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Translation Clinical
Oncology

An adaptive phase II basket trial design

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Basel
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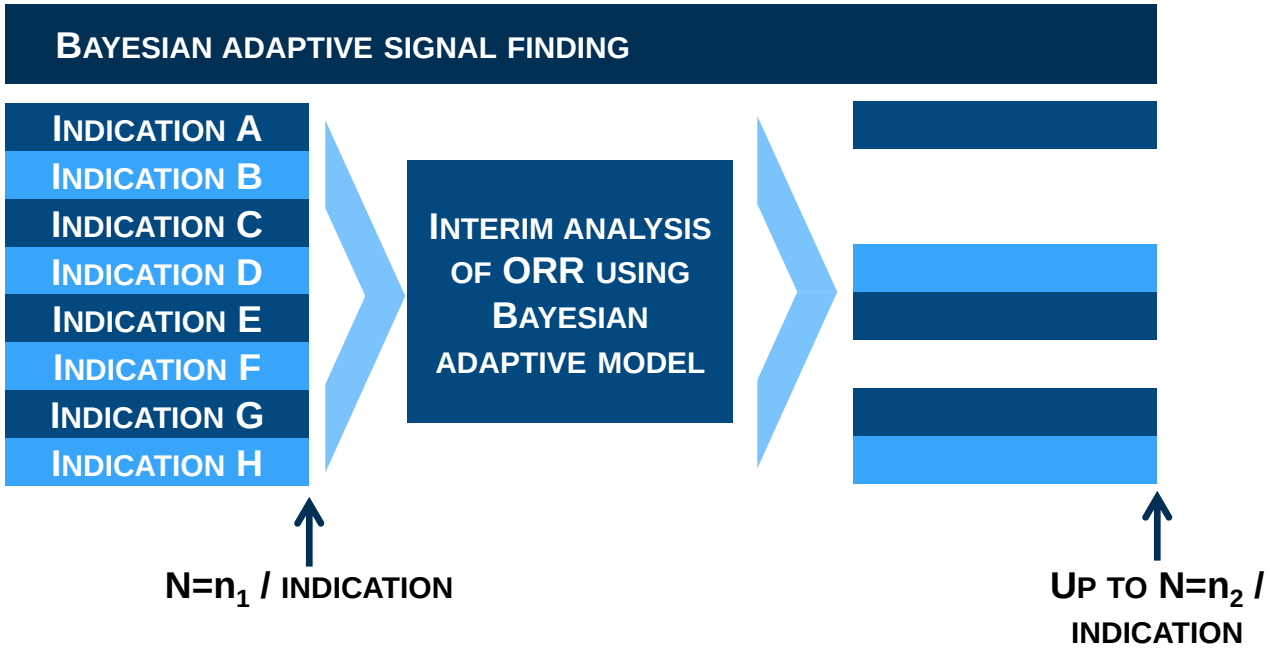
An adaptive phase II basket trial design

1. Trial design overview
2. Bayesian hierarchical model: EXNEX
3. Some design issues
4. Last words

Bayesian adaptive signal finding



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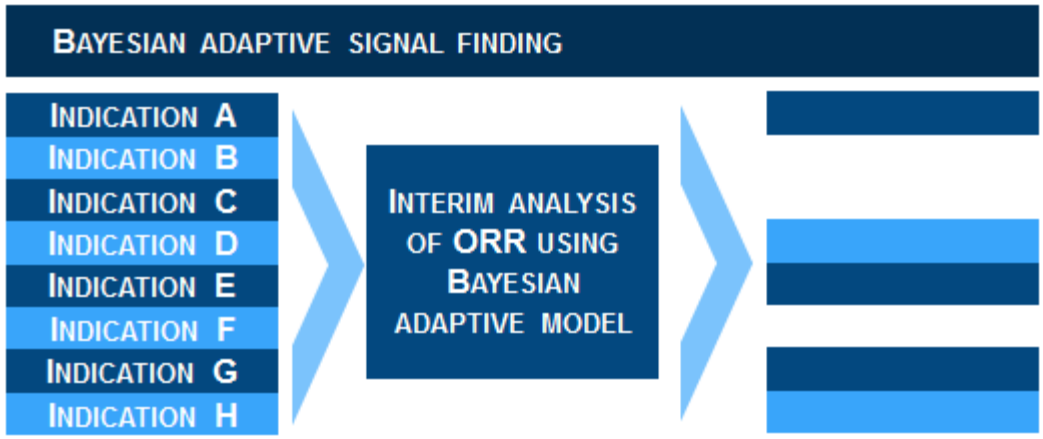
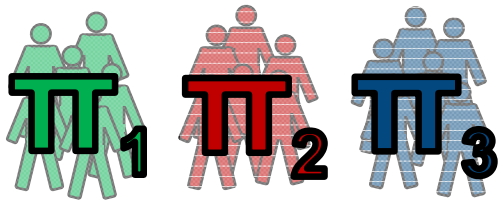
Bayesian adaptive signal finding



- Multiple indications
- Small (initial) sample sizes
  - Initial futility decision after response outcome observed for $N=n_1$ patients
- How to make optimal use of available data?

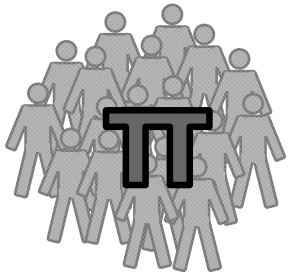
Bayesian adaptive signal finding

Making optimal use of available data



Independent strata

Each stratum has independent P(response)

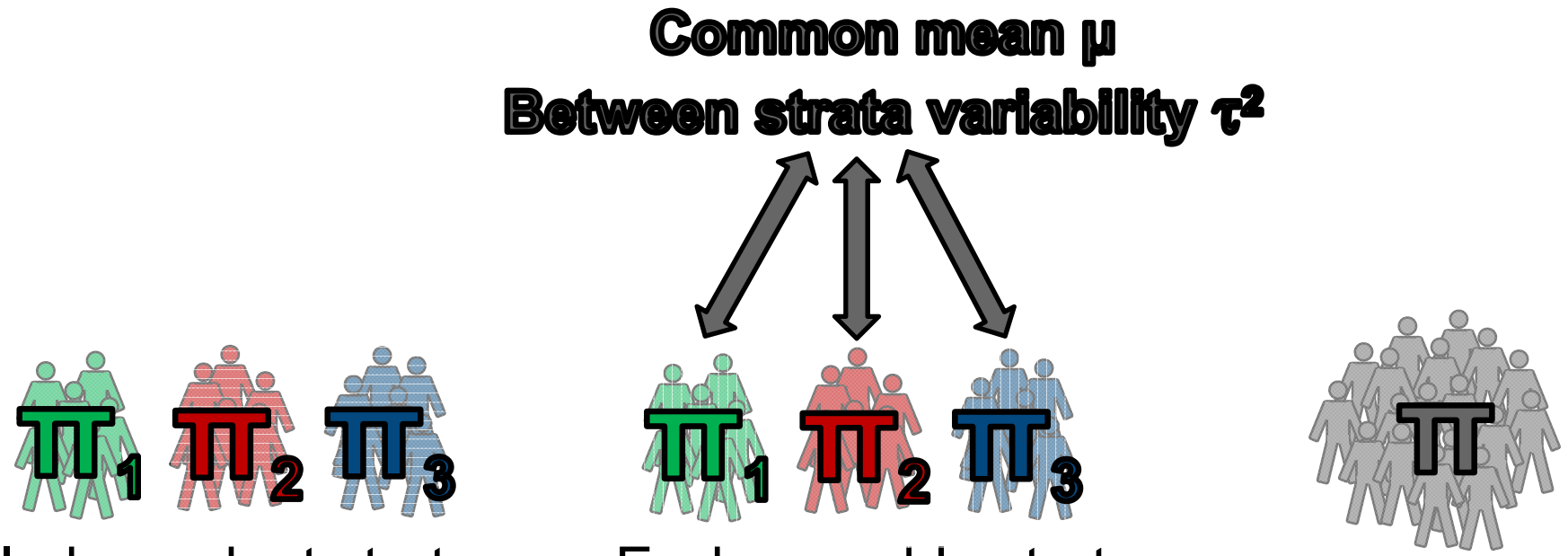


'Pooled'

Common P(response)

Bayesian adaptive signal finding

Making optimal use of available data



Independent strata

Each stratum has independent P(response)

Exchangeable strata

'Similar' P(response)

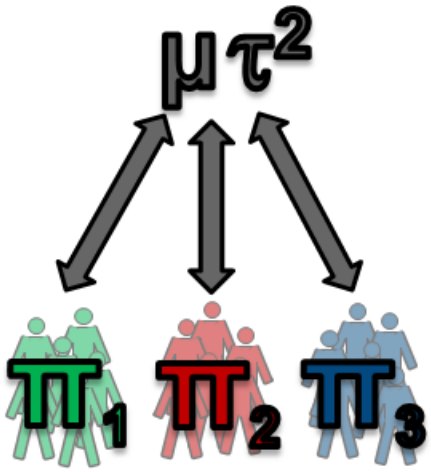
Hierarchical model allows sharing of information

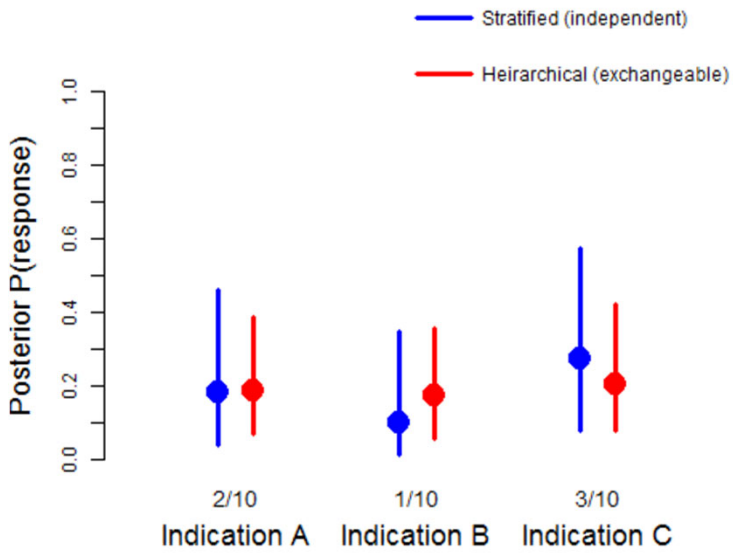
'Pooled'

Common P(response)

Hierarchical models

- Increased precision
- Shrinkage towards common mean





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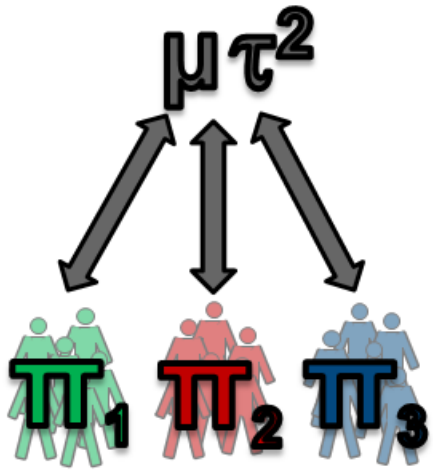
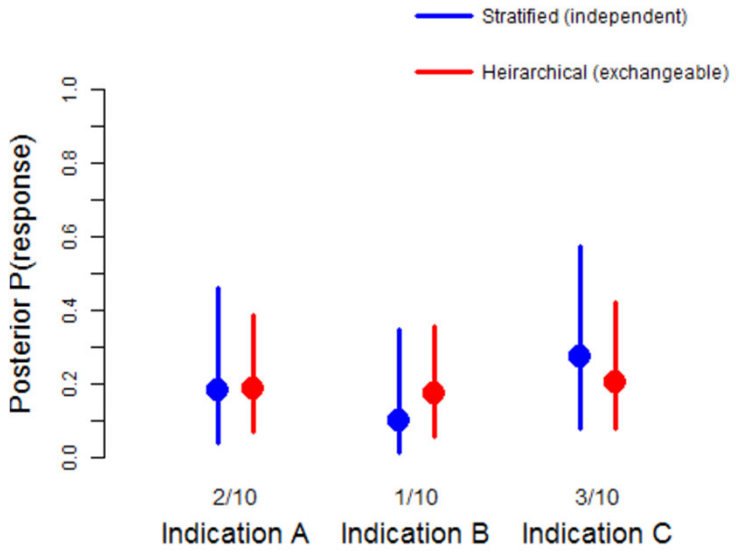
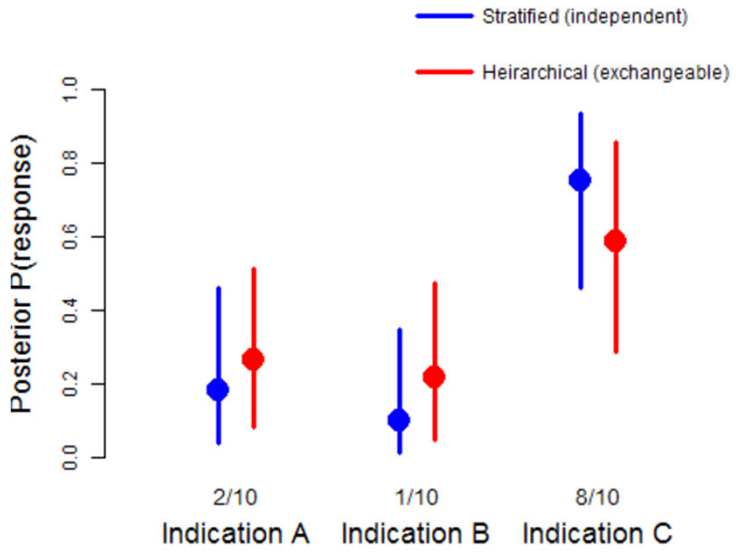
Hierarchical models

- Increased precision
- Shrinkage towards common mean





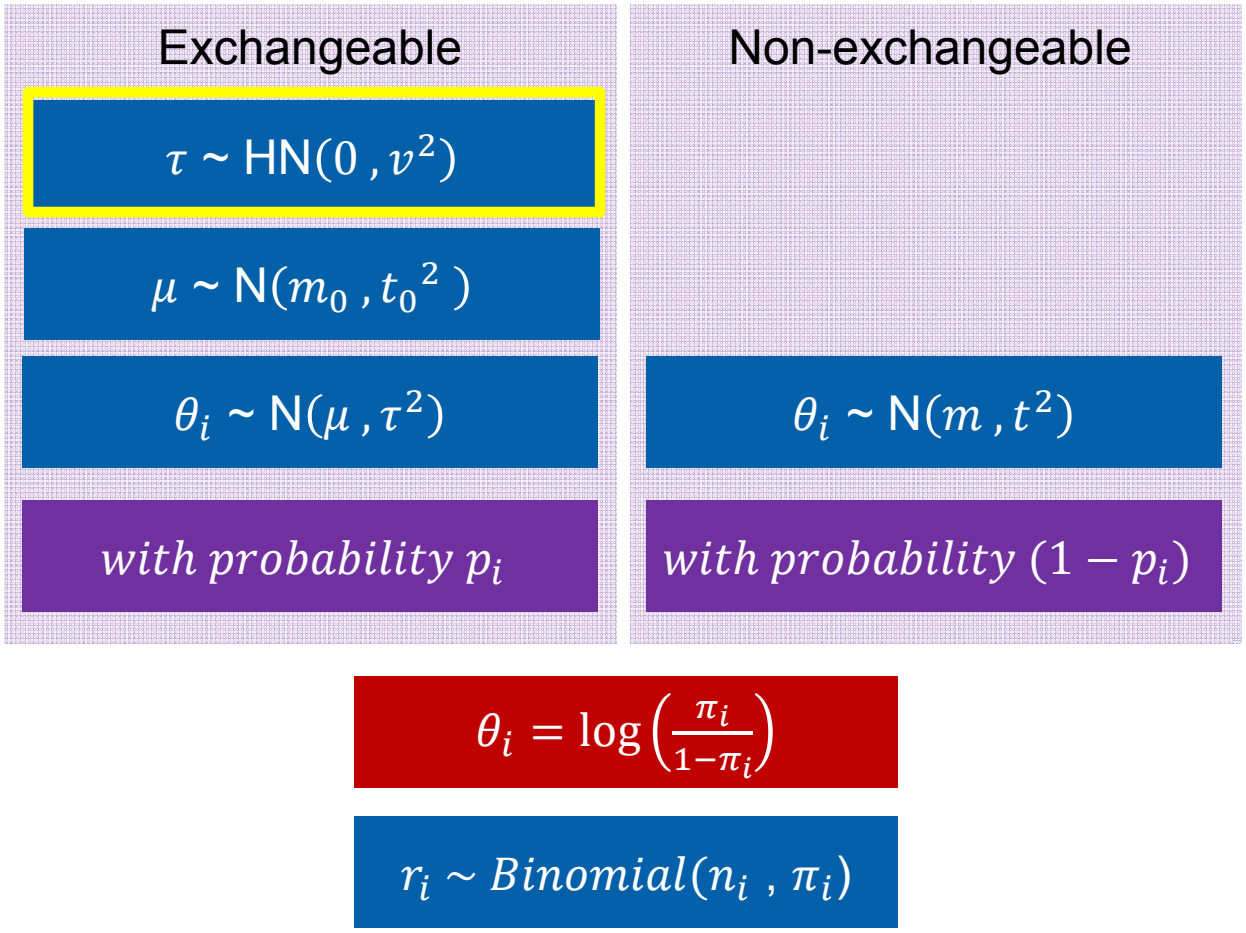


EXNEX

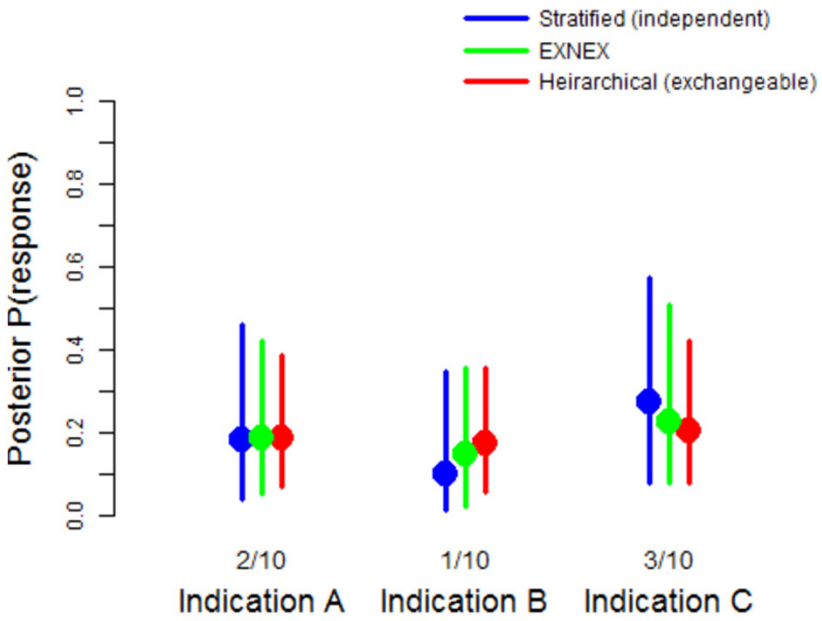
Mixture of hierarchical and stratified approaches

- Exchangeable vs Independent is **not a dichotomy**
- Each strata is assigned a **probability** of belonging to the exchangeable group
- That probability updates as data accumulates
  - Strata initially expected to have similar outcome may prove otherwise
  - Equally, strata initially thought dissimilar may prove to have similar outcome
- Dynamic borrowing of information between indications
  - More borrowing between indications with similar outcome

EXNEX
Mixture model



EXNEX model



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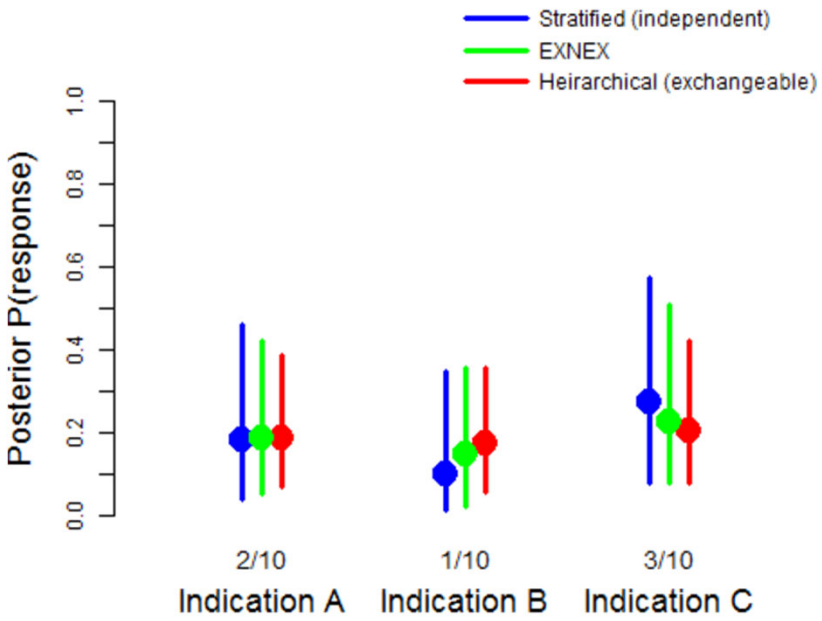
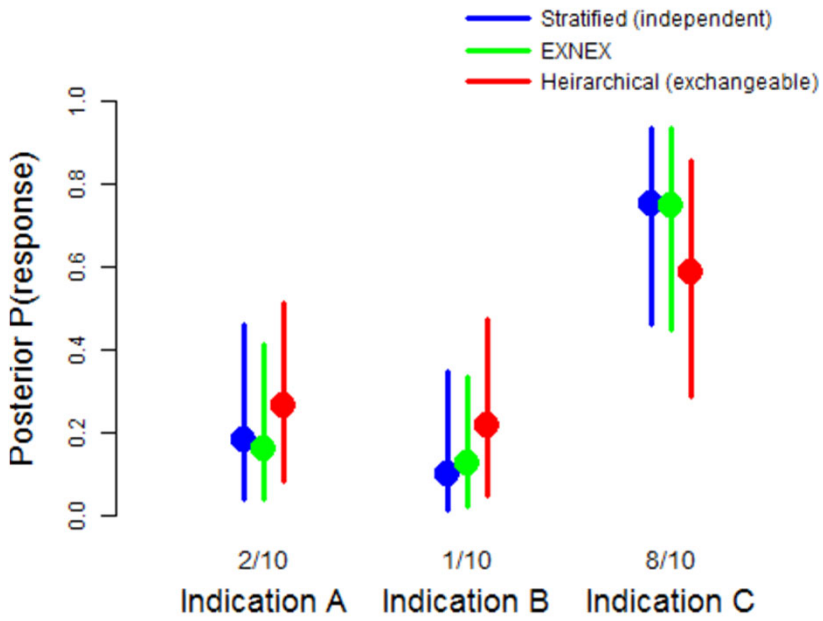
EXNEX model





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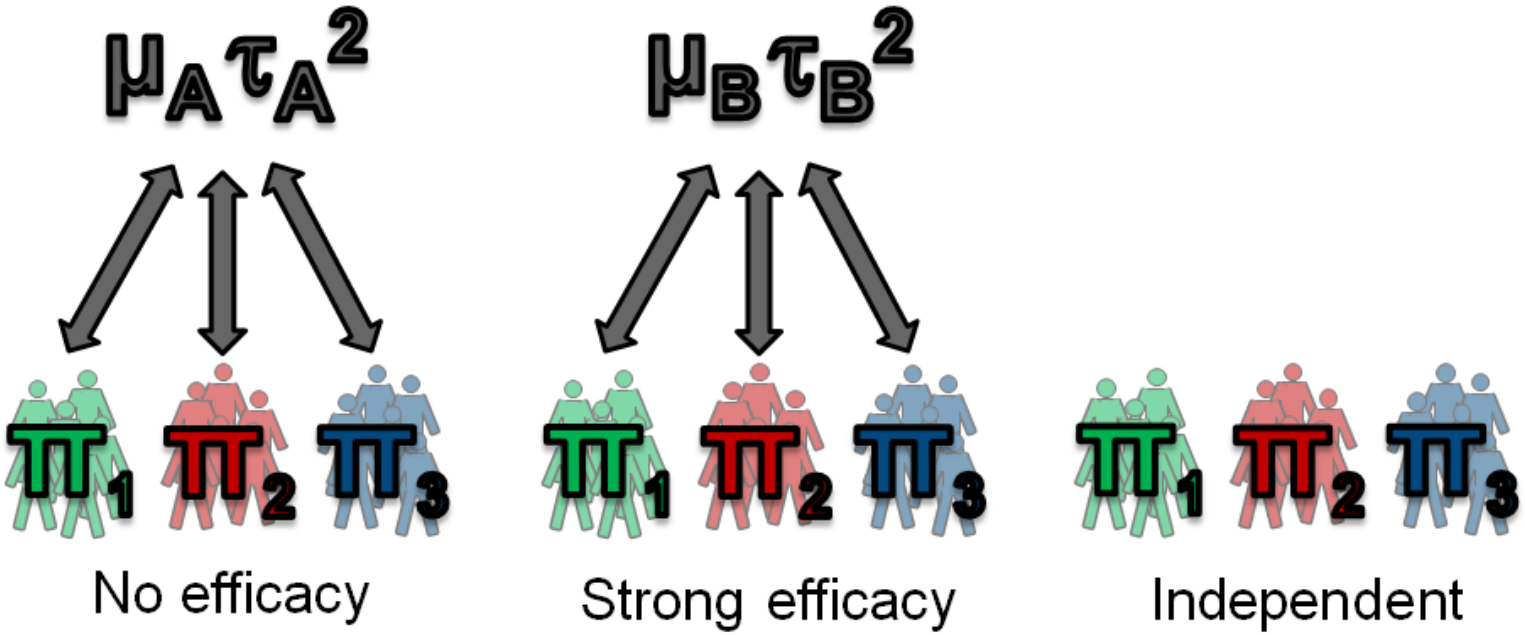
Design considerations
Exchangeability groups

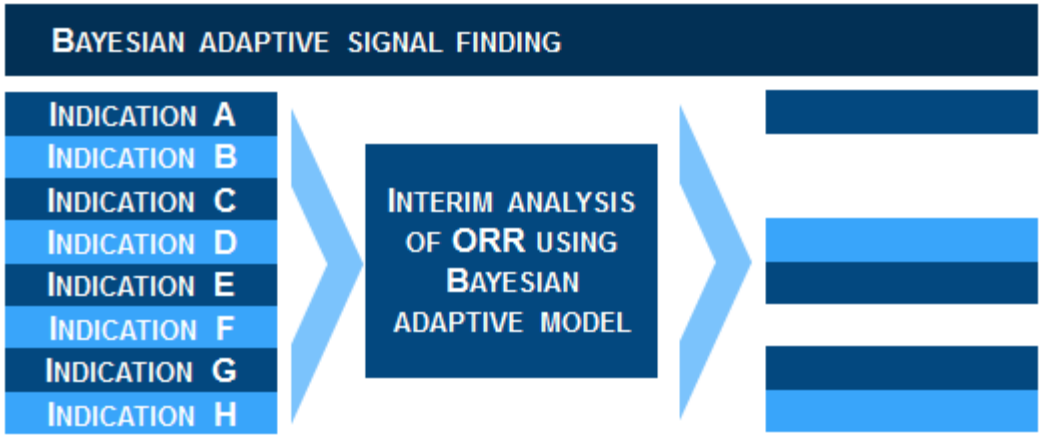
- Multiple exchangeability groups are possible



Design considerations
Exchangeability

- Exchangeability can be defined on:
- Probability of response
  - Appropriate if we expect to see similar response rates in some or all indications
- Odds ratio of response
  - More suitable for examples where indications have different historical
  - Hypothesis is to see similar improvement over historical rates

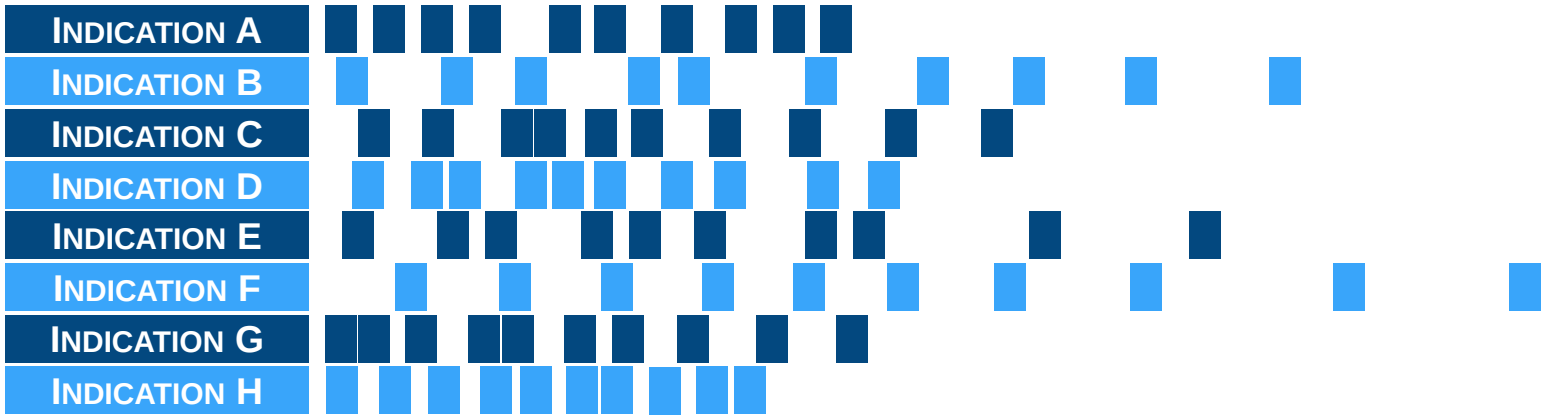
Design considerations
Futility decision making



- Intention is to make an interim stop/go decision for each indication after n_1 patients have been enrolled
- At each interim data from all patients is used
- Futility decision rule applied to each stratum

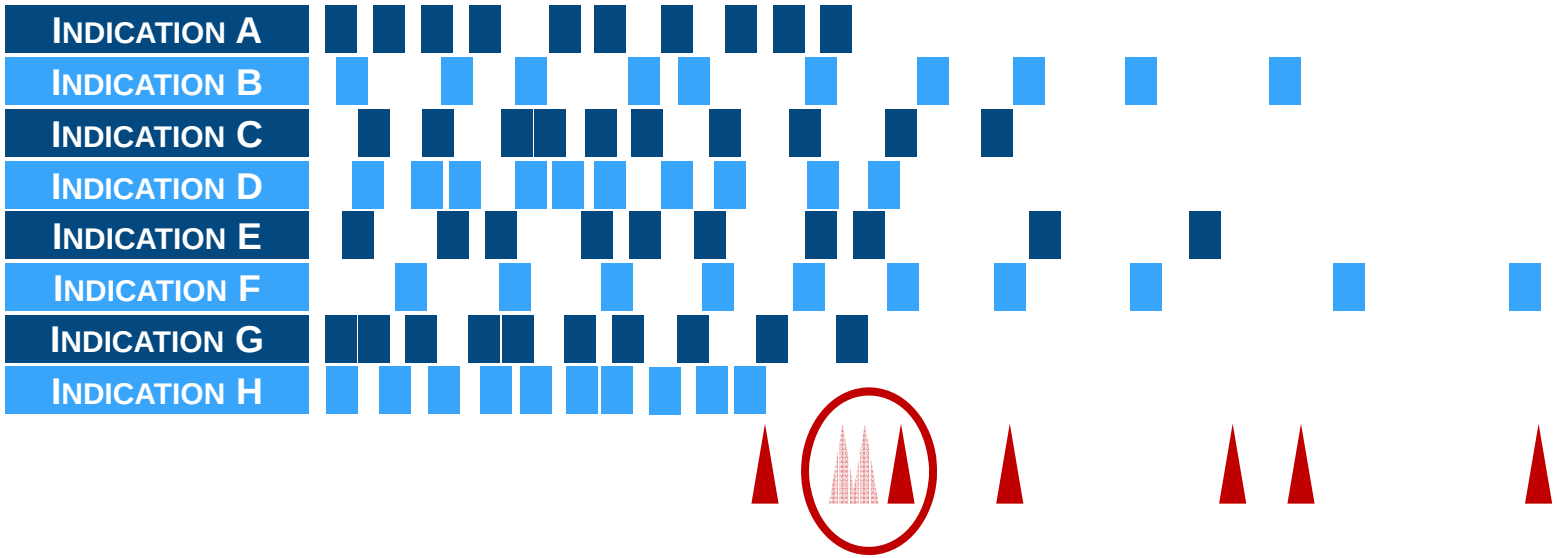
$$P(\pi_i \leq c_i) > \varepsilon$$

Design considerations
Futility decision making



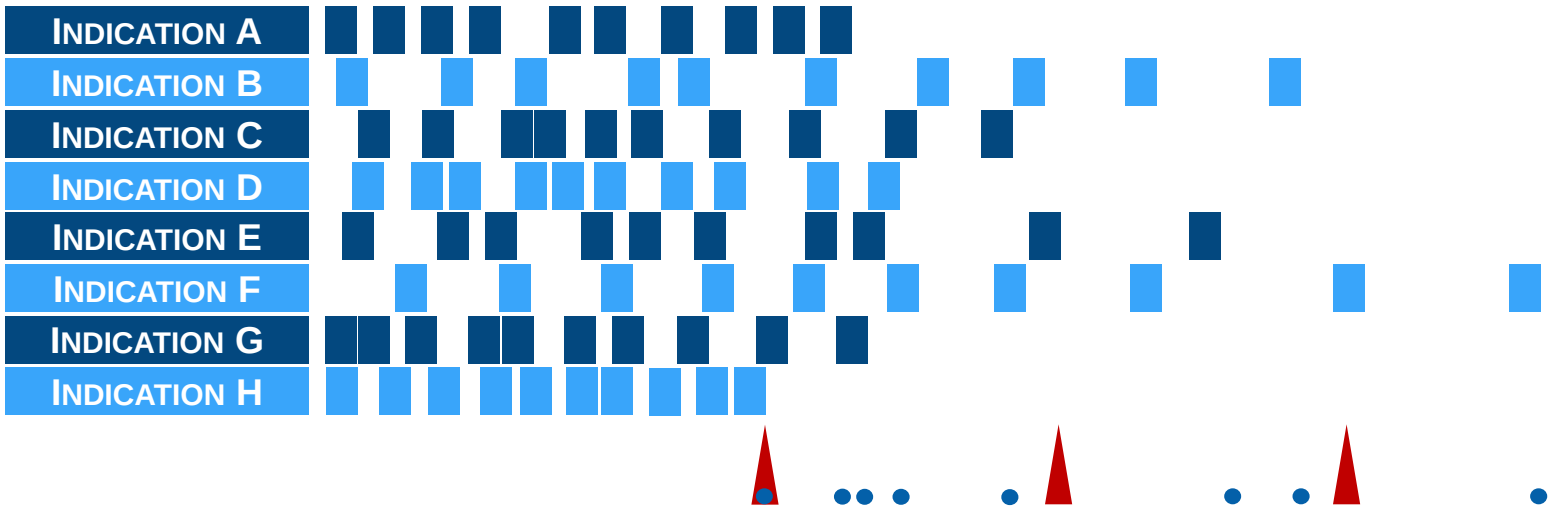
- Enrolment rates can vary substantially
- Only strata reaching a minimum enrolment limit are eligible for closure
- Strategy for interim futility analyses allowing for:
  - Decisions being taken at the appropriate time
  - Operational feasibility!

Design considerations
Interim decision strategies



1. Trigger an interim as each strata reaches $N=n_1$
   – With flexibility to shift decision time points based on projected enrolment

Design considerations
Interim decision strategies



2. Trigger initial interim when first strata reaches $N=n_1$
   - Subsequent interims held periodically (e.g. quarterly)

Last words

- Flexible, adaptive, signal finding framework
- Simulation studies demonstrate:
  - Appropriate decision making at interim
  - Good control of overall false positive/negative rates
- High level of complexity
  - Statistically
  - Operationally

Acknowledgements

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Thank you

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