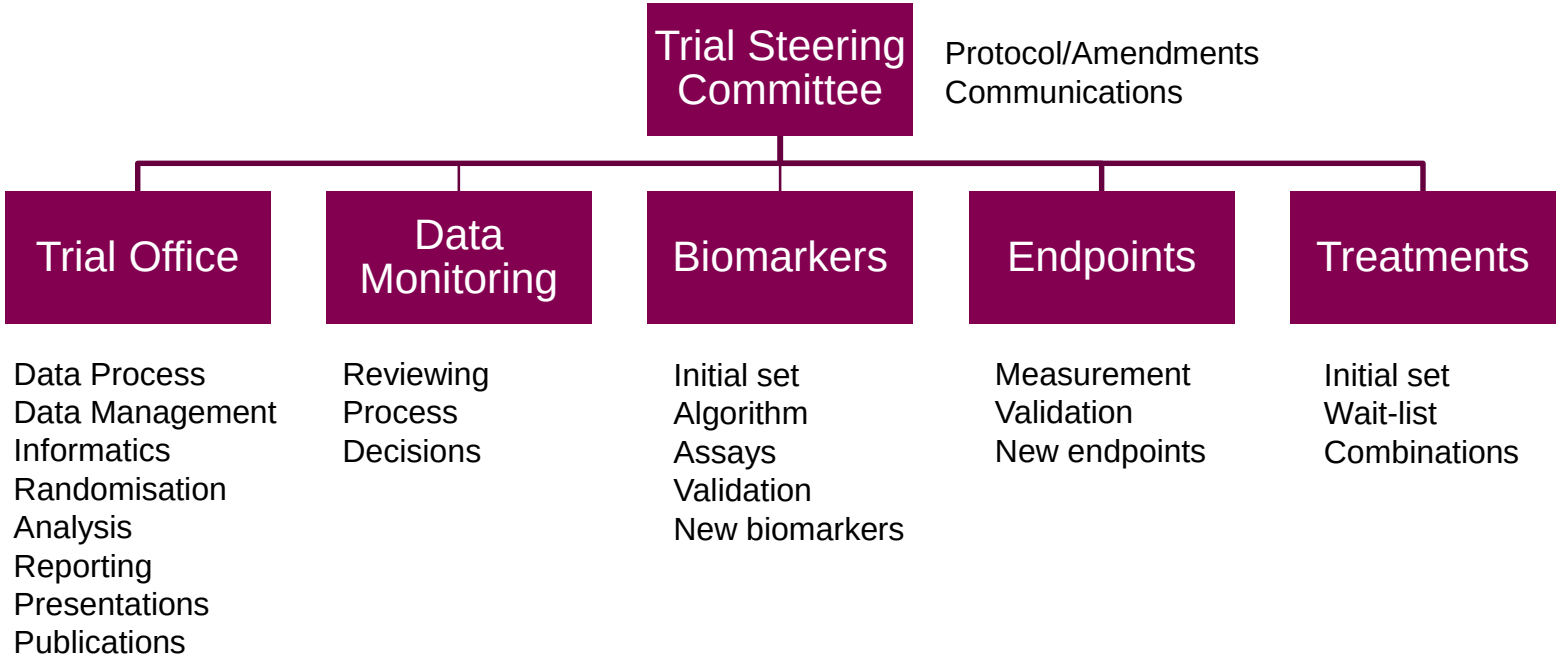
Short term endpoint	Explicit model for outcomes	Bayesian sharing
Prognostic v predictive effects	Adaptive randomisation	Sharing of control groups
Decision criteria	Trial simulation	Data office

Trial Governance: I-SPY2



Das and Lo (2017)

Trial Governance



Keys to Success

Trial Governance	Clear Objectives	Decision Criteria
Biomarker Algorithm	Modular Protocol	Short term endpoint
Data Flow	Centralised Analysis	Wait list Priority

Implications for Drug Development

- Drug development is disease-based
  - Project teams focus on disease not drugs
  - Budgets
  - Resourcing
  - Outsourcing
- Initially slow start and planning, but quick start up once initiated
- Learning trials
  - Biomarkers
  - Endpoints

- Early phase platform trial is ideal for combinations
- Could be slow if too many biomarker modules
- Quality, time and cost metrics need baselining and collecting

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