# Decision Making in Basket Trials: A Hierarchical Weights Approach

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BAYES 2016 Conference
Leuven - 2016

# Outline

# Introduction: Basket Trials

**Definition of Basket trial (here!)**

Multi-arm trail to test a mechanism of action (MoA) in multiple indications

- MoA often applicable across of indications
  e.g. Cancer immuno-therapy (CIT)
- Fast decision making on MoA
- Fast decision making in most promising indication

# Introduction: Basket Trials

## Context

- Early phase oncology trials
- Extension cohorts

**Goal of basket trial designs:** (here !)

- Establish evidence of MoA across indications
- Strengthen the evidence of MoA by borrowing from multiple indications

Pre-requisite: Belief that if some indications show efficacy
$\Rightarrow$ increased confidence of efficacy in other indication

# Introduction: Basket Trials or not? (here!)

## What is within our definition of basket trials:

- Same agent tested in multiple indications sensitive to the MoA of the drug
- Different agents (combinations) with the same MoA in one or more indications

$\Rightarrow$ Borrowing makes sense

## What is not our definition of basket trials:

- Umbrella trials = Different MoA (eg. different drugs) in single indication
- Trials with treatment selection by biomarker / mutation

$\Rightarrow$ Borrowing between indications questionable

# Introduction: Framework

- Binary response
- Bayesian decision making
- Dose already predefined (no dose escalation within basket trial)

Existing approaches:

- Hierachical structure on response (eg. Thall et al. 2003)
- Mixture of hierarchy (Neuenschwander et al. 2015)

**Limitation of the hierarchical structure on response**

ORR linked through common hyperparameter

$\Rightarrow$ Same ORR/difference across indications

# Bayesian decision making (Gating): **Single indication**

- Early phase gating: Decision to stop or continue development
- Decision criteria based on **Posterior probability** :

$$\text{GO}: \quad PP = P[p > \theta_u | \text{data}] > 0.8$$

  - $p$ = probability of response
  - $\theta_u$ = upper target
  - 0.8 = confidence level

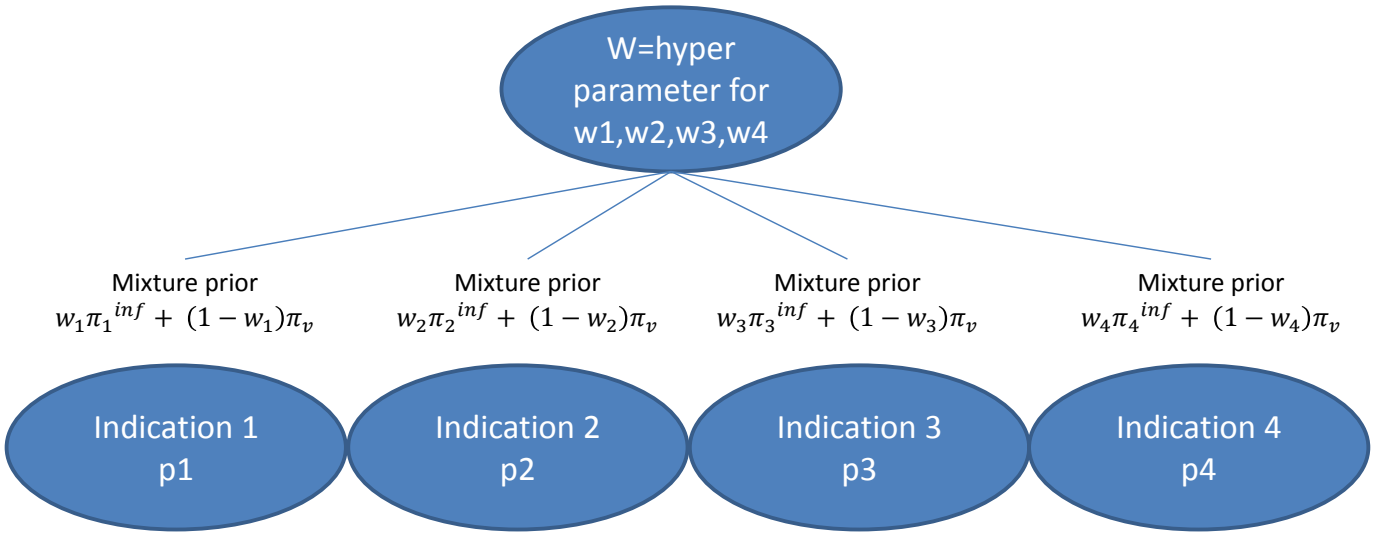
- $P[p > \theta_u | \text{data}]$ computed from beta$(r + a, n - r + b)$
  $n$ = number of subjects in ind., $r$ = number of responses

- Prior $(a, b)$ chosen as vague or SOC

# Basket trial :

Alternative proposal: **Hierarchical Weights Design**

# Basket trial : Hierarchical Weights Design




**Idea:**

- Prior for $p_j$ is a **mixture**
- Hierarchy on **weights**
- $\pi_j^{inf}$ favors target
- Gating based on PP computed from mixture prior

# Hierarchical Weights Design

Prior on $p_j$ = **mixture prior** :

$$\pi(p_j) = w_j \, \pi_j^{inf}(p_j) \; + \; (1 - w_j)\pi_v(p_j)$$

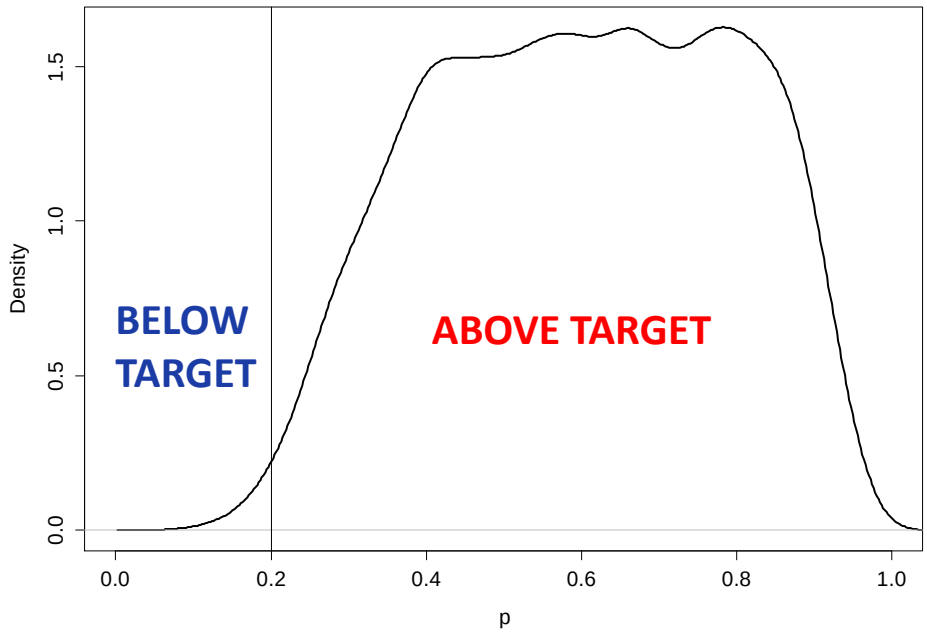
where

- $w_j$ is an indication-specific weight:
  - $w_j$ **not pre-specified**
  - Hierarchical structure on $w_j$:
    - $\text{logit}(w_j) \sim N(\theta, \sigma_j)$
    - Hyper parameter for weights $\theta \sim N(\text{logit}(0.1), \sigma)$
      $\Rightarrow$ Mean for $\theta$ favors vague prior
    - $\sigma_j$ and $\sigma$ small to force borrowing
- $\pi_v(p_j)$ is a vague prior for $p_j = \text{Beta}(1/2,1/2)$

# Informative part of prior $\pi_j^{inf}(p_j)$

$\pi_j^{inf}(p_j)$ informative prior with mass above target for $p_j$

- **Indication specific**
- Corresponds to efficacious treatment (above target)



# Gating

**GO and No GO decisions:** Posterior probability computed from 2 different priors:

1. $PP_{Go} = P[p_j > \text{GO target} | \text{obs. in all ind.}]$

   GO gate $\Leftarrow \pi_j^{inf}(p_j)$ close to GO target and above

2. $PP_{NoGo} = P[p_j < \text{No GO target} | \text{obs. in all ind}]$

   No GO gate $\Leftarrow \pi_j^{inf}(p_j)$ close to No GO target and below

Gating as follows:

- GO if $PP_{Go} > 0.8$,
- if not, No GO if $PP_{NoGo} > 0.8$,
- else no decisions

# Simulations

- 5 indications
- n=20 per indication
- Different Targets:

| | Ind 1 - 4 | Ind 5 |
|---|---|---|
| Target GO | 0.20 | 0.50 |
| Target NO GO | 0.10 | 0.20 |

# Simulations: results 1/5

- Low efficacy in all indications

| | ind 1 | ind 2 | ind 3 | ind 4 | ind 5 |
|---|---|---|---|---|---|
| True resp. prob. | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 |
| Prob. Go decision hier. basket | 0 | 0 | 0 | 0 | 0 |
| Prob. Go decision no borrowing | 0 | 0 | 0 | 0 | 0 |
| Prob. NO Go decision hier. basket | 0.44 | 0.51 | 0.48 | 0.45 | 0.92 |
| Prob. NO Go decision no borrowing | 0.34 | 0.38 | 0.35 | 0.33 | 0.92 |

- Increase in NO GO decision

# Simulations: results 2/5

- Efficacy in a single indications

| | ind 1 | ind 2 | ind 3 | ind 4 | ind 5 |
|---|---|---|---|---|---|
| True resp. prob. | 0.05 | 0.05 | 0.05 | 0.05 | 0.60 |
| Prob. Go decision hier. basket | 0 | 0 | 0 | 0 | 0.58 |
| Prob. Go decision no borrowing | 0 | 0 | 0 | 0 | 0.58 |
| Prob. NO Go decision hier. basket | 0.44 | 0.45 | 0.44 | 0.43 | 0 |
| Prob. NO Go decision no borrowing | 0.34 | 0.38 | 0.35 | 0.33 | 0 |

- No difference in prob. GO decision ind. 5
- Much higher NO GO decision on low efficacy ind.

# Simulations: results 3/5

- Borderline efficacy for 3 ind.

| | ind 1 | ind 2 | ind 3 | ind 4 | ind 5 |
|---|---|---|---|---|---|
| True resp. prob. | 0.05 | 0.05 | 0.30 | 0.30 | 0.55 |
| Prob. Go decision hier. basket | 0 | 0 | 0.68 | 0.67 | 0.43 |
| Prob. Go decision no borrowing | 0 | 0 | 0.59 | 0.61 | 0.41 |
| Prob. NO Go decision hier. basket | 0.42 | 0.45 | 0 | 0 | 0 |
| Prob. NO Go decision no borrowing | 0.34 | 0.38 | 0 | 0 | 0 |

- Bordeline efficacy "promoted" to GO
- Low efficacy NO GO increased

# Simulations: results 4/5

- Borderline efficacy for 3 ind. and clear efficacy in 1 ind.

| | ind 1 | ind 2 | ind 3 | ind 4 | ind 5 |
|---|---|---|---|---|---|
| True resp. prob. | 0.05 | 0.30 | 0.30 | 0.30 | 0.65 |
| Prob. Go decision hier. basket | 0 | 0.70 | 0.76 | 0.76 | 0.80 |
| Prob. Go decision no borrowing | 0 | 0.56 | 0.59 | 0.61 | 0.75 |
| Prob. NO Go decision hier. basket | 0.39 | 0.01 | 0 | 0 | 0 |
| Prob. NO Go decision no borrowing | 0.34 | 0 | 0 | 0 | 0 |

- Increased probability to GO compared to previous scenario in bordeline Borrowing works !

- No increase in NO GO probability

# Simulations: results 5/5

- 4 borderline ind.

| | ind 1 | ind 2 | ind 3 | ind 4 | ind 5 |
|---|---|---|---|---|---|
| True resp. prob. | 0.25 | 0.30 | 0.30 | 0.30 | 0.10 |
| Prob. Go decision hier. basket | 0.55 | 0.67 | 0.72 | 0.73 | 0 |
| Prob. Go decision no borrowing | 0.38 | 0.56 | 0.59 | 0.61 | 0 |
| Prob. NO Go decision hier. basket | 0.01 | 0.01 | 0 | 0 | 0.67 |
| Prob. NO Go decision no borrowing | 0 | 0 | 0 | 0 | 0.66 |

- Increase prob. GO for the borderline ind.
- Smaller increase compared to previous scenario because smaller evidence

# Discussion

**Hierarchical weights proposal:**

- **Desired borrowing properties**
- **Allows for different target in indications**
- Careful choice of prior needed
- Small sample size $\Rightarrow$ Discreteness may lead to no difference in P[GO] (still some benefit on posterior prop.)

To do:

- Comparison with existing approaches
- Staggered read-out of indications
- Include small randomization cohorts

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Thank you!