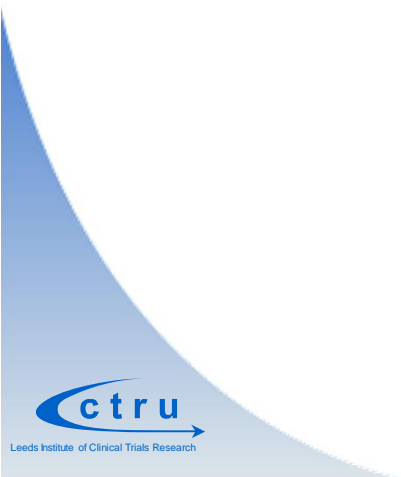


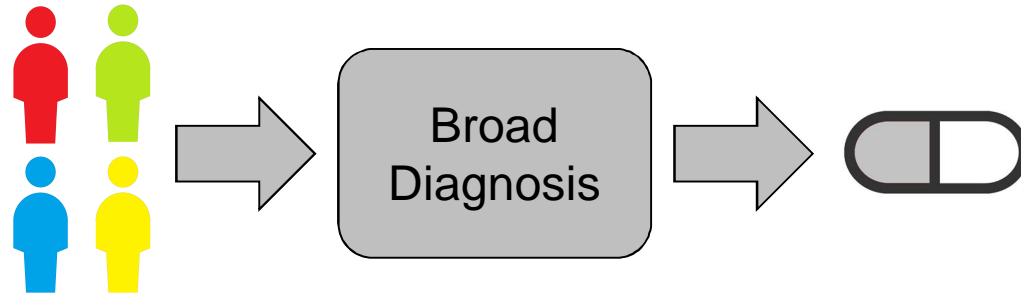
Novel Trial Design

Andrew Hall

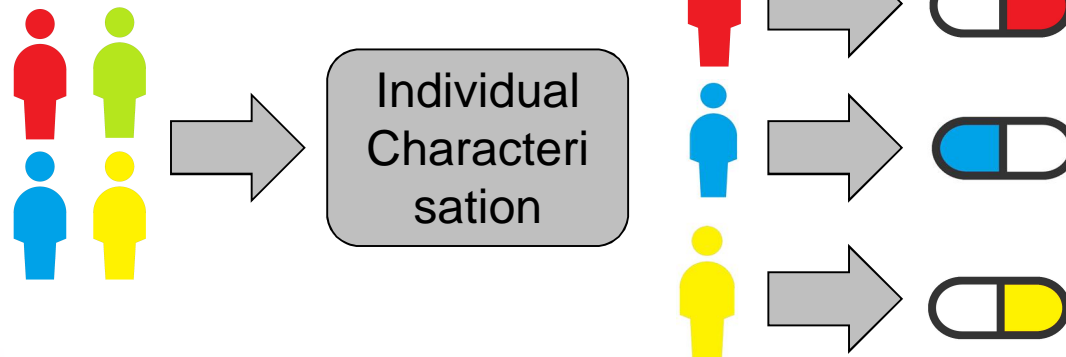


Trial Innovation

Tradition approach



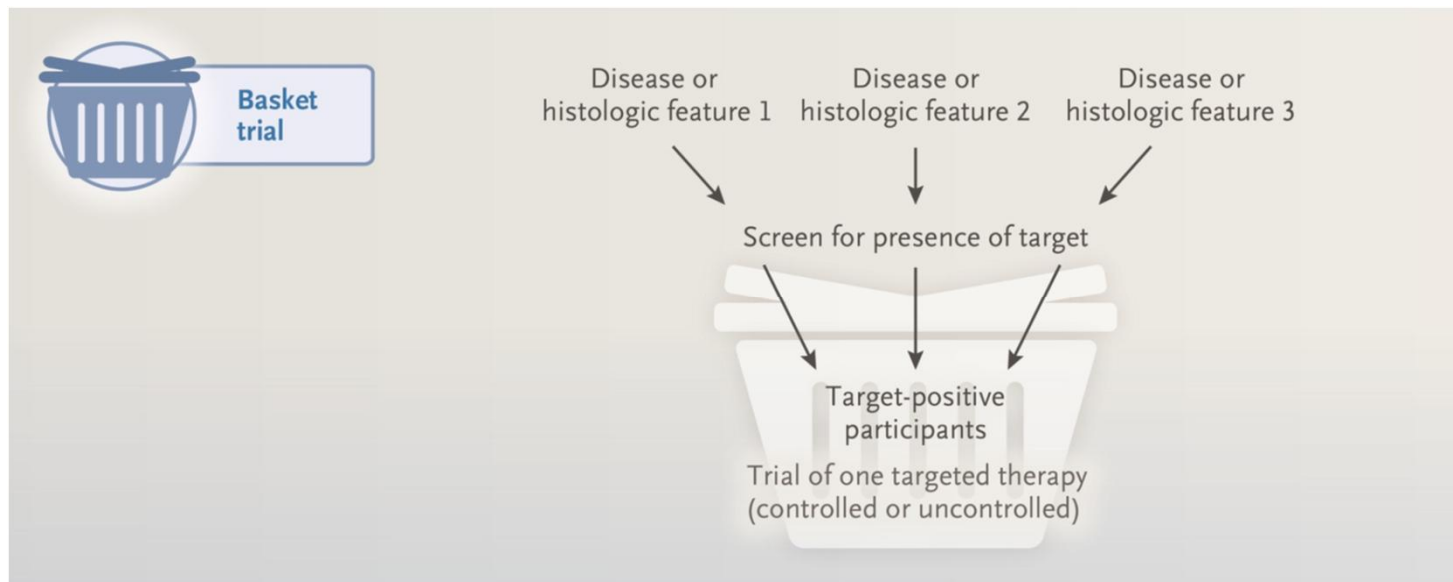
Precision medicine



- Conventional approach investigating one or two interventions in a single disease
- Precision medicine trials to evaluate targeted therapies in sub types of disease
- More complex questions need answering more efficiently in less time

Master protocols

- **Basket:** Study a single targeted therapy in the context of multiple diseases or disease subtypes



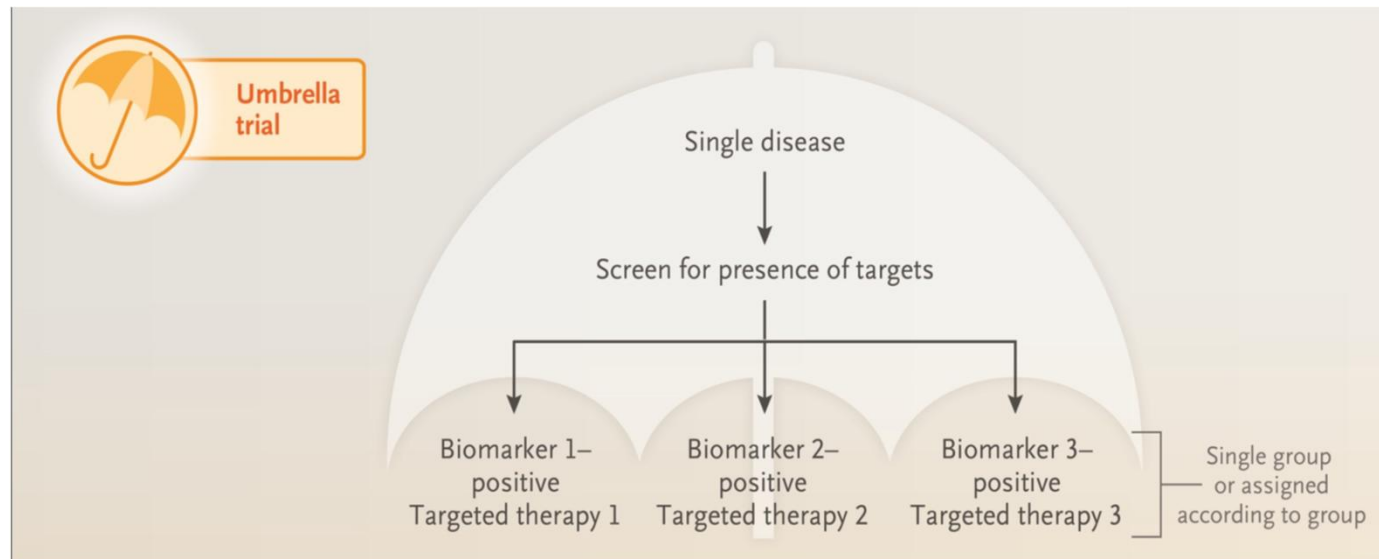
WOODCOCK et al. 2017



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Master protocols

- **Basket:** Study a single targeted therapy in the context of multiple diseases or disease subtypes
- **Umbrella:** To study multiple targeted therapies in the context of a single disease



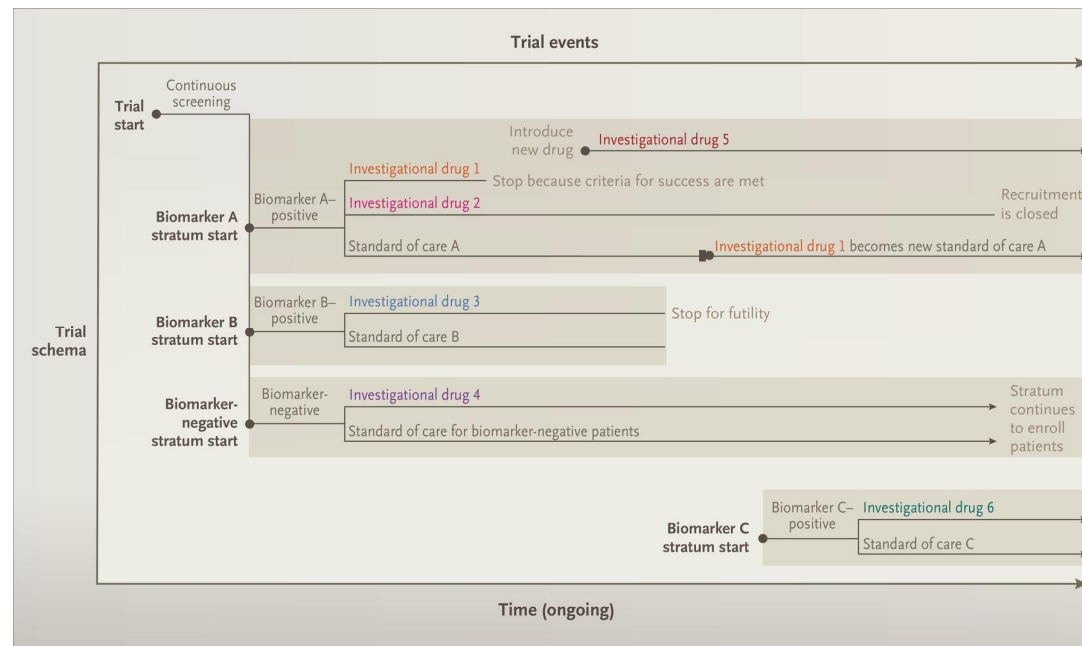
WOODCOCK et al. 2017



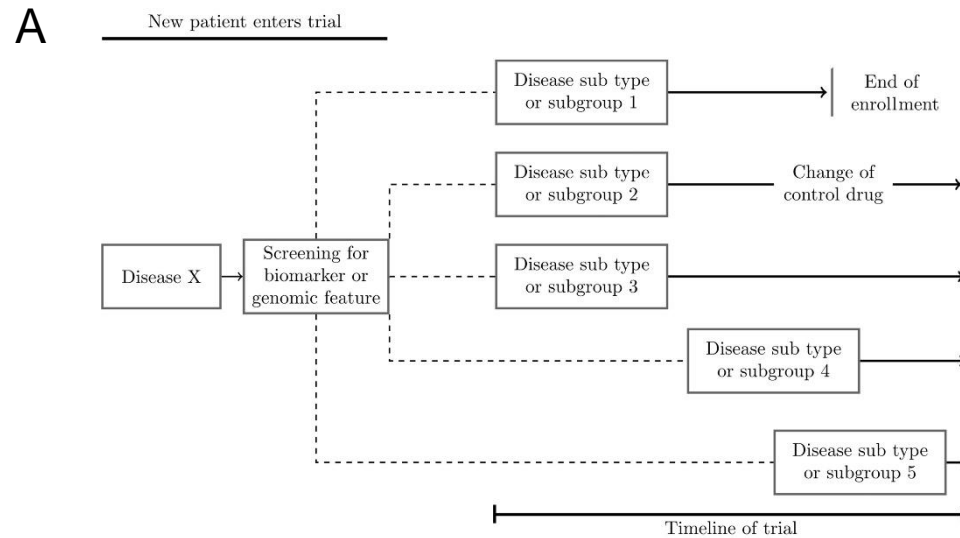
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Master protocols

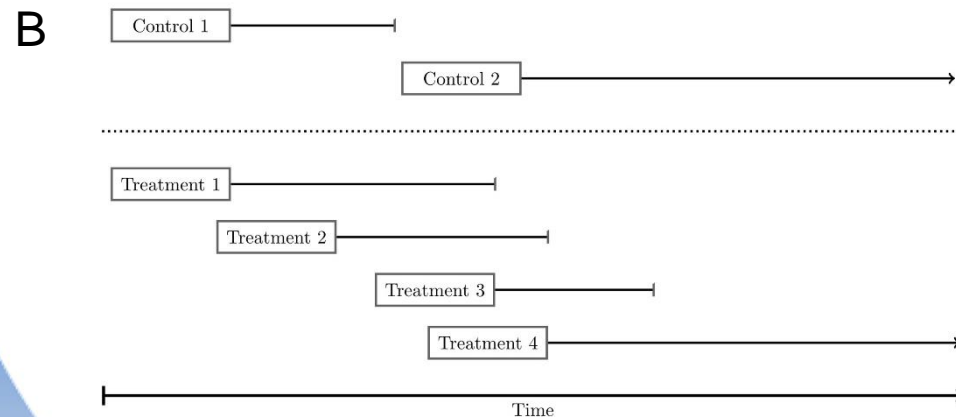
- **Basket:** a single targeted therapy in the context of multiple diseases or disease subtypes
- **Umbrella:** To study multiple targeted therapies in the context of a single disease
- **Platform:** multiple treatments within a single disease, possibly several disease subtypes, perpetual design of trial



Features of Platform Trials



(A) Schematic overview of a platform trial.

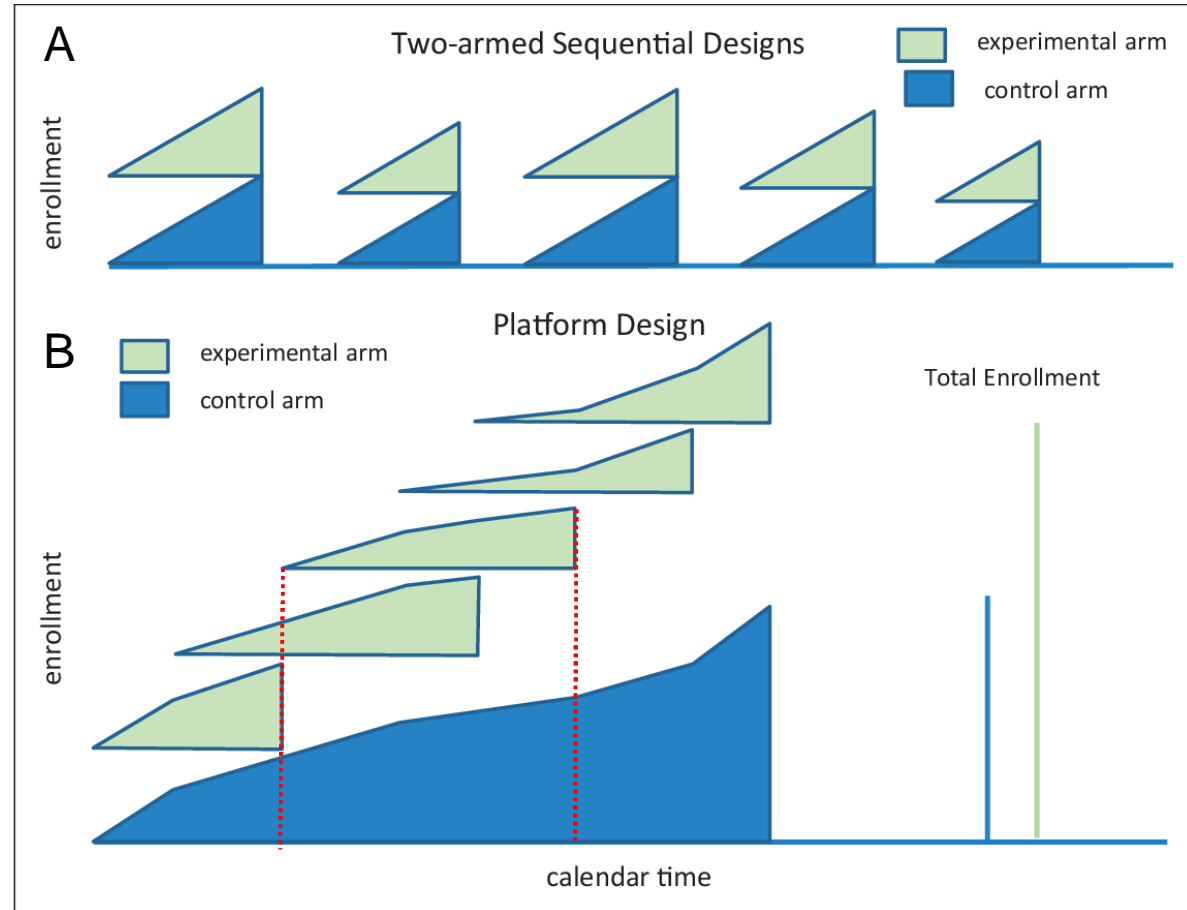


(B) Schematic overview of a single disease sub type or subgroup sub study of a platform trial.

- Umbrella type platform (A) and single disease platform or subgroup study (B).
- Decision algorithm to drop arms at interim analyses
- I-SPY2 is an example of a platform that has had drugs graduate and receive accelerated approval from the FDA

Control Arms

- Efficiency in a reduced number of patients on control arm
- Concurrency of control data for analysis
- Multiple questions in the same protocol may need to consider multiplicity adjustments



Hobbs et al 2016

Potential Advantages

- Sample size efficiencies
- Quicker time overall for development, compared to multiple separate trials
 - Common trial infrastructure reduces the time to set up a new arm of the study
- Attractive due to smaller chance of getting conventional therapy
- Potentially broader entry criteria
- More easily compare treatments across arms

Challenges and Complexities

- Operational
 - More time to develop initially in contrast to a traditional trial due to complexity
 - Statistically challenging - many different scenarios, modeling and simulation work can be extensive
 - Once opened complex to evaluate multiple regimens at time as apposed to a single regimen – monitoring committees
- Loss of autonomy
 - Sponsors must follow rules of master protocol, which may not be perfectly aligned with their drug development program
 - Some platforms offer more flexibility to the sponsor than others

ProMMise Platform

A Platform trial for Relapsed patients to evaluate Ongoing novel therapies in Multiple Myeloma In combination with Standard of care therapies (PROMMISE)

Relapsed/
Refractory
myeloma
1-3 prior lines
of therapy



Belamaf* monotherapy

Belamaf* +
Low dose
chemotherapy +
dexamethasone

Belamaf* +
PI + chemo +
Dex

Belamaf* +
CD38

Belamaf* ocular
sub-study

Stop/go:
Endpoint:
Toxicity

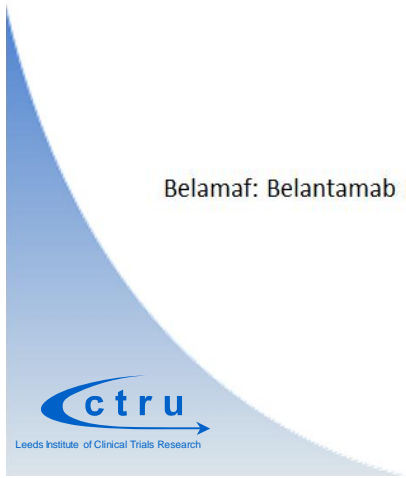
Cohort
Expansion
Endpoint:
1°: Safety
2°: Response
(≥VGPR), PFS,
OS
3°: translational
analysis

approx
20 per arm

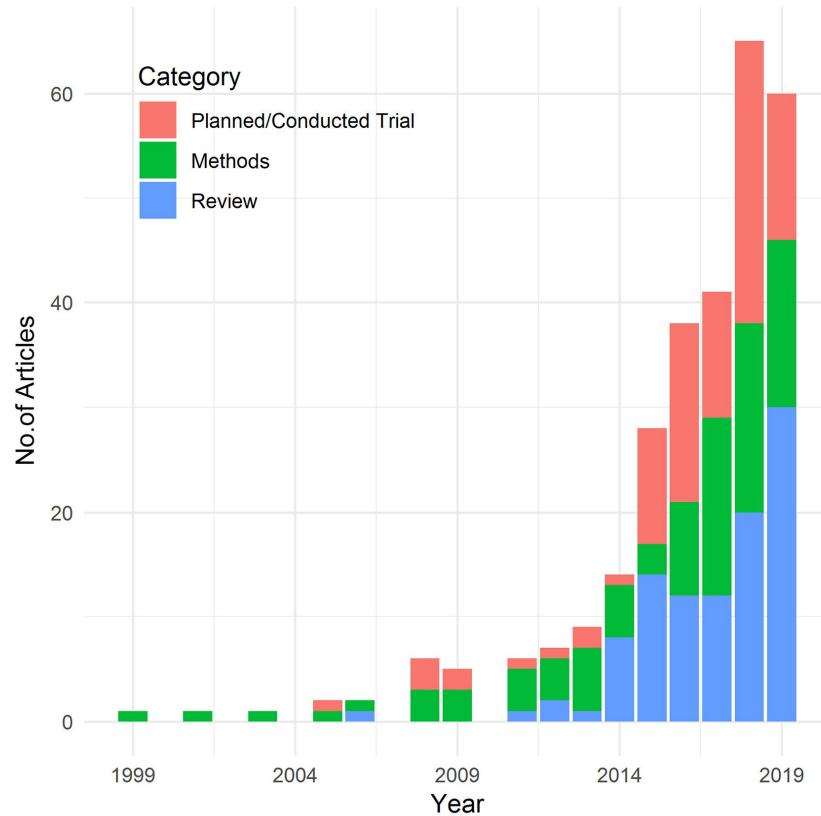
- Arms likely to open at different times
- Each arm to be compared with Belamaf* monotherapy

Belamaf: Belantamab Mafodotin

CI: Rakesh Popat



Moving Forwards

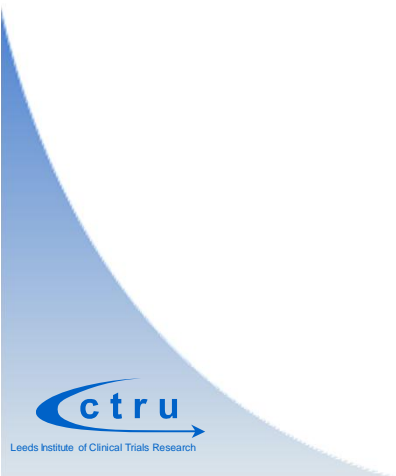


Meyer et al. 2020

- Implementation not yet wide scale despite potential efficiencies
- Great care needed to account for operational and statistical challenges
- As targets become more precise, coordinated research efforts become inevitable

References

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- I-SPY 2 treatment schema (from <https://www.ispytrials.org/i-spy-platform/i-spy2>, Accessed on November 9, 2020. © 2020 Quantum Leap Healthcare Collaborative
- HOBBS, B. P., CHEN, N. & LEE, J. platform design using predictive probability. 2016.



Overview

- Changing landscape of precision medicine
- Master protocols – definitions
- Platforms in a more detail
- Benefits and Challenges
- Example of a platform trial

