Exploring early interim analyses in basket designs in Oncology
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Basket designs and Bayesian hierarchical model
Basket designs

• Basket trial*
  – One experimental treatment
  – (Patients with similar genomic features)
  – Different disease types (Renfro and Sargent, 2016)

• Questions
  – Does the treatment work sufficiently?
  – Can we identify cohorts with a promising effect?

* Renfro and Sargent (2016)
Basket designs - analysis approaches

Stratification

- Assumes independent cohorts
- Low precision

Pooling

- Assumes the same underlying response rate in all cohorts
- Potentially large bias

Bayesian hierarchical model (BHM)

- Assumes exchangeability between cohorts
- Parameter of between-cohort variation determines the extent of borrowing
BHM adjusting for target rate (Berry et al., 2013)

- Random cohort effect in terms of log-odds of response rate
- Likelihood

\[ r_i | p_j \sim Bin(p_j, n_j) \]

\[ \theta_j = \log \left( \frac{p_j}{1 - p_j} \right) - \log \left( \frac{\tilde{p}_j}{1 - \tilde{p}_j} \right) \]

Exchangeability of log-odds after adjusting for target rates

- Prior

\[ \theta_j | \mu, \tau \sim N(\mu, \tau^2) \]

\[ \mu \sim N(m_\mu, v_\mu) \]

\[ \tau \sim HN(s_\tau) \]

Informative prior on between-cohort variability; scale parameter choice see Neuenschwander et al. 2015

- Implementation: R interface to JAGS, R2JAGS package
Recruitment and analysis strategies
Recruitment and analysis strategies

- Interim analyses performed to limit exposure of additional patients to an ineffective drug
- Futility could be based on within-cohort analysis only or borrow information across cohorts
- Possible consequences of futility
  - Stop recruitment into cohort
  - Do not develop drug further for cohort (no-go)
  - Exclude cohort from later analyses (“test-then-pool”, Viele et al. 2013)
Recruitment and analysis strategies

• Strategy 1

Overall go at first cohort go
Overall nogo if all cohorts nogo
Overall consider, else
Recruitment and analysis strategies

- **Strategy 1**

  ![Diagram](image)

  Interim futility analysis
  Decision for cohort i
  use only data of cohort i
  nogo if <r responders

  Recruitment
  I: Interim (here futility)
  F: Final

  Overall go at first cohort go
  Overall nogo if all cohorts nogo
  Overall consider, else
Recruitment and analysis strategies

- **Strategy 1**

  
  ![Diagram](image)

  Overall go at first cohort go
  Overall nogo if all cohorts nogo
  Overall consider, else

  Final analysis
  Decision for cohort i use all data from all cohorts based on posterior of BHM

  Recruitment
  I: Interim (here futility)
  F: Final

  Time
Recruitment and analysis strategies

- **Strategy 2**
  
  ![Diagram](image)

  - **Interim futility analysis**
    - Decision for cohort $i$
    - Use all data from all cohorts based on posterior of BHM

  - **Recruitment**
    - $I$: Interim (here futility)
    - $F$: Final

  - **Overall go at first cohort go**
    - Overall nogo if all cohorts nogo
    - Overall consider, else

Exploring early interim analyses in basket designs in Oncology, 24 May 2019
Recruitment and analysis strategies

- Strategy 2

Recruitment
- I: Interim (here futility)
- F: Final

Overall go at first cohort go
Overall nogo if all cohorts nogo
Overall consider, else

Final analysis
Decision for cohort i use all data from all cohorts based on posterior of BHM
Recruitment and analysis strategies

• Strategy 3

Recruitment
I: Interim (here futility)
F: Final

Interim futility analysis
Decision for cohort i
use only data of cohort i
nogo if <r responders

Overall go at first cohort go
Overall nogo if all cohorts nogo
Overall consider, else
Recruitment and analysis strategies

- Strategy 3

Recruitment
I: Interim (here futility)
F: Final

Time

Overall go at first cohort go
Overall nogo if all cohorts nogo
Overall consider, else

Final analysis
Decision for cohort i
use all data from non-futile cohorts
based on posterior of BHM

I
nogo
cons

F
nogo
cons

go
nogo
cons

I
nogo
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F
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go
nogo
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nogo
cons

go
nogo
cons

F
Recruitment and analysis strategies

- **Strategy 4**

  Overall go at first cohort go
  Overall nogo if all cohorts nogo
  Overall consider, else

  Interim / final analysis
  Decision for cohort i
  use all data from all cohorts
  based on posterior of BHM

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<th>Interim</th>
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Recruitment and analysis strategies

• Strategy 4

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In case of interim futility, stop recruitment for cohort
Model-based decision rule

Cohort i

NoGo

Consider

Go

$q_{50,i} < c_{1,i}$

else

$q_{50,i} > c_{2,i}$

$q_{50,i}$ median posterior response rate cohort i

$c_{1,i}, c_{2,i}$ cohort specific decision boundary

Variation

$q_{\gamma,i} < c_{1,i}$

else

$q_{1-\gamma,i} > c_{2,i}$

$q_{\gamma,i}$ $\gamma$-quantile of posterior distribution
Recruitment and analysis strategies

- **Strategy 1-3:** Futility after 10 patients, final after 20 (per cohort)
- **Strategy 4:** Interim analysis every 5 patients, Final at 4*20 max.
Response scenarios
Response scenarios

- Positive and negative scenarios
- Positive nugget scenario
- Mixed response scenario

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Model parameters
Model parameters

• Model adjustment parameter $\tilde{p}_j$
• Controls borrowing
• Target rate by cohort set to assumed response rate if drug works (as in Berry et al 2013)

• Inter-cohort variability prior $\tau \sim HN (s_\tau)$
  – $scale = 0.5$ allows for range of $\tau$ up to substantial heterogeneity
Operating characteristics
Operating characteristics

- Decision probabilities in scenarios
- Average sample size and duration
Simulation results
## Scenario 1

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NoGo, Consider, Go: Probability in %, N average number evaluable, t average duration (months)
## Scenario 2

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NoGo, Consider, Go: Probability in %, N average number evaluable, t average duration (months)
### Scenario 3

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NoGo, Consider, Go: Probability in %, N average number evaluable, t average duration (months)
### Scenario 4

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NoGo, Consider, Go: Probability in %, N average number evaluable, t average duration (months)
Questions?

Optional subtitle