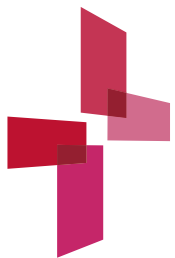


Organisation of adaptive platform trials

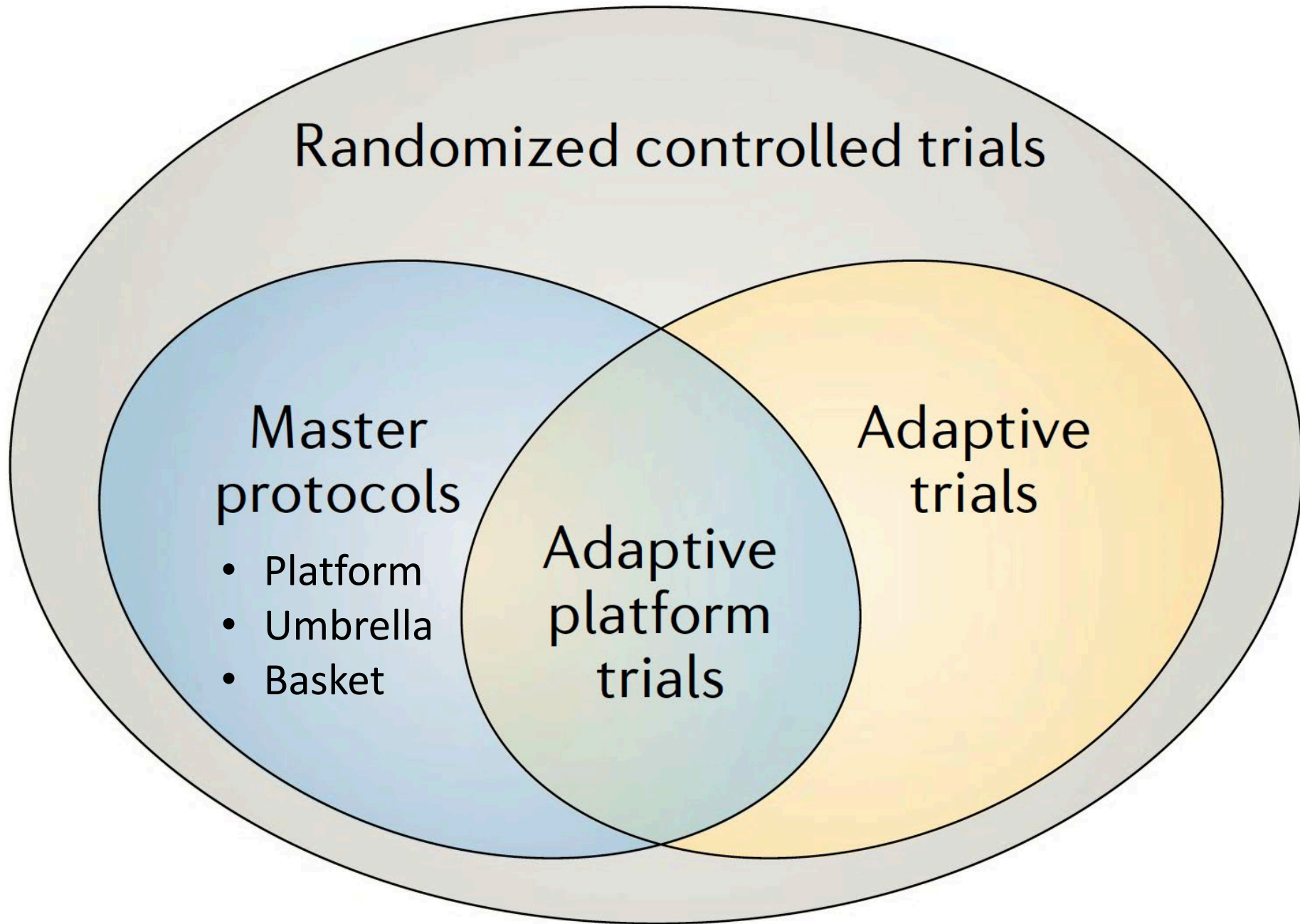
Colin McArthur



Australian
Clinical
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Alliance

www.clinicaltrialsalliance.org.au

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How are adaptive platform trials different?

Platforms

- evidence to optimise management of a “condition”
- evaluation of multiple treatments simultaneously and sequentially
- can be perpetual

Domains / interventions

- may be limited to subgroups or strata defined by disease stage, severity, patient age, phenotype, biomarkers, etc
- use of common controls (simultaneous, non-simultaneous, historic)
- comparisons between interventions often sought
- blinding is difficult with multiple interventions

Adaptations

- design features are modified during trial conduct based on accruing data



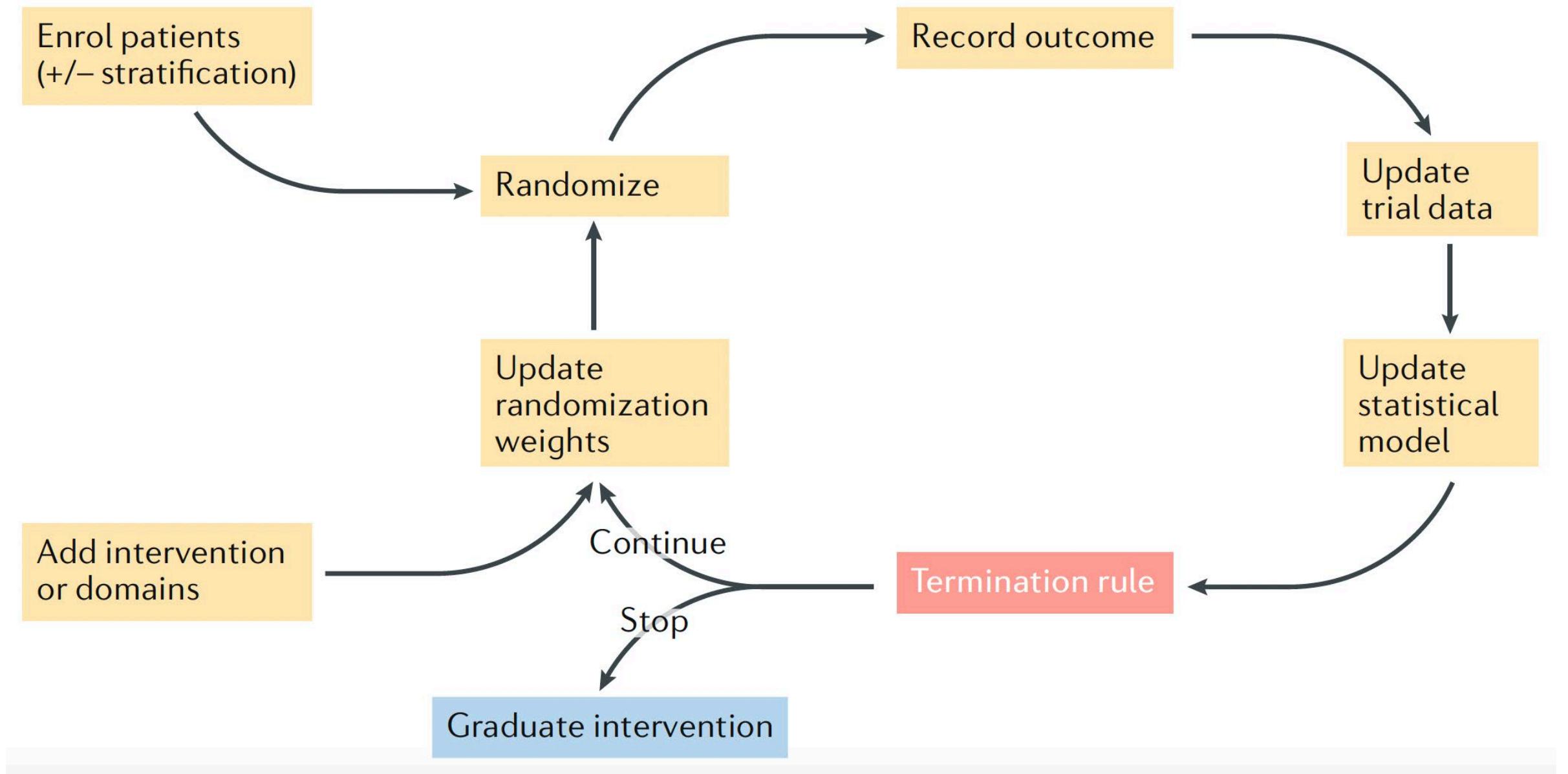
Adaptive Trials

DATA

N

S

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Potential adaptations: examples

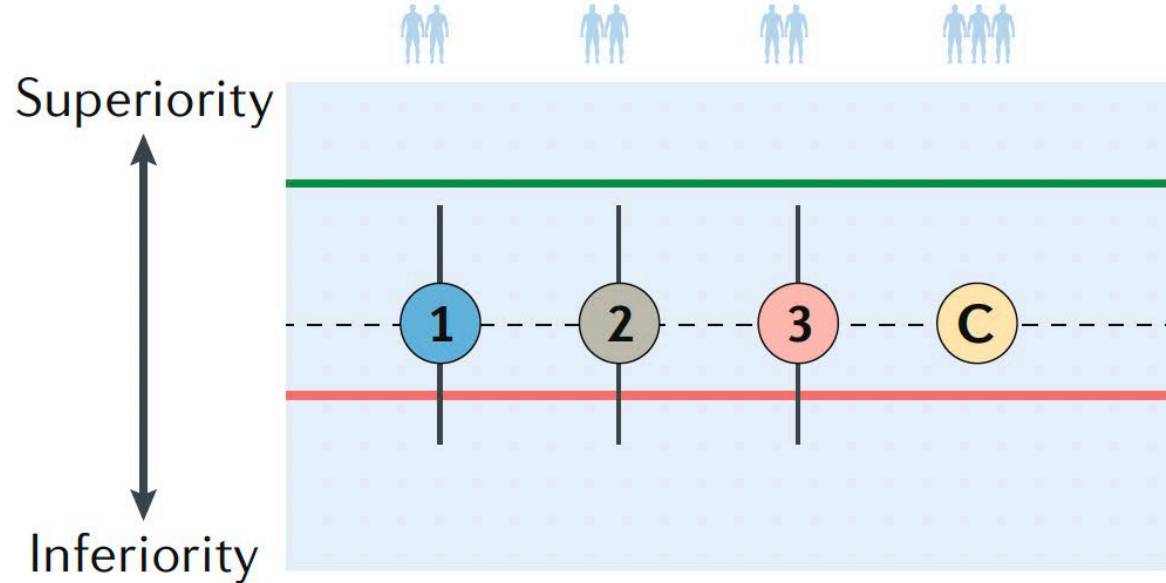
- Sample size adjustment based on expected power and event rates
- Eligibility criteria modification to enrich sub-populations or reduce hazard
- Varied randomisation proportions including response-adaptive randomisation
- Assessment of treatment-by-treatment or treatment-by-state interactions
- Addition/removal of interventions or domains entirely or by stratum
- Safety measures to trigger adaptation separately from primary outcome

Potential adaptations: design and documentation

- Pre-specification adaptations and their triggers
- Pre-specification of statistical model e.g. adjustments, borrowing
- Pre-specified statistical thresholds e.g. effectiveness, futility or harm
- Use of simulations to characterise expected trial performance

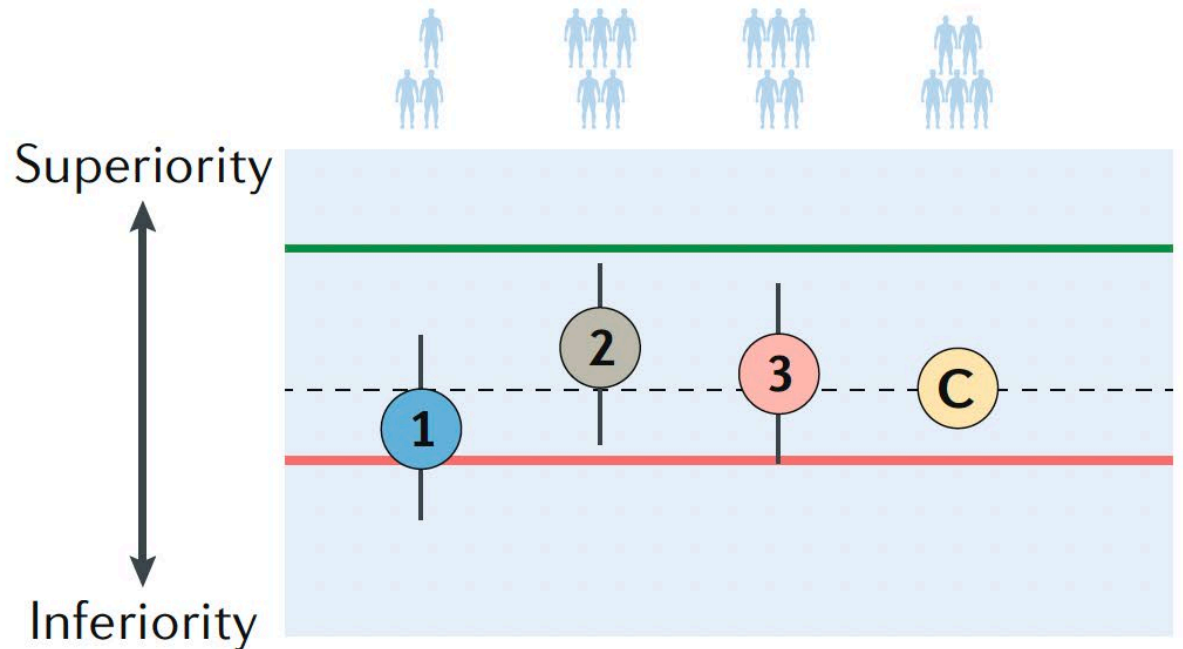
Adaptive analysis and response-adaptive randomisation

Study / domain initiation



- Wide uncertainty
- Balanced randomisation

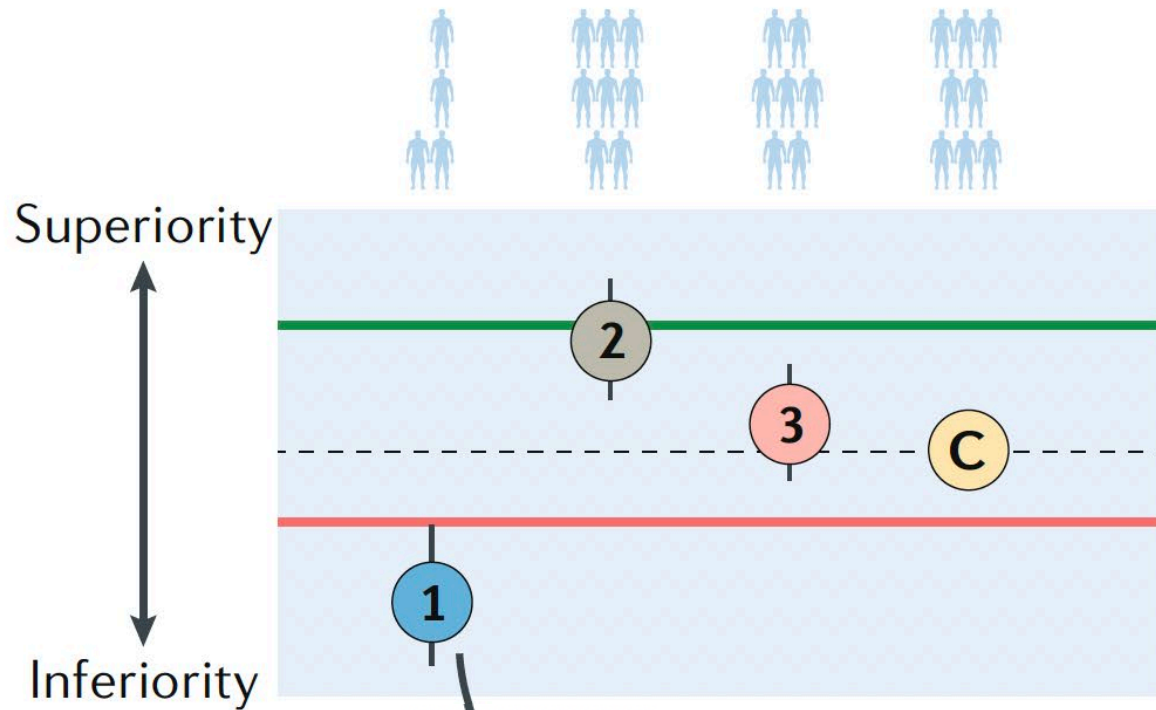
Adaptive analysis



- Interventions 2 & 3 trend to superiority
- Narrowing confidence intervals
- Randomisation proportions #2 & #3 > #1

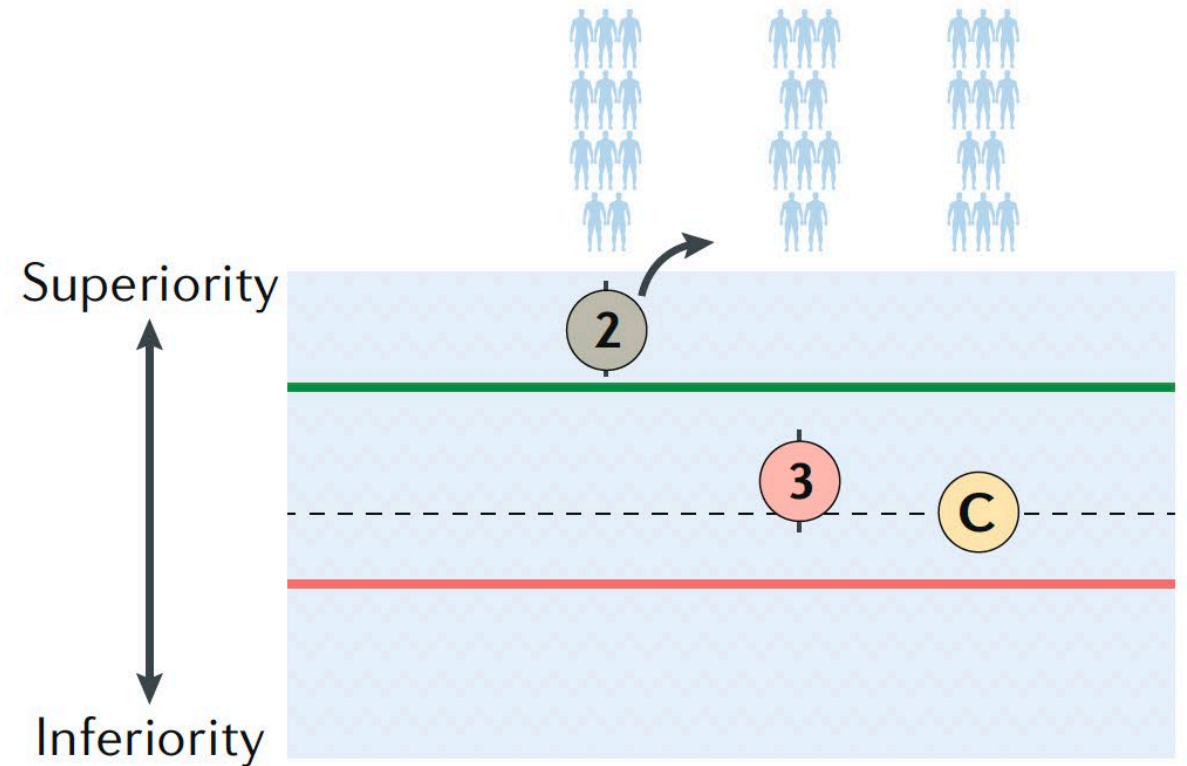
Adaptive analysis and response-adaptive randomisation

Discontinuation of inferior intervention



- Harm / inferiority threshold reached for #1
- Narrowed uncertainty bounds for #2 and #3 with more assignments

Trigger for superior intervention



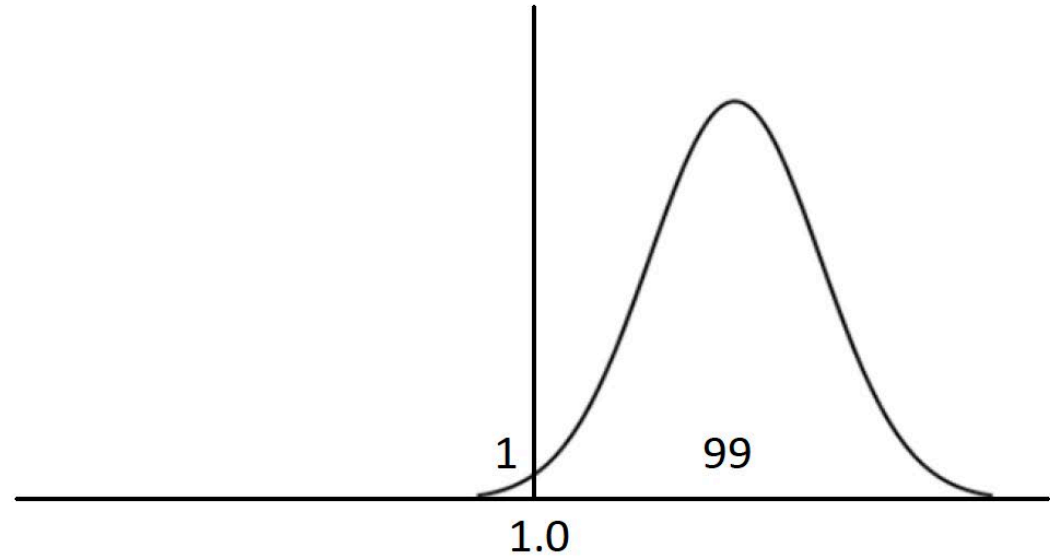
- Further narrowing of confidence intervals
- Intervention 2 superior
- #2 could become control vs alternatives

Response-adaptive randomisation

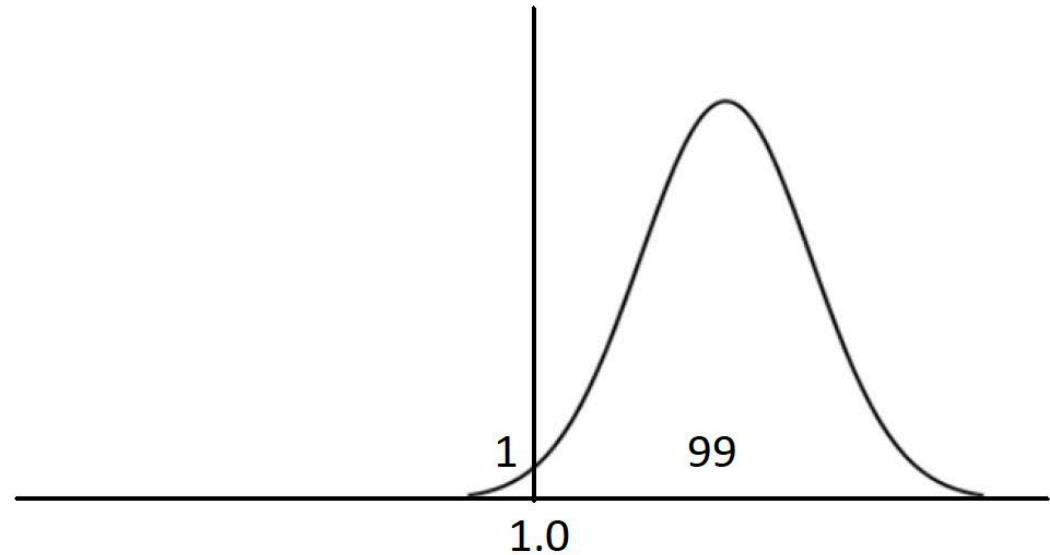
- Randomisation proportions modified based on accruing data so that better performing interventions are allocated more commonly and poor performers less
- Participation benefit as new patients gain from (blinded) data during trial conduct
- Full RAR in proportion to probability of superiority can lead to very unbalanced allocations:
 - Risk of unblinding at site level e.g. if 80% of patients are getting one allocation
 - Loss of power due to imbalance having greater effect than the treatment effect
 - Maximum perhaps 70:30
- ‘Mild RAR’ with tight limits (e.g. 55:45) is an option

Bayesian statistical trigger concepts

Superiority: Intervention better than all other interventions
Prob OR > 1.0 ≥ 0.99



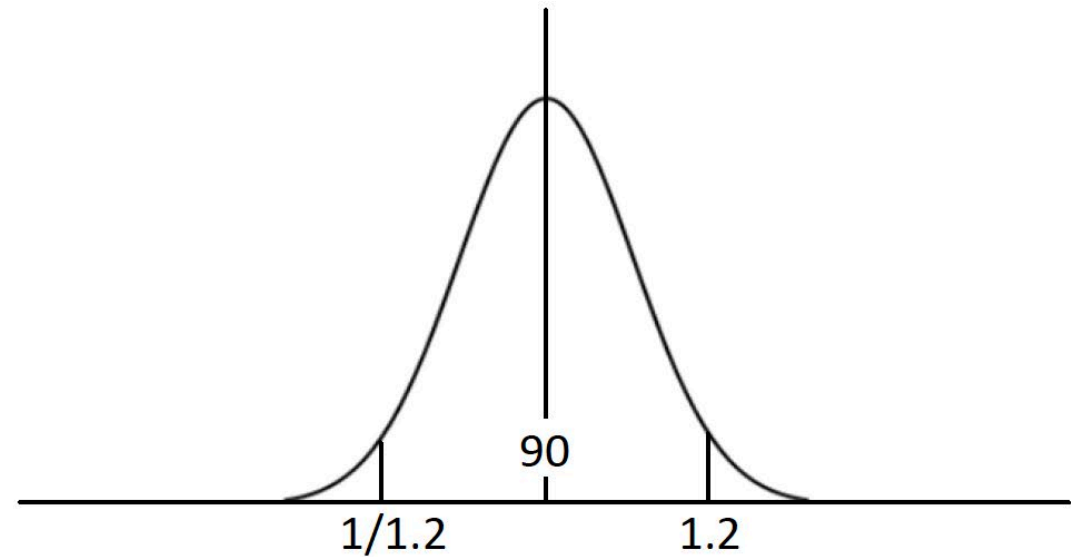
Effective: Intervention better than a standard of care control
Prob OR > 1.0 ≥ 0.99



Bayesian statistical trigger concepts

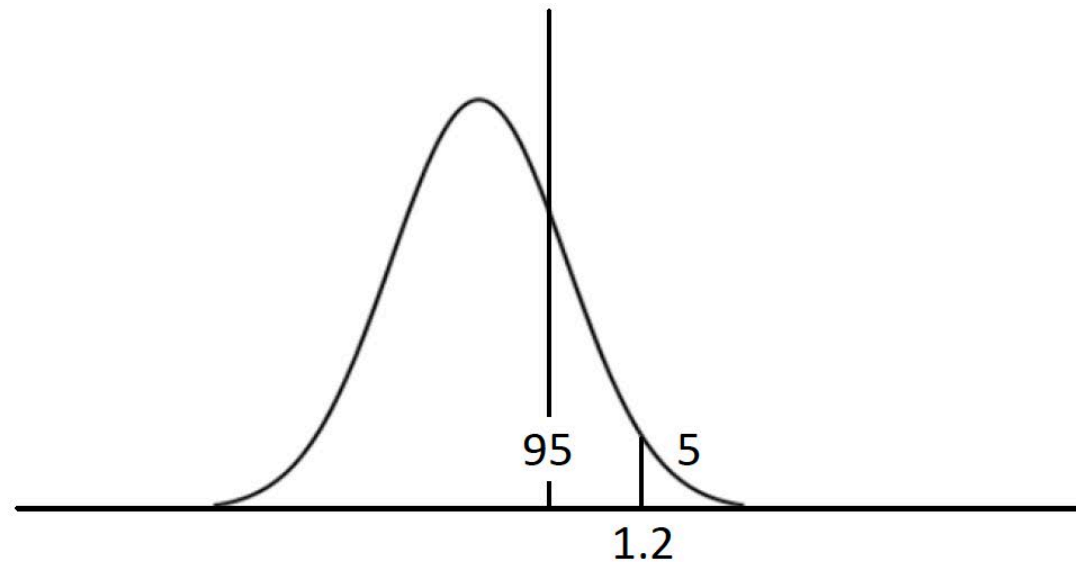
Equivalent: A pair of interventions differ by < 20%

Prob $1/1.2 < OR < 1.2 \geq 0.90$



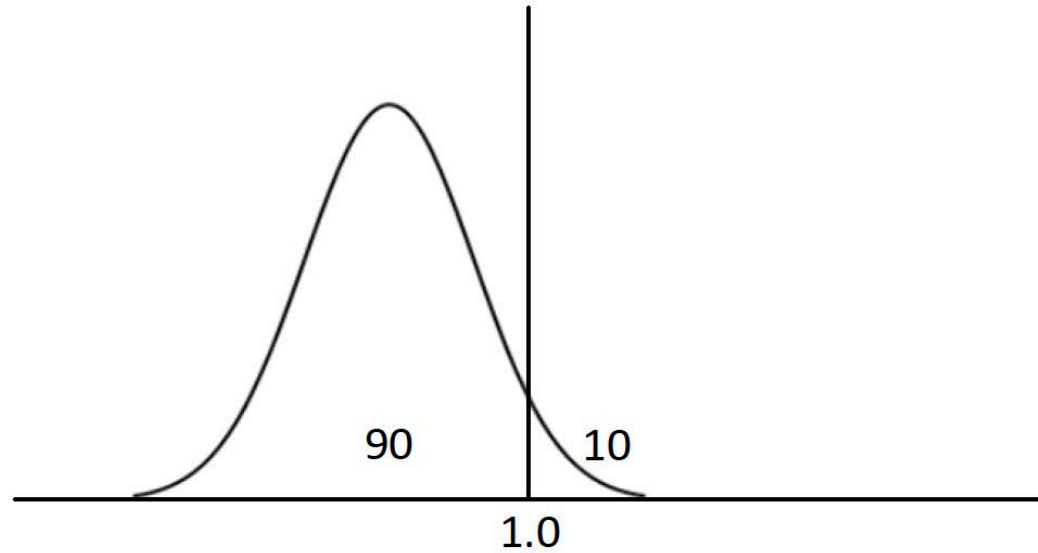
Futility: Low probability an intervention is effective

Prob $OR < 1.2 \geq 0.95$

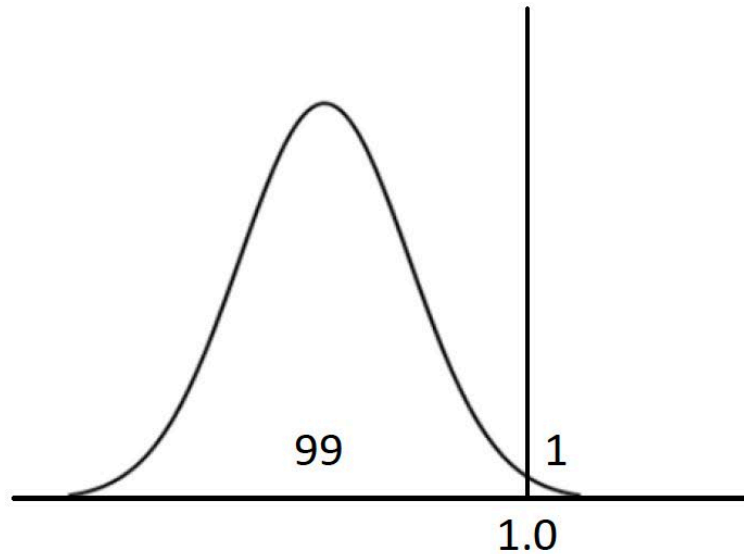


Bayesian statistical trigger concepts

Harm: Intervention worse than a standard of care control
Prob OR $< 1.0 \geq 0.90$

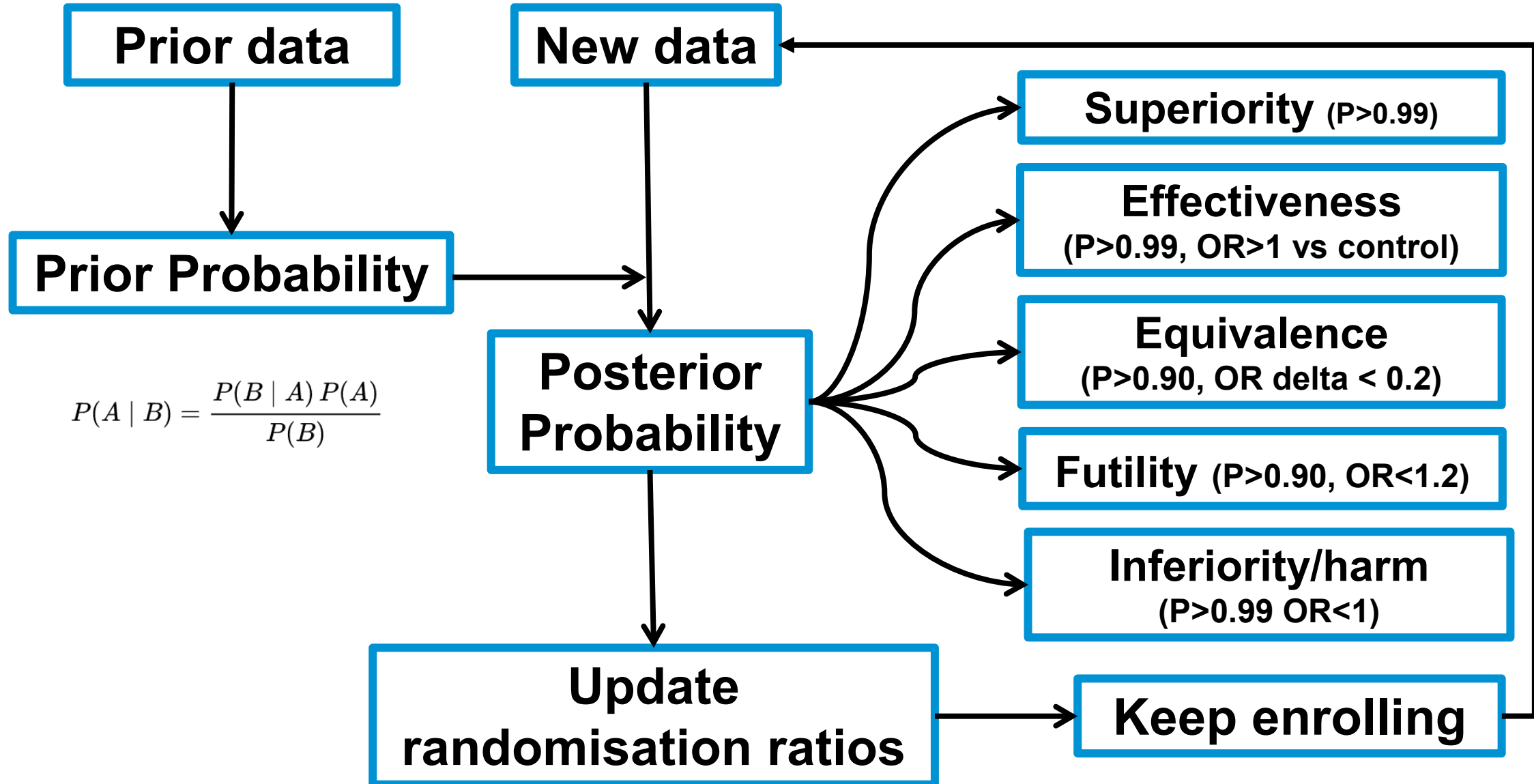


Inferiority: Intervention worse than all other interventions
Prob OR $< 1.0 \geq 0.99$



Adaptive Bayesian analysis

Answer questions when sufficient data has accrued, not at a pre-specified sample size



Adaptations following statistical triggers - examples

- Superiority** - close domain, add intervention to SOC for other domains
 - superior intervention becomes control vs new intervention
- Effectiveness** - drop control, continue to compare all active interventions
- Equivalence** - pool interventions for subsequent analyses
- Futility** - discontinue intervention (use as early trigger for possible harm)
- Inferiority/harm** - discontinue intervention

Re-design and re-build the plane
....while flying it



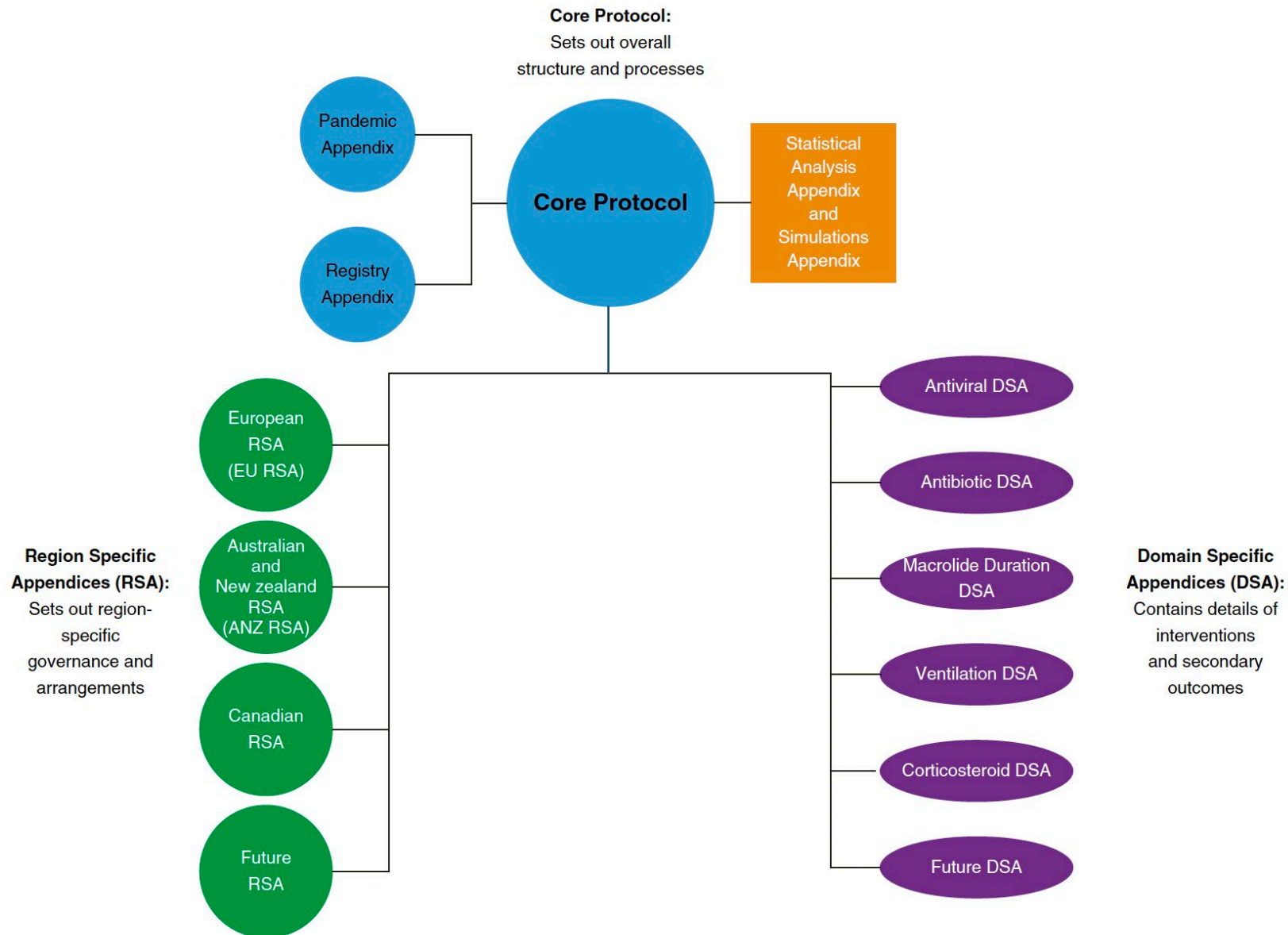
Trial management committee functions

- Wider breadth of **subject matter expertise** required
- **Simultaneous activities** e.g. analysis and reporting of one aspect while adapting trial design while continuing to recruit, monitor and submit data under existing design
- For more complex platforms, **sub-committees** often required e.g. domain content experts, statistical, reporting, regional management
- **Data flow and quality** to support both adaptive analyses and full results
- Timely **monitoring** required as data is analysed regularly (and published)

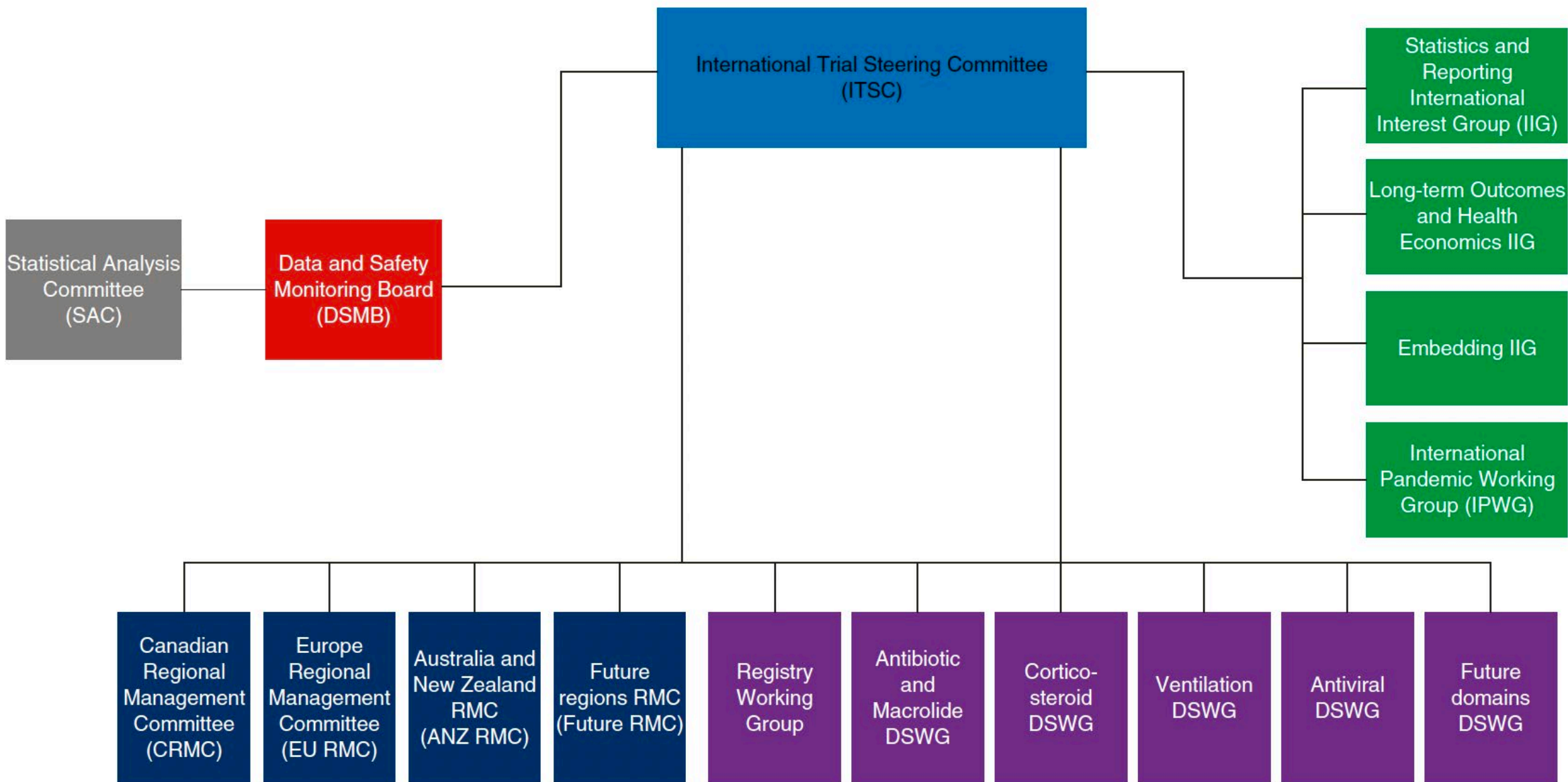
Trial management committee functions

- **Maintaining blinding** to accruing data & analyses (+/- RAR) can be challenging
- **DSMB** receive adaptive analyses and provide recommendations
- Deciding / implementing **design adaptations** and **communication back to DSMB**
- **Simulations** are often required to assess potential adaptations
- **Co-ordination** with/between sub-committees, regions, sites
- **Funding** complexity (no fixed sample size or trial duration)

Modular protocol example: REMAP-CAP

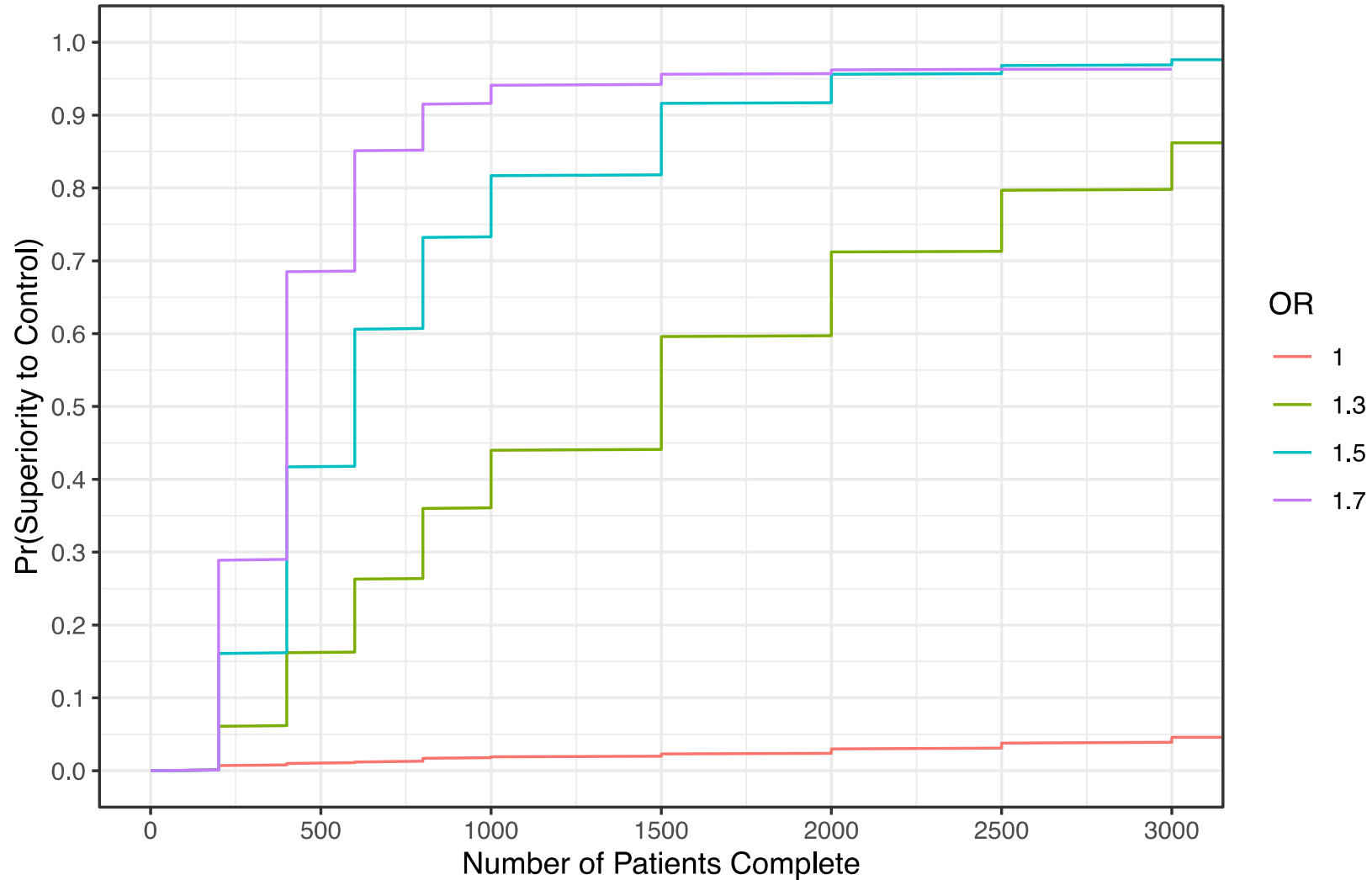


Governance structure example: REMAP-CAP



Simulation example from REMAP-CAP (ordinal scale outcome)

2v1 Domain: Pr(Superiority to Control) vs Patients Complete
One effective arm, non-nested treatment effects



Data flow and analysis

- Adaptive trials require (timely) data!
- Allocations and primary outcome (and earlier intermediate surrogate if used)
- Safety secondary outcomes
- Eligibility for randomisation when more than one intervention
 - Patient-level contra-indication may exclude from one but bias the comparators (e.g. renal failure)
 - Limit comparisons to patients eligible for both options
- Monitoring and data quality can be significant issues
- Separation of statistical support for (multi-domain) platforms
 - Unblinded for adaptive analyses vs blinded to accruing data for design changes

Independent Data and Safety Monitoring Committee

- More expansive and regular role
- Need to fully understand the design and potential adaptations
- Receive and interpret results of adaptive analyses from unblinded statisticians
- Safety outcomes may be provided separately
- Recommendations must not unblind accruing data for still recruiting interventions
- Expertise should include familiarity with statistical methods used (e.g. Bayesian)
- Trial management committee communication important (design adaptations)
- Federated / multi-platform collaborations pose particular challenges for DSMCs

Summary

- Adaptive platform trials are powerful and efficient
- Significant increase in operational complexity
- Well suited to Bayesian statistical methods
- Care needed in initial design and adaptations
- Simulations are (almost) essential
- Robust data flow processes during trial are crucial
- Increased role for independent data and safety monitoring