A GENERALIZED FRAMEWORK OF OPTIMAL TWO-STAGE DESIGNS FOR EXPLORATORY BASKET TRIALS

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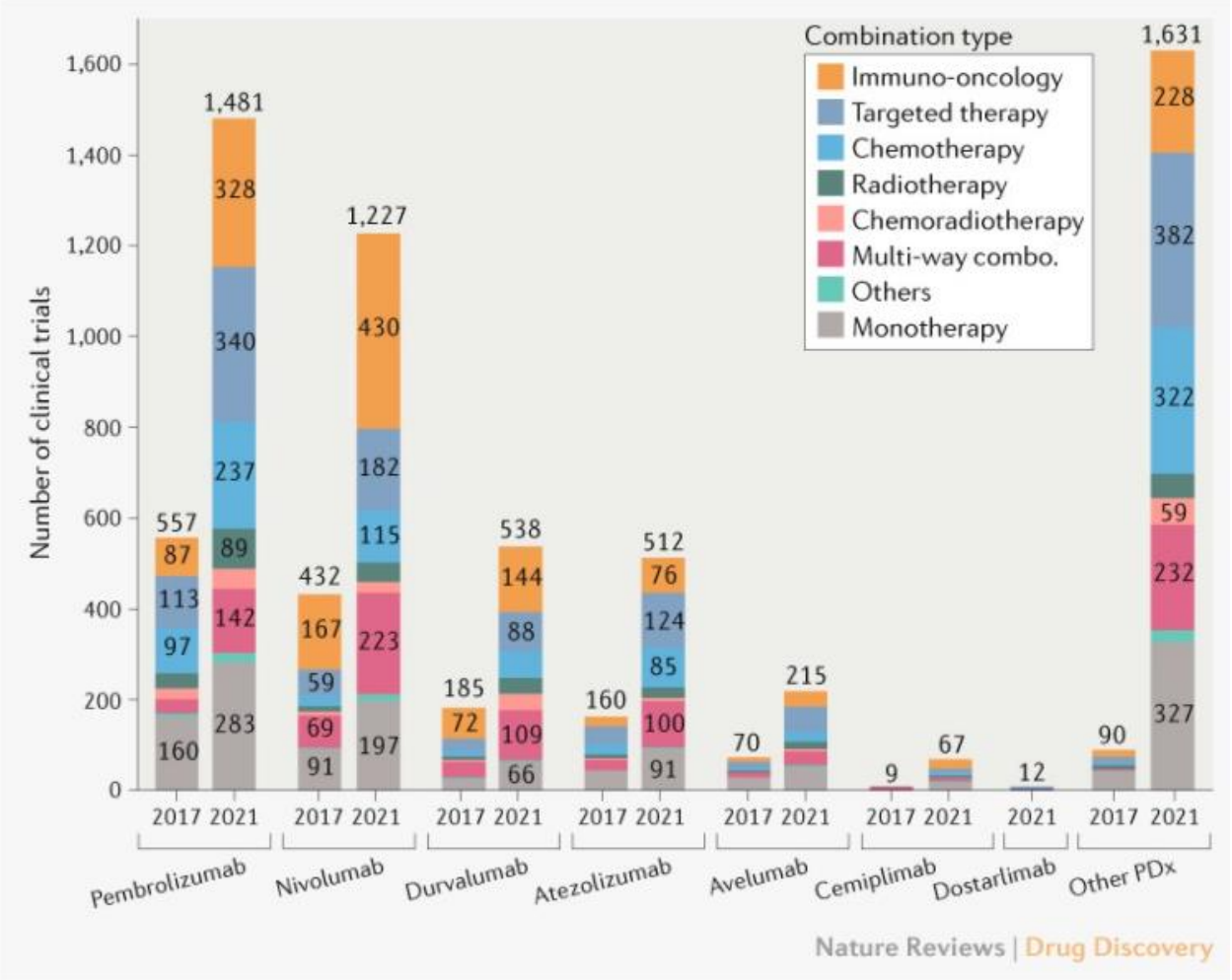
ASA NJ & PT Chapters Annual Symposium
June 23rd, 2023

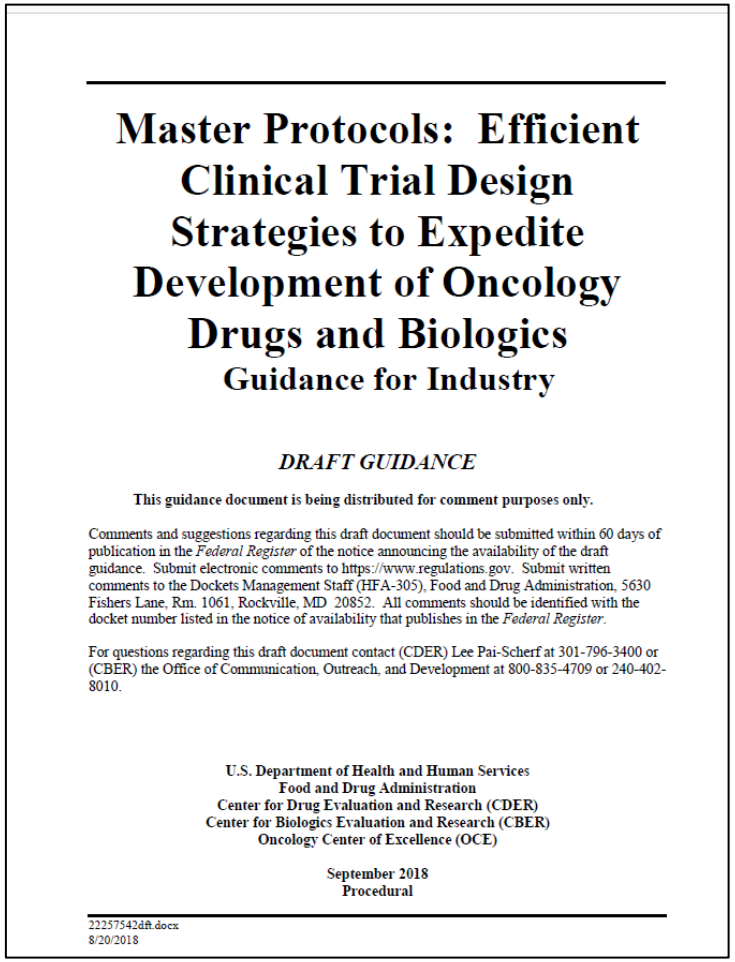
Background

Explosive Oncology Trials



As of Dec 2021, there are 5,683 clinical trials assessing anti-PD1/PDL1 mAbs – as monotherapy or in combination with other treatments; 278% increase in the past 5 years (Upadhaya et al. 2022, *Nature Reviews Drug Discovery*)

Master Protocol Trials



Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Lee Pai-Scherf at 301-796-3400 or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

September 2018
Procedural

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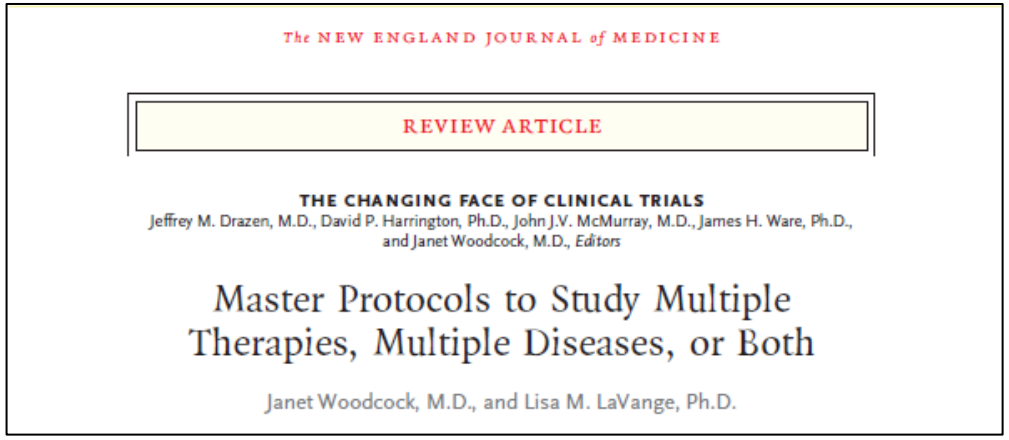
8/20/2018



The NEW ENGLAND JOURNAL of MEDICINE

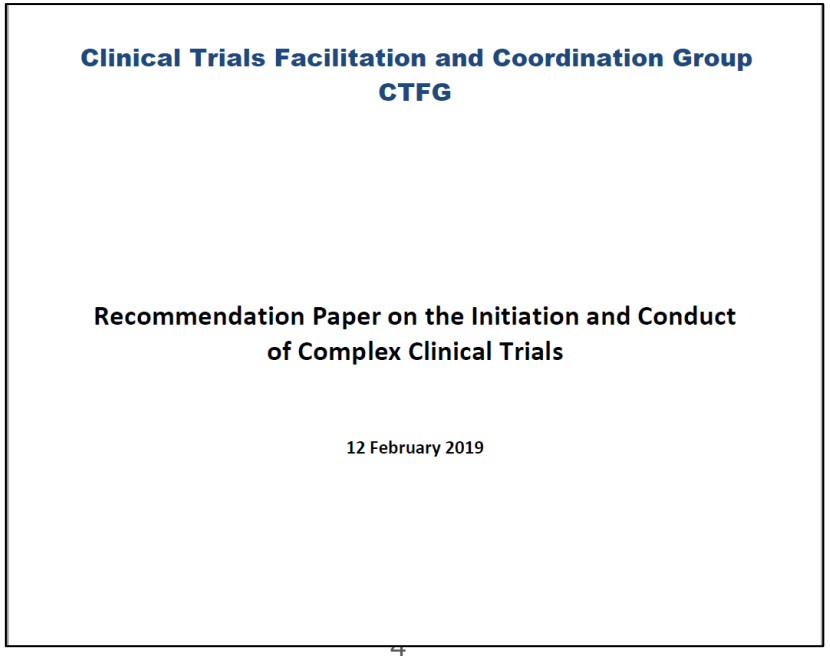
REVIEW ARTICLE

THE CHANGING FACE OF CLINICAL TRIALS

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D., and Janet Woodcock, M.D., *Editors*

Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both

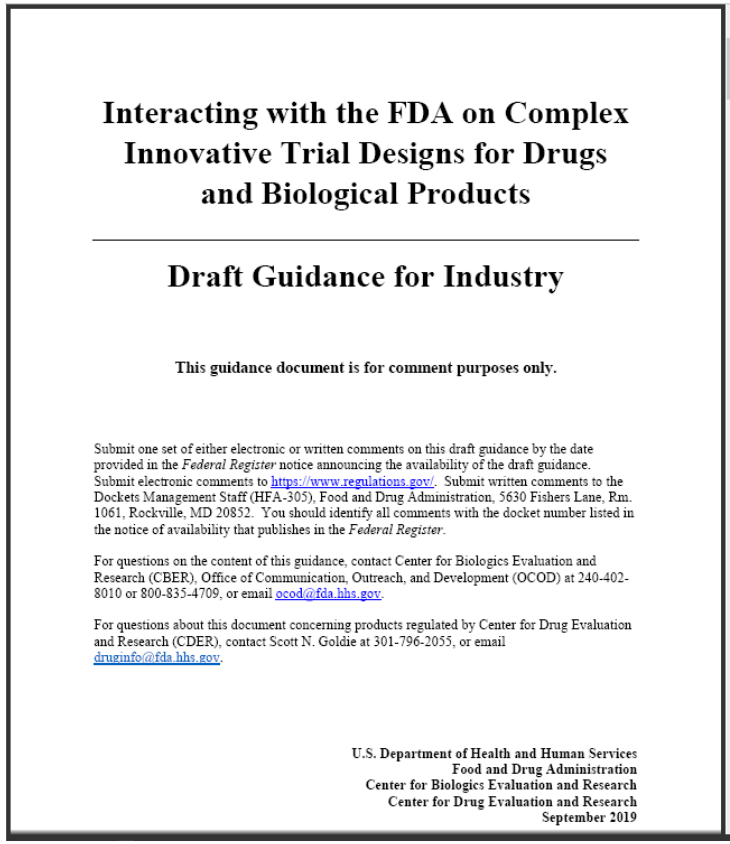
Janet Woodcock, M.D., and Lisa M. LaVange, Ph.D.



Clinical Trials Facilitation and Coordination Group
CTFG

Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials

12 February 2019



Interacting with the FDA on Complex Innovative Trial Designs for Drugs and Biological Products

Draft Guidance for Industry

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For questions about this document concerning products regulated by Center for Drug Evaluation and Research (CDER), contact Scott N. Goldie at 301-796-2055, or email druginfo@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Center for Drug Evaluation and Research
September 2019

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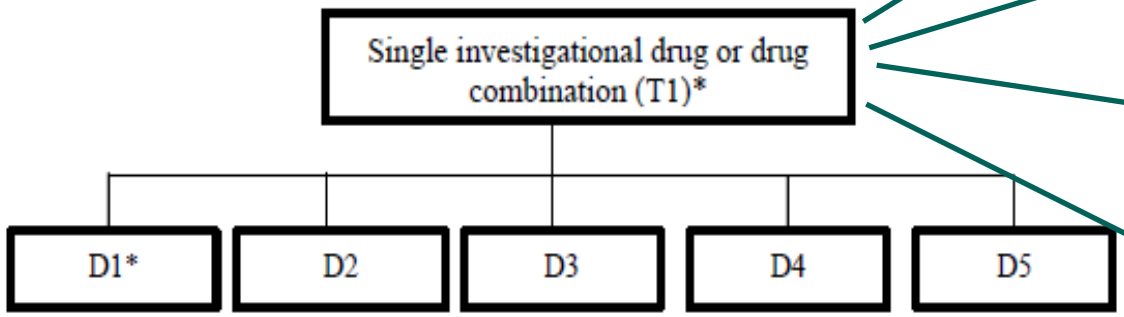
Basket Trials

- FDA has broad definitions on basket trials.

A master protocol designed to test a single investigational drug or drug combination in different populations defined by disease stage, histology, number of prior therapies, genetic or other biomarkers, or demographic characteristics is commonly referred to as a *basket trial* (shown in Figure 1).

Figure 1: Schematic Representation of a Master Protocol With *Basket Trial* Design



* T = investigational drug; D = protocol defined subpopulation in multiple disease subtypes.

Lines of therapy, e.g. adjuvant, neoadjuvant, 1st line, 2nd line…

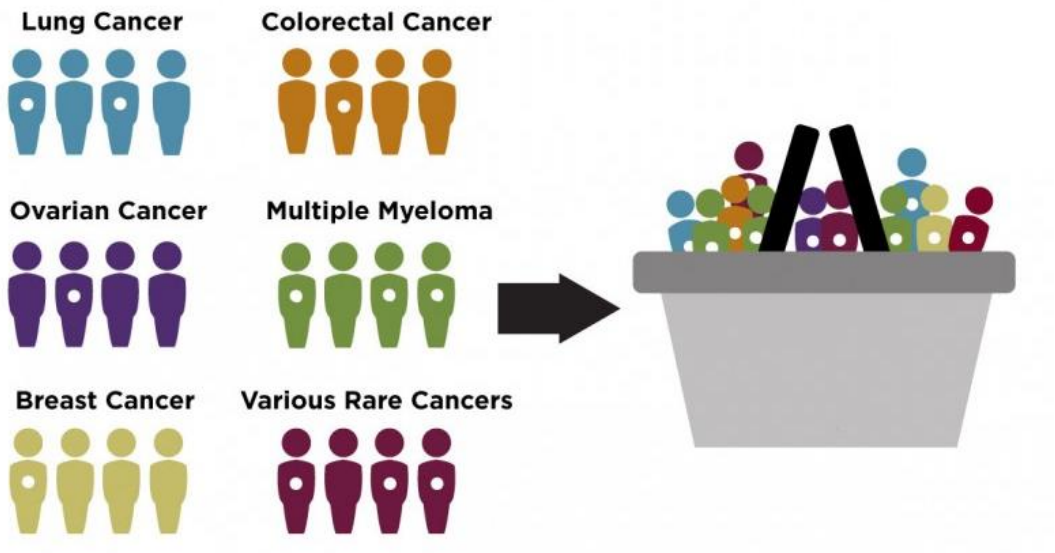
Stage I, II, III…

Biomarker A, B, C

Age group, tobacco, family history, etc..

Basket Trials

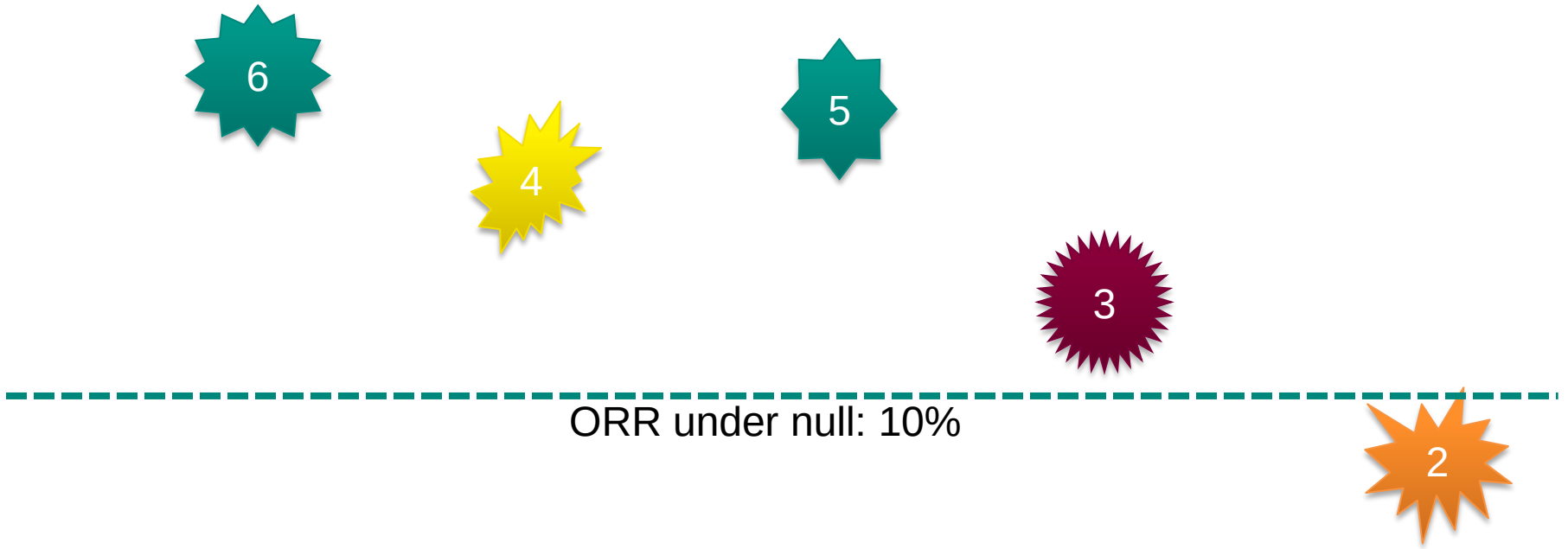
- Basket trials are most widely designed to test the treatment effect of a drug on different indications.
- Purpose: to identify “active” indications to the test drug.
- Endpoint: overall response rate (ORR) in the exploratory phase.



Does the drug work in any of the indications?

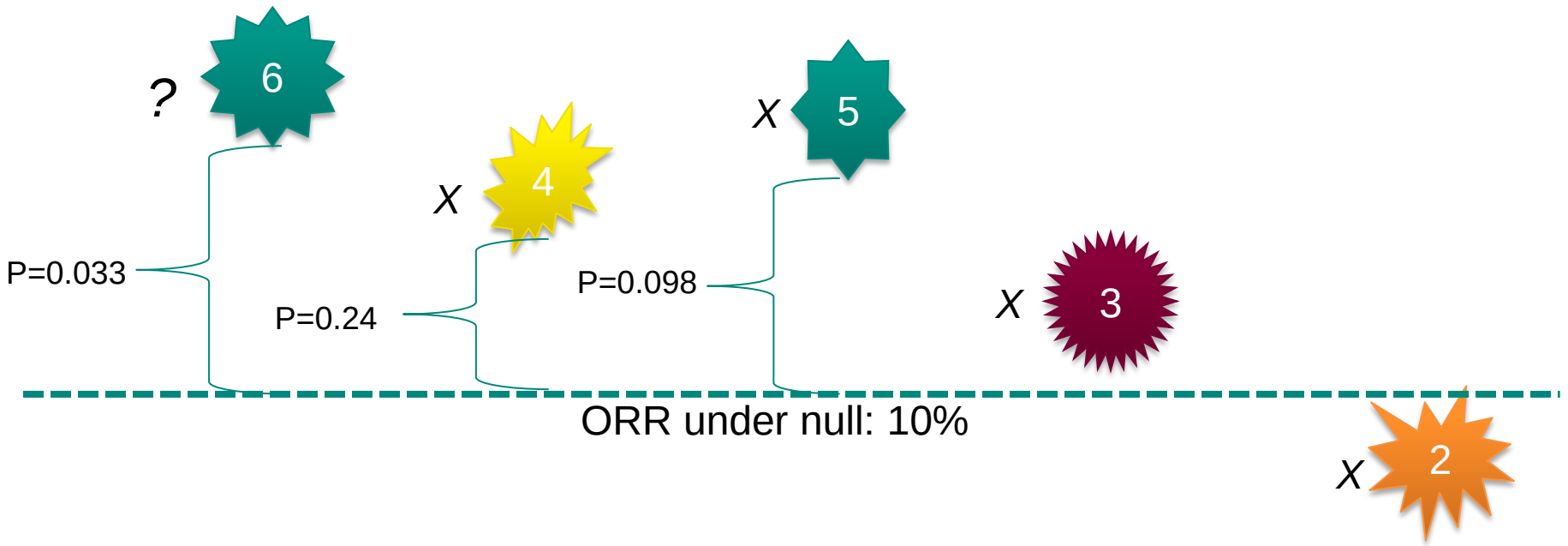
Hypothetical Outcome of a Basket Trial

- Five tumor cohorts (n=25 each) in patients refractory to PD-1 treatment (ORR under null: 10%)
- Number of responses range from 2 (8%) to 6 (24%)



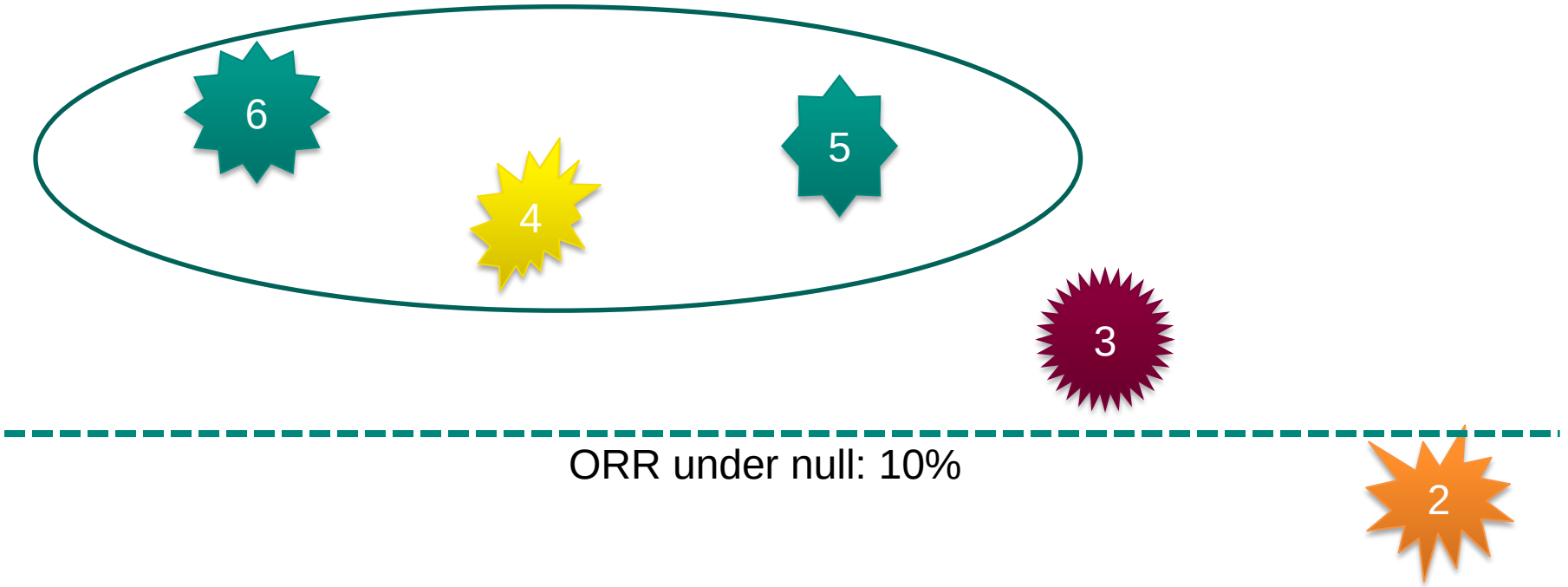
Independent Evaluation

- Each tumor cohort is evaluated separately, with or without multiplicity adjustment



Ad-hoc Assessment

- *Clinical director 1:* Look at the 3 top ones! The drug is working!!
- *Clinical director 2:* This is cherry-picking!



Information Borrowing

- Pooling all the indications to conduct analysis.
  - Too extreme information borrowing.
  - Treatment effect from active indications will be diluted by inactive ones.
- Bayesian information borrowing
  - Thall et al. 2003, Berry et al. 2013, Simon et al., 2016, Cunanan et al., 2017
  - Too complicated in practice
  - Not robust under small sample size with inflated type I error

Is there a simple and robust approach to “pick the cherries”?

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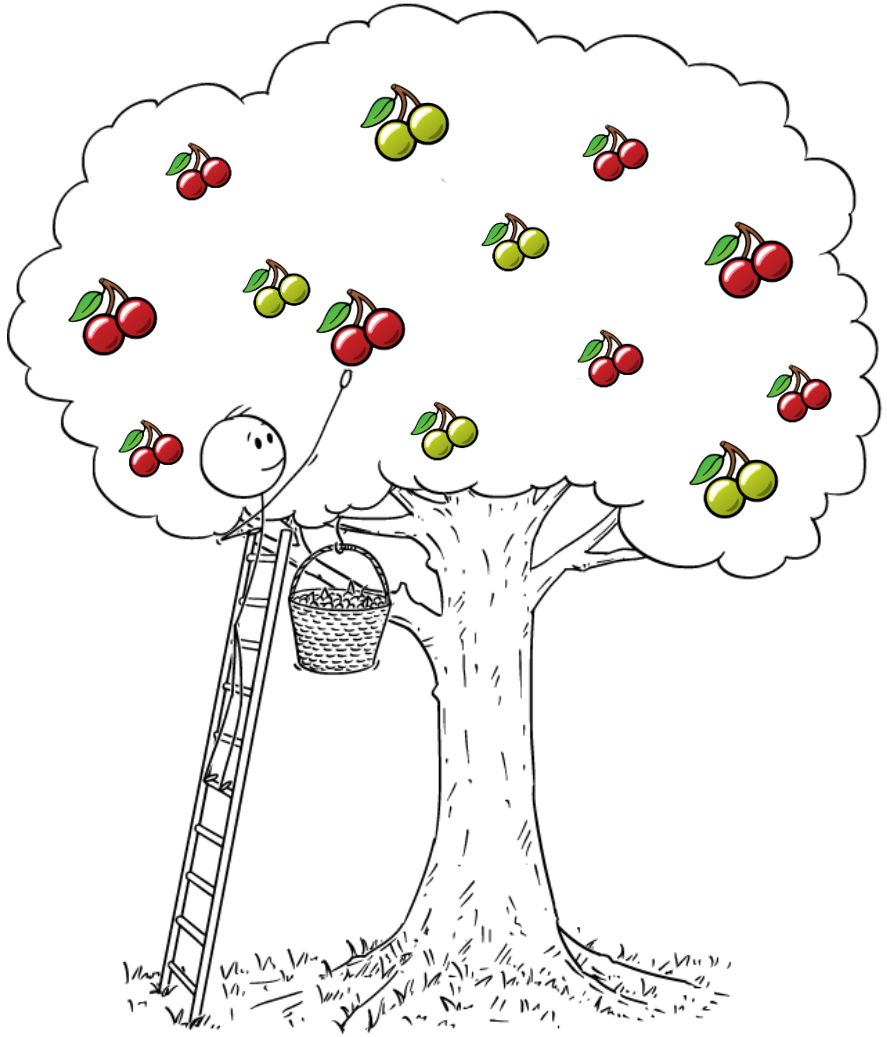
Pruning & Pooling (Chen et al. 2016)



- Prune “inactive” indications first and then conduct pooling analysis on the rest indications.
- Penalty adjustment will be paid on the pooling analysis for the possible erroneous pooling.

Two-stage Designs with Pruning & Pooling

Design Overview

- Test if the drug is effective on at least one indication
  - Global null hypothesis: the test drug is ineffective on any indications
- Flexibility: investigators are allowed to specify null/alternative response rates for different indications
- A natural extension of Simon's optimal two-stage design from one-arm to multi-arms
  - Type I and II error rates explicitly controlled
  - Minimize the expected sample size under null hypothesis or minimize the maximum sample size
- Using pruning & pooling approach
  - Prune inactive indications in stage 1 and conduct pooling analysis in stage 2 on the rest indications

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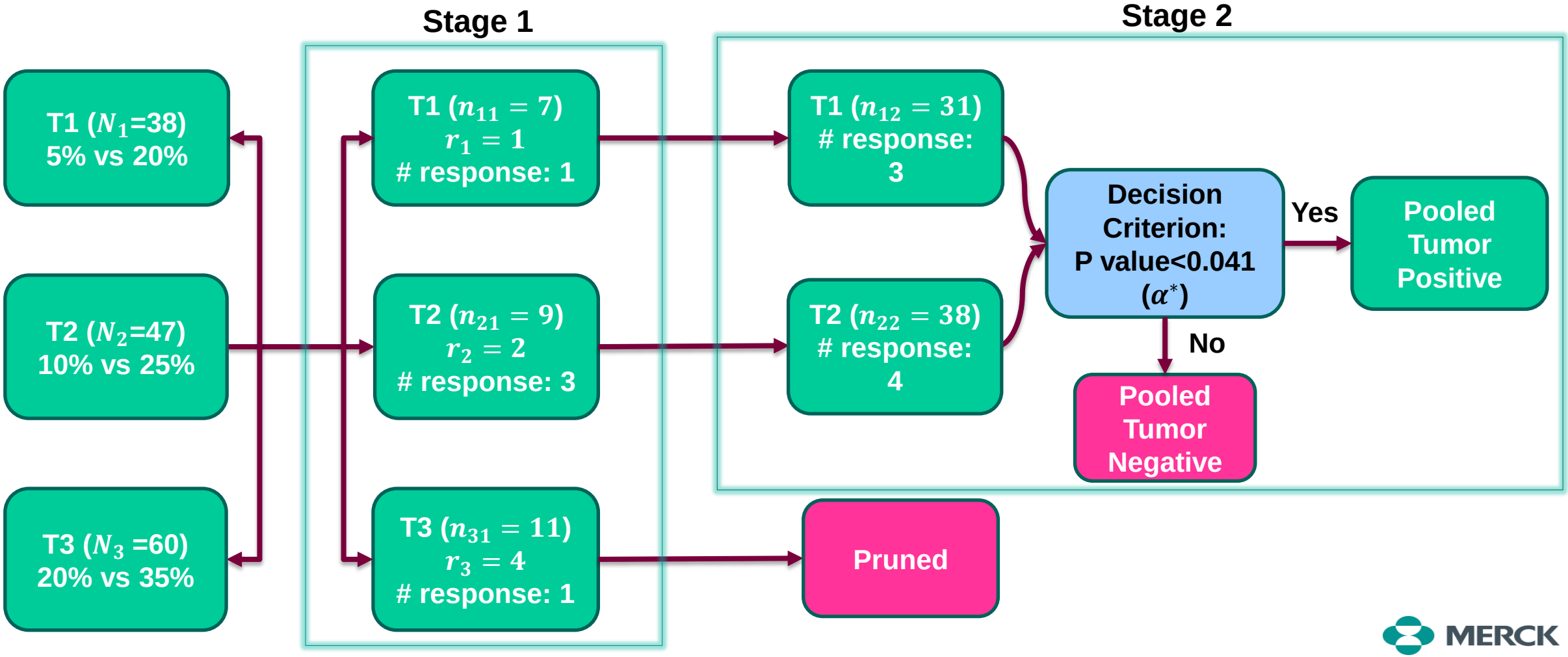
Input Parameters

- K: number of tumor indications in the basket trial
- $\boldsymbol{p_0} = (p_{10}, \cdots, p_{K0})$, $\boldsymbol{p_1} = (p_{11}, \cdots, p_{K1})$: probability vectors for null and alternative hypothesis
  - $H_{k0}: p_k = p_{k0}$, $H_{k1}: p_k = p_{k1}$, $k = 1, \cdots, K$; (p_k: true response rate of the k^{th} indication)
- α: global type I error level
- β: expected overall type II error level

Design Parameters

- $\boldsymbol{n_1} = (n_{11}, \cdots, n_{K1}), \boldsymbol{n_2} = (n_{12}, \cdots, n_{K2})$: number of patients enrolled in each indication in stage 1 and stage 2
- $\boldsymbol{N} = (N_1 = n_{11} + n_{12}, \cdots, N_K = n_{K1} + n_{K2})$: maximum sample size
- $\boldsymbol{r} = (r_1, \cdots, r_K)$: pruning bar in stage 1
  - The k^{th} indication will be pruned if the number of responses is less than r_k
- α^*: critical value of pooling analysis

Trial Example 1



Probability of Rejecting Global Null

- X_{k1}, X_{k2} : number of responses in stage 1 and stage 2 for indication k.
- $\boldsymbol{m} = (m_1, \cdots, m_K)$: pooling indicator, where $m_k = 1_{X_{k1} \geq r_k}$; $M = \sum m_k$.
- $\boldsymbol{g} = (g_1, \cdots, g_K)$: active indicator, where $g_k = 1$ means indication k is active; 0 otherwise.
- Probability of rejecting global null

Stage 1: probability of pruning & pooling

Stage 2: probability of pooling analysis being significant

$$F(\boldsymbol{r}, \boldsymbol{n_1}, \boldsymbol{n_2}, \alpha^*, \boldsymbol{p_0}, \boldsymbol{p_1} | \boldsymbol{g}, \boldsymbol{m})$$

$$= \prod_{k=1}^{K} \{[B_{1k}^{1-m_k}(1 - B_{1k}^{m_k})]^{g_k} [B_{0k}^{1-m_k}(1 - B_{0k}^{m_k})]^{1-g_k}\}$$

$$\times \sum_{x_{11}=r_1}^{n_{11}} \cdots \sum_{x_{M1}=r_M}^{n_{M1}} \{\Pr(X_{k1} = x_{k1}, k = 1, \cdots, M) \times \Pr(\sum_{k=1}^{M} (X_{k1} + X_{k2}) > R_{M(\alpha^*)})\}$$

B_{0k}: $Binom(r_k - 1; n_k, p_{k0})$, B_{1k}: $Binom(r_k - 1; n_k, p_{k1})$.

Type I Error Rate

- Under global null (no treatment effects on any indications): $\boldsymbol{g} = (0, \cdots, 0)$
- Type I error rate:

$$\alpha = \sum_{\{\boldsymbol{m}:\sum m_k \geq 1\}} F(\boldsymbol{r}, \boldsymbol{n_1}, \boldsymbol{n_2}, \alpha^*, \boldsymbol{p_0}, \boldsymbol{p_1} | \boldsymbol{g} = (0, \cdots, 0), \boldsymbol{m})$$

- Solve α^* given global type I error level α.

Type II Error Rate

- Given $G = \sum g_k$ active indications and $K - G$ inactive indications

- When $G \geq 1$, the power of design is:

$$1 - \beta(G) = \frac{1}{Card(\{\boldsymbol{g}: \sum g_k = G\})} \sum_{\{\boldsymbol{g}:\sum g_k = G\}} \sum_{\{\boldsymbol{m}:\sum m_k \geq 1\}} F(\boldsymbol{r}, \boldsymbol{n_1}, \boldsymbol{n_2}, \alpha^*, \boldsymbol{p_0}, \boldsymbol{p_1} | \boldsymbol{g}, \boldsymbol{m})$$

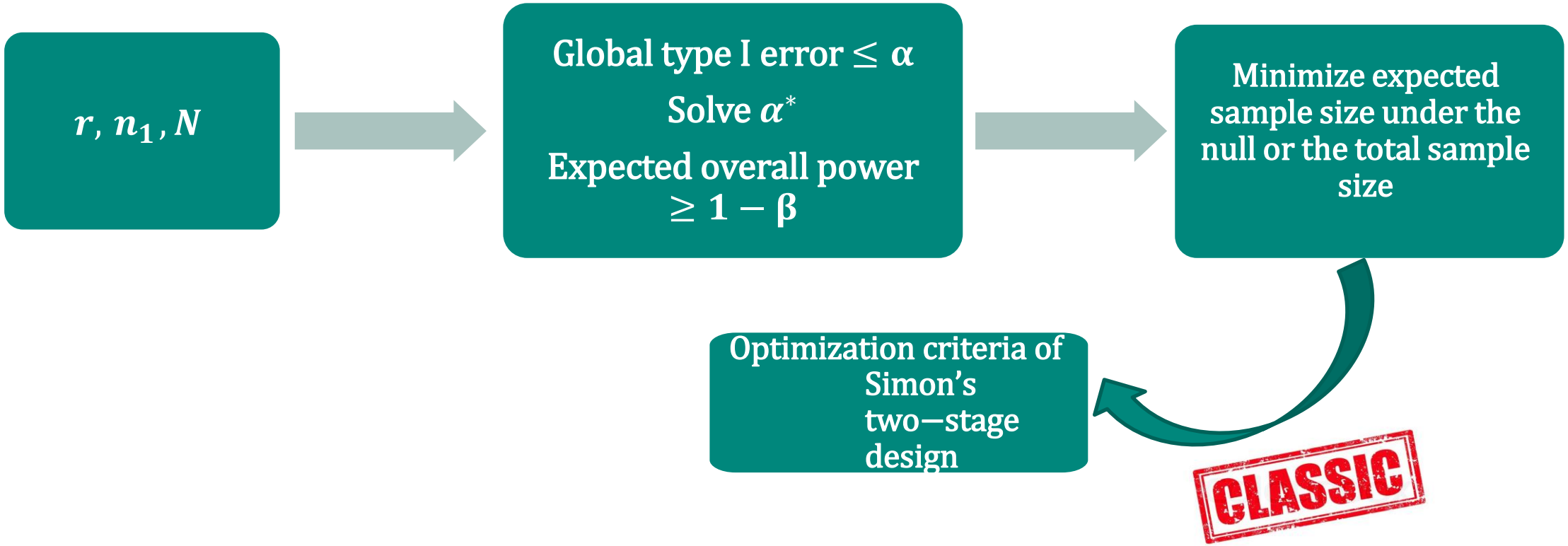
Probability of rejecting global null

- Under the non-informative uniform assumption on the number of truly active indications, the overall type II error rate is:

$$\beta = \frac{1}{K} \sum_{G=1}^{K} \beta(G)$$

Optimize Design Parameters

- $r, n_1, N, \alpha^{\star}$: design parameters need to be optimized



Sample Size Calculation

- The expected sample size under the null hypothesis

$$EN(\boldsymbol{r}, \boldsymbol{n_1}, \boldsymbol{n_2}, \alpha^*, \boldsymbol{p_0}) = \sum_{k=1}^{K} n_{k2}\, Pr(X_{k1} \geq r_k) + \sum_{k=1}^{K} n_{k1}$$

$$= \sum_{k=1}^{K} n_{k2}(1 - B(r_{k1} - 1; n_{k1}, p_{k0})) + \sum_{k=1}^{K} n_{k1}$$

- Closed-form sample size!

Examples of Optimized Design Parameters

$\boldsymbol{K = 4}$					
$\boldsymbol{p_0}$ (%)	$\boldsymbol{N}$	$\boldsymbol{n_1}$	$\boldsymbol{r}$	α^* (%)	EN
(5, 5, 20, 20)	(30, 30, 52, 52)	(7, 7, 11, 11)	(1,1,4,4)	3.2	63
$\boldsymbol{K = 6}$					
(5, 5,10, 10, 20, 20)	(29, 29, 37, 37, 49, 49)	(5, 5, 7, 7, 10, 10)	(1,1,2,2,4,4)	2.6	73
(5, 5, 5, 20, 20, 20)	(27, 27, 27, 49, 49, 49)	(5, 5, 5, 10, 10, 10)	(1,1,1,4,4,4)	2.5	74
$\boldsymbol{K = 8}$					
(5, 5, 5,10, 10, 20, 20, 20)	(24, 24, 24, 29, 29, 37, 37, 37)	(4, 4, 4, 8, 8, 8, 8, 8)	(1, 1, 1, 2, 2, 3, 3, 3)	1.6	89

- Target 15% improvement in alternative response rates

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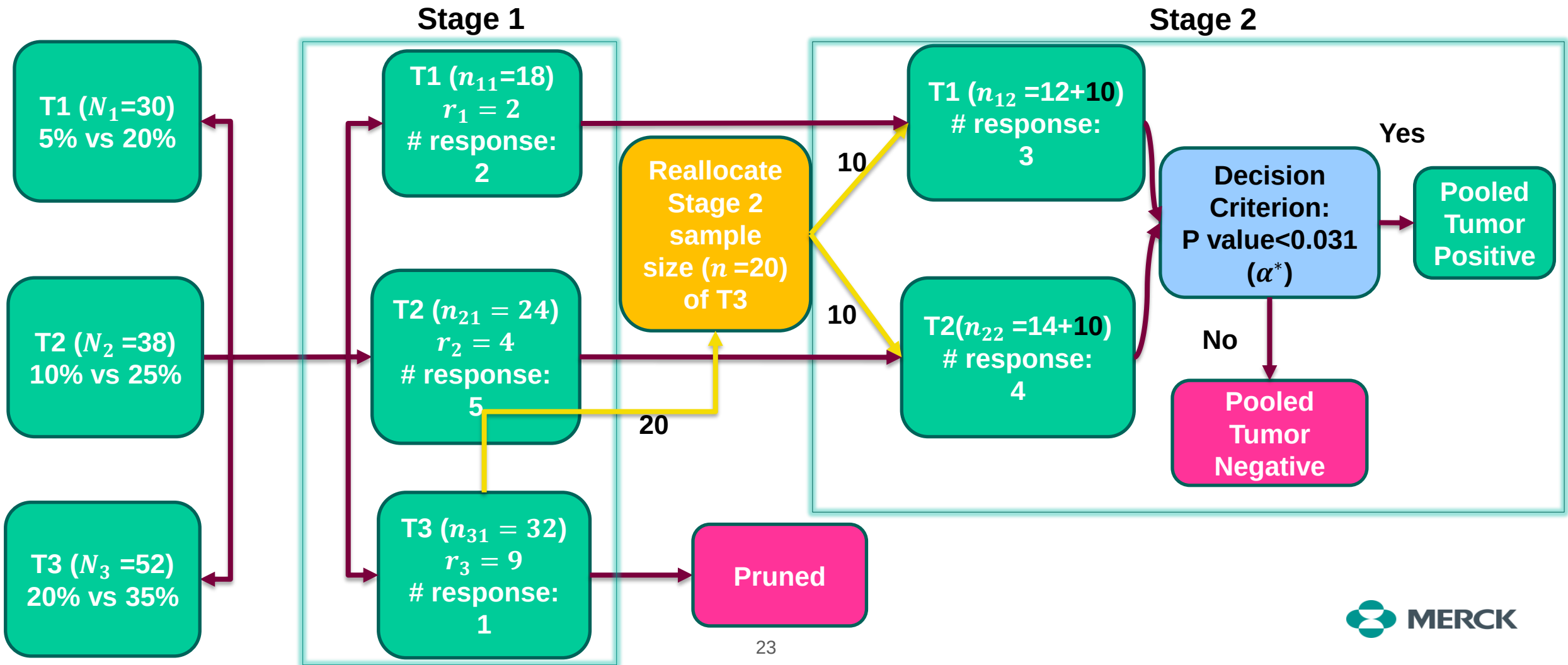
Trial Example 2: with fixed budget



Numerical Study

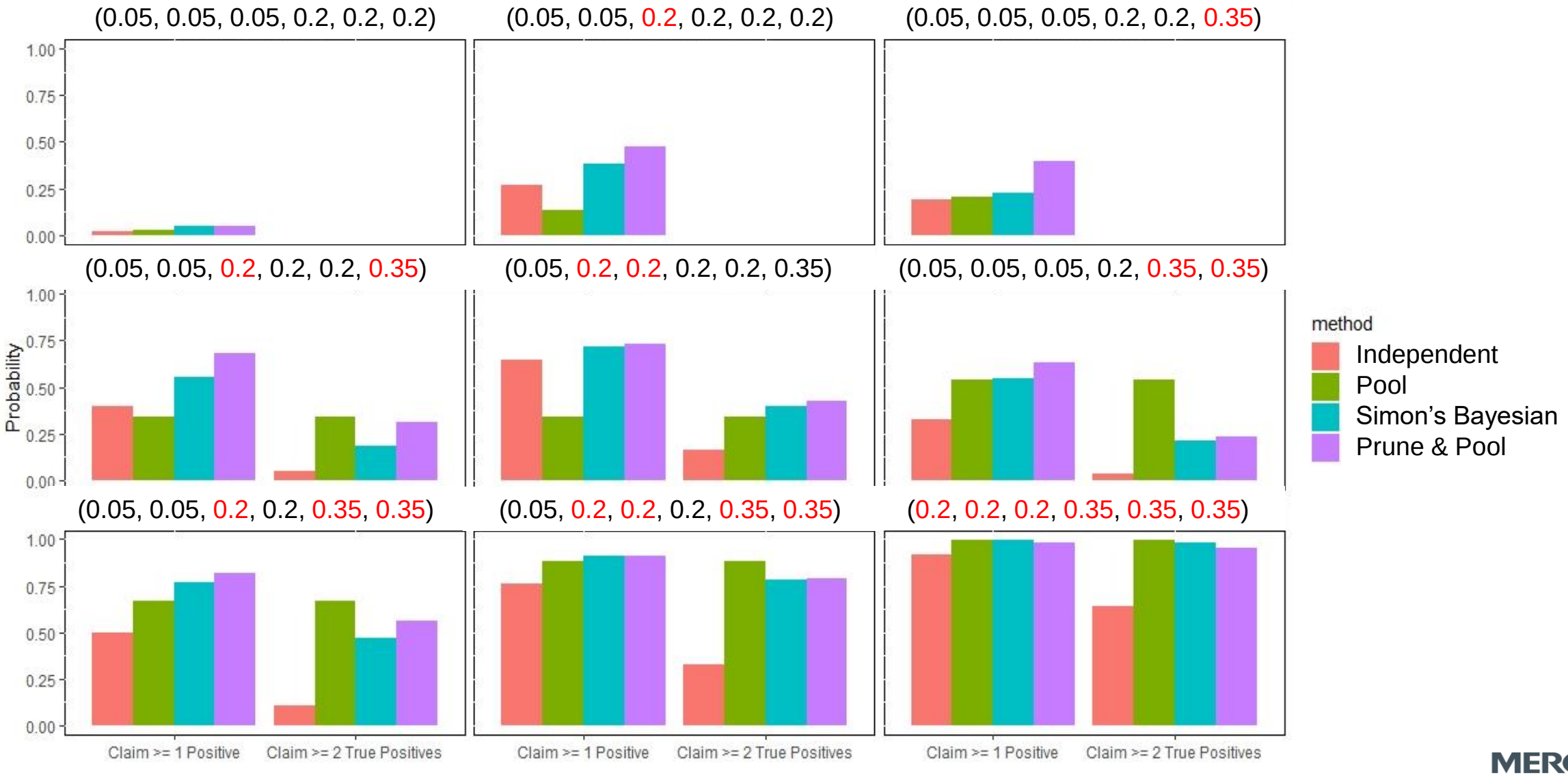
Hypothetical Trial Settings

- Consider $K = 6$ indications;
- Null response rates: $\boldsymbol{p_0} = (0.05,0.05,0.05,0.2,0.2,0.2)$;
- Alternative response rates: $\boldsymbol{p_1} = (0.2,0.2,0.2,0.35,0.35,0.35)$;
- Controlled type I error level $\alpha = 0.05$; type II error level $\beta = 0.20$;
- Optimized design parameters:
  - $\boldsymbol{N} = (27,27,27,49,49,49)$
  - $\boldsymbol{n_1} = (5,5,5,10,10,10)$
  - $\boldsymbol{r} = (1,1,1,4,4,4)$
- 10,000 simulated trials.

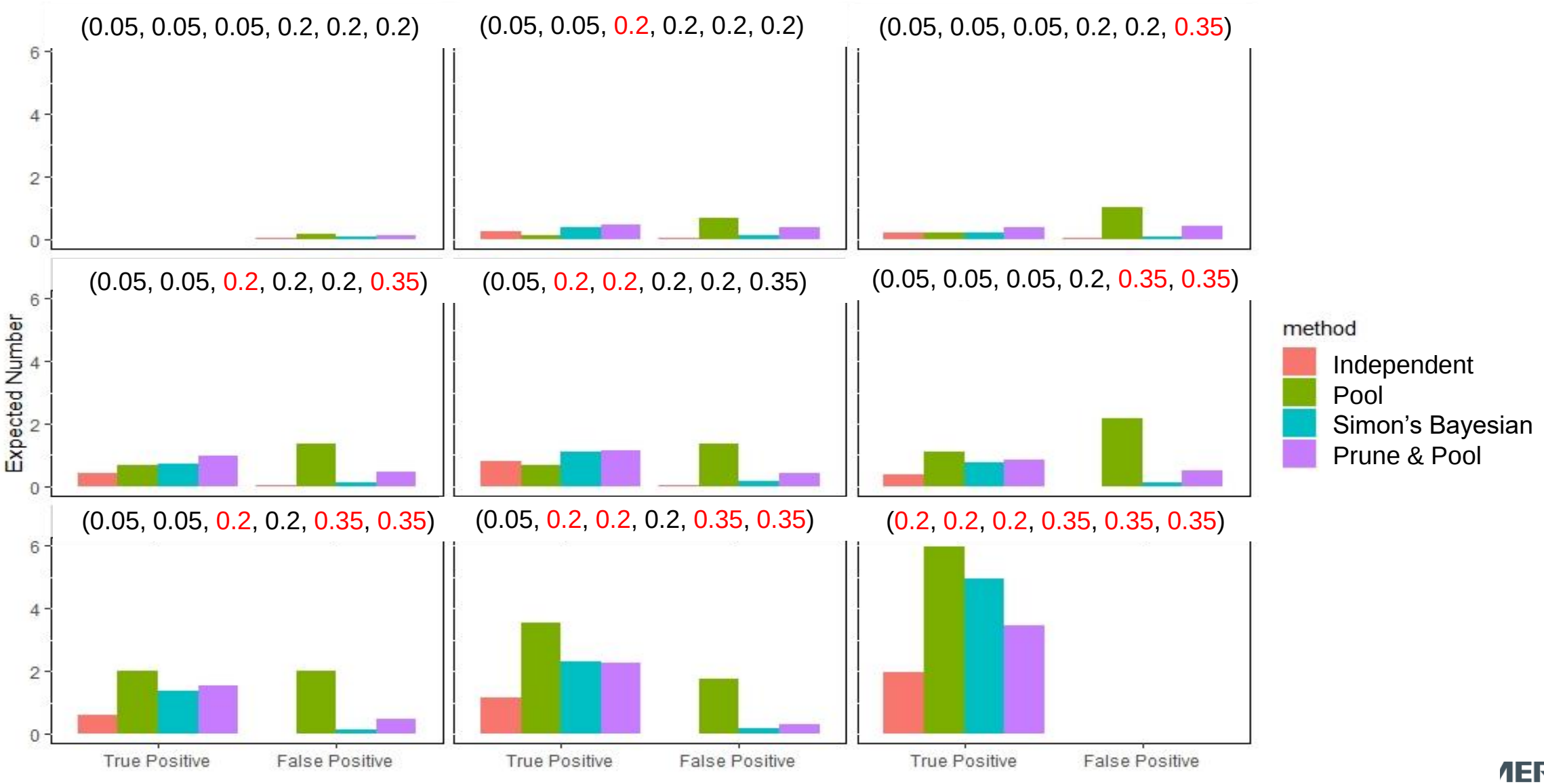
Performance Metrics

- Probability of claiming the drug works, which is defined as the percentage of the simulated trials in which the drug was claimed as effective in at least one indication.
- Probability of identifying at least two true positives, which is defined as the percentage of the simulated trials in which the drug was claimed as effective in at least 2 truly active indications.
- The expected number of true positives, which is defined as the average number of active indications correctly identified as active in the simulated trials.
- The expected number of false positives, which is defined as the average number of inactive indications incorrectly identified as active in the simulated trials.

Power of claiming positive



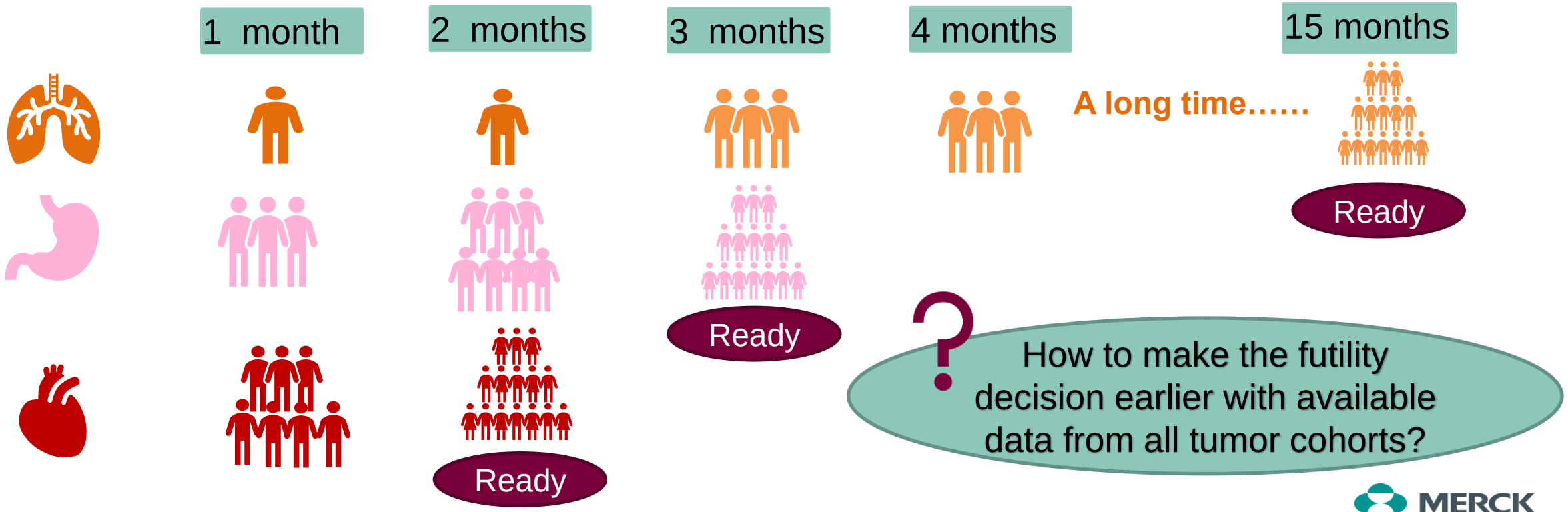
True/False positives



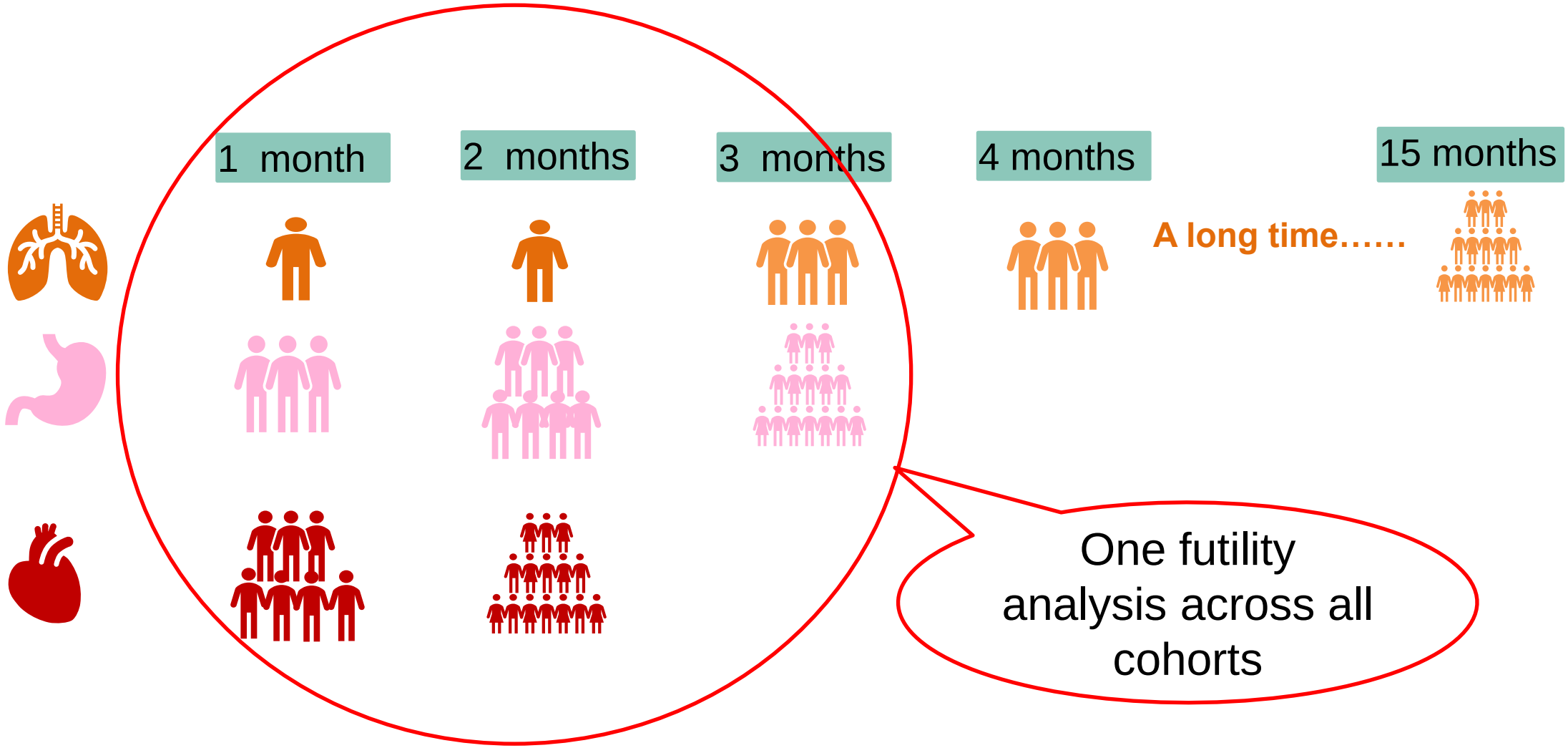
Design with Aggregated Futility Analysis

Motivation

- In a basket trial, tumor cohorts usually have different enrollment speed.
- Current practice is to perform interim futility analysis separately for each cohort once a pre-specific number of patients are enrolled.



Proposed Solution – Aggregated Futility Analysis



Overview of Design with Aggregated Futility Analysis

- The total sample size across all cohorts is pre-specified for the futility analysis, while the sample size per cohort is unspecified and flexible.
- Conduct one futility analysis by pooling all tumor indications and making one futility decision across all tumor cohorts.
- Use pruning and pooling method for the final analysis.

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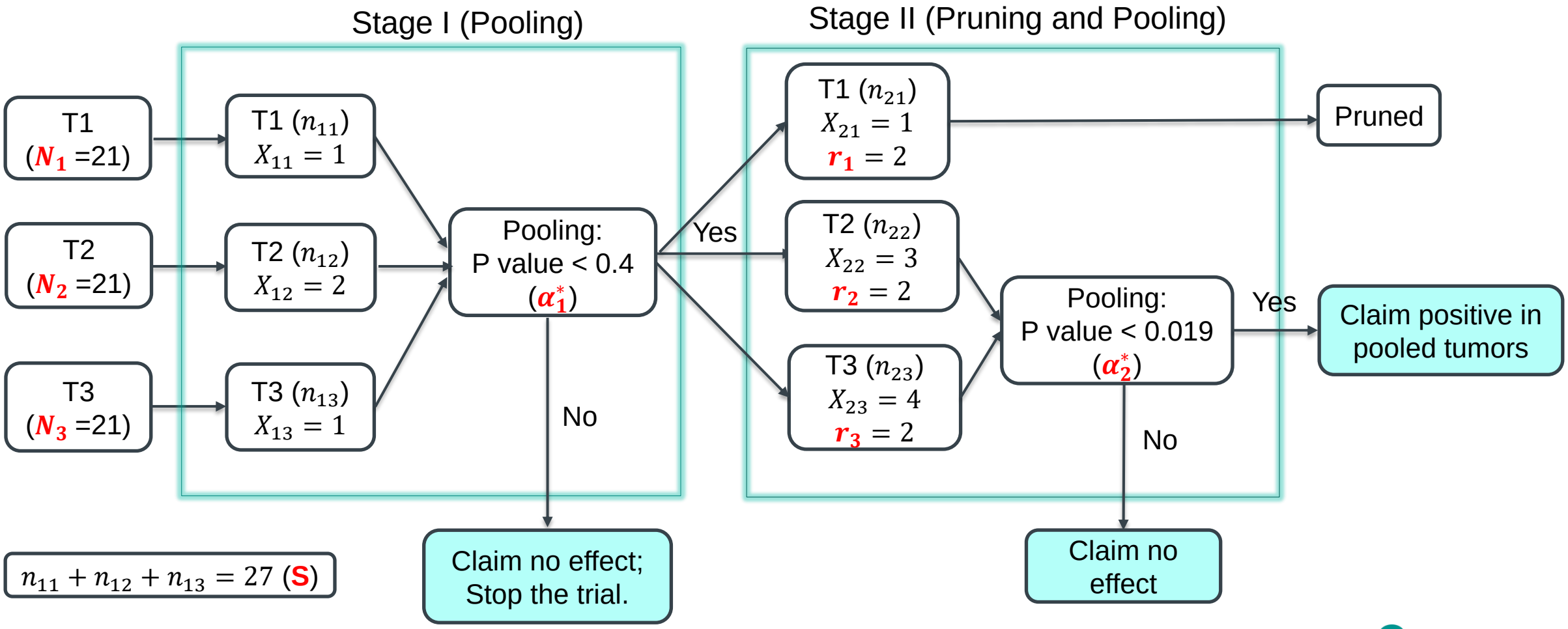
Example of Design with Aggregated Futility Analysis

$H_0: p_k = 5\%; \quad H_1: p_k = 20\%$



Compared with Optimal Design

Four tumor cohorts (K=4) under Homogeneous Setting

p_0	p_1	**Design with aggregated futility analysis**			**Optimal design (individual futility analysis)**		
		SS (Futility Analysis)	Total SS	Expected SS (under Null)	SS (Futility Analysis)	Total SS	Expected SS (under Null)
1%	15%	23	44	27.3	24	60	26.1
5%	20%	37	84	50.2	28	88	46.1
10%	25%	47	128	73.6	40	136	65.3
Both designs control global type-I error at 0.05 and target expected power at 0.8.							

Design with aggregated futility analysis tends to have less total SS, though the SS for futility analysis and expected SS under null could be slightly larger.

Summary

Take-home messages

- The optimal two-stage basket trial design is a natural extension of Simon's optimal two-stage design from one-arm to multi-arms.
- To allow more flexibility, we can consider two-stage design with aggregated futility analysis in the first stage.
- The proposed designs are straightforward to implement and have good and comparable operating characteristics as other information borrowing approaches.

Discussion

- Confirmatory trials with different types of endpoints, e.g., continuous, time-to-event, can also be optimized similarly.
- More patients may be enrolled to confirm the initial findings as inactive (or less active) indications may be included in the pooled analysis.
- Benefit of finding an active new drug often outweighs the risk of wrong tumor selection
  - Additional investigation follows only if drug is deemed active with confidence
- Additional evidence may be necessary to decide on which exact indications to expand cohort to large-scale confirmatory studies, and a risk-mitigated approach may be considered in case of uncertainty.
  - E.g. An adaptive 2-in-1 design for seamless phase 2/3 trials (Chen, et al 2018)

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Reference

- Chen, C., Li, X., Yuan, S., Antonijevic, Z., Kalamegham, R., & Beckman, R. A. (2016) Statistical design and considerations of a phase 3 basket trial for simultaneous investigation of multiple tumor types in one study. *Statistics in Biopharmaceutical Research*.
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- Master protocols: Efficient Clinical Trial Design strategies to Expedite Development of Oncology Drugs and Biologics. FDA Guidance for Industry.

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thank you
danke
謝謝
рахмат
ngiyabonga
teşekkür ederim
спасибо
gracias
tapadh leat
dank je
bedankt
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