MRC Biostatistics Unit

UNIVERSITY OF CAMBRIDGE

Adaptive Methods in Clinical Research

Lecture 4: Master protocols

Thomas Jaki

MRC Biostatistics Unit

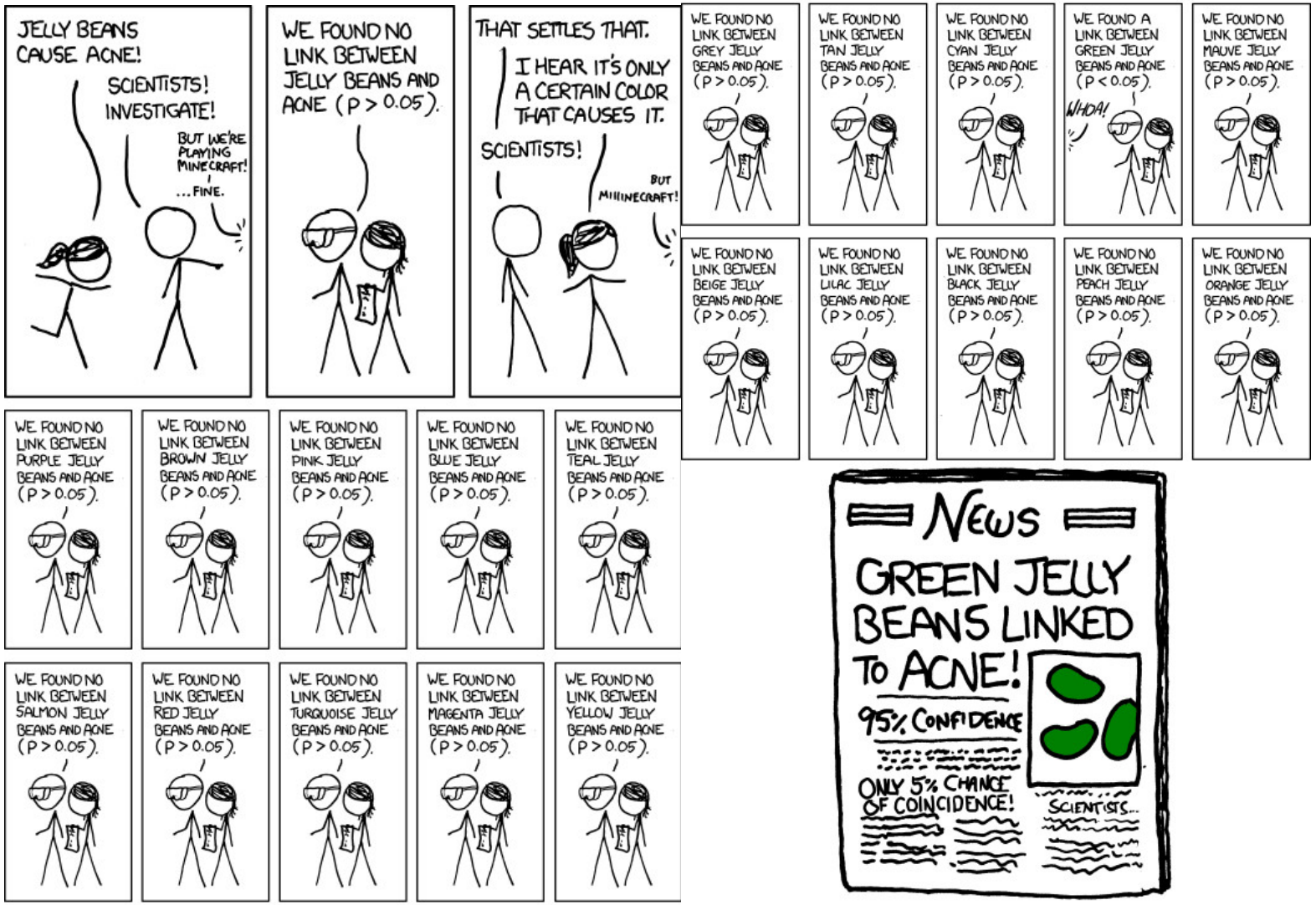
31 October 2023

Master protocols

Master protocols are a *new* type of study that seeks to answer multiple questions within a single study

- Platform trials
- Basket trials
- Umbrella trials

Multiple testing



https://xkcd.com/882/

Family-wise error rate (FWER)

Weak control

$$\mathbb{P}_{\boldsymbol{\theta}}(\text{Reject at least one true null hypotheses}|\mathcal{H}_0) \leq \nu.$$

Strong control

$$\max \mathbb{P}_{\boldsymbol{\theta}}(\text{Reject at least one true null hypotheses}) \leq \nu.$$

False discovery rate (FDR)

Controls proportion of false discoveries among the discoveries

When to adjust for multiplicity

Parker & Weir (2020)

- Other treatment arms irrelevant for making decision about a particular treatment
  $\Rightarrow$ Do not adjust
- When testing different subgroups, doses, ...
  $\Rightarrow$ Consider adjusting

When to adjust for multiplicity

Parker & Weir (2020)

- Other treatment arms irrelevant for making decision about a particular treatment
  $\Rightarrow$ Do not adjust
- When testing different subgroups, doses, ...
  $\Rightarrow$ Consider adjusting

Bretz & König (2020)

- Not all null hypothesis are simultaneously true (weak control)
- Multiple hypotheses are often tested for a single submission (e.g. Basket trial)
  $\Rightarrow$ Adjust in confirmatory setting

When to adjust for multiplicity

Parker & Weir (2020)

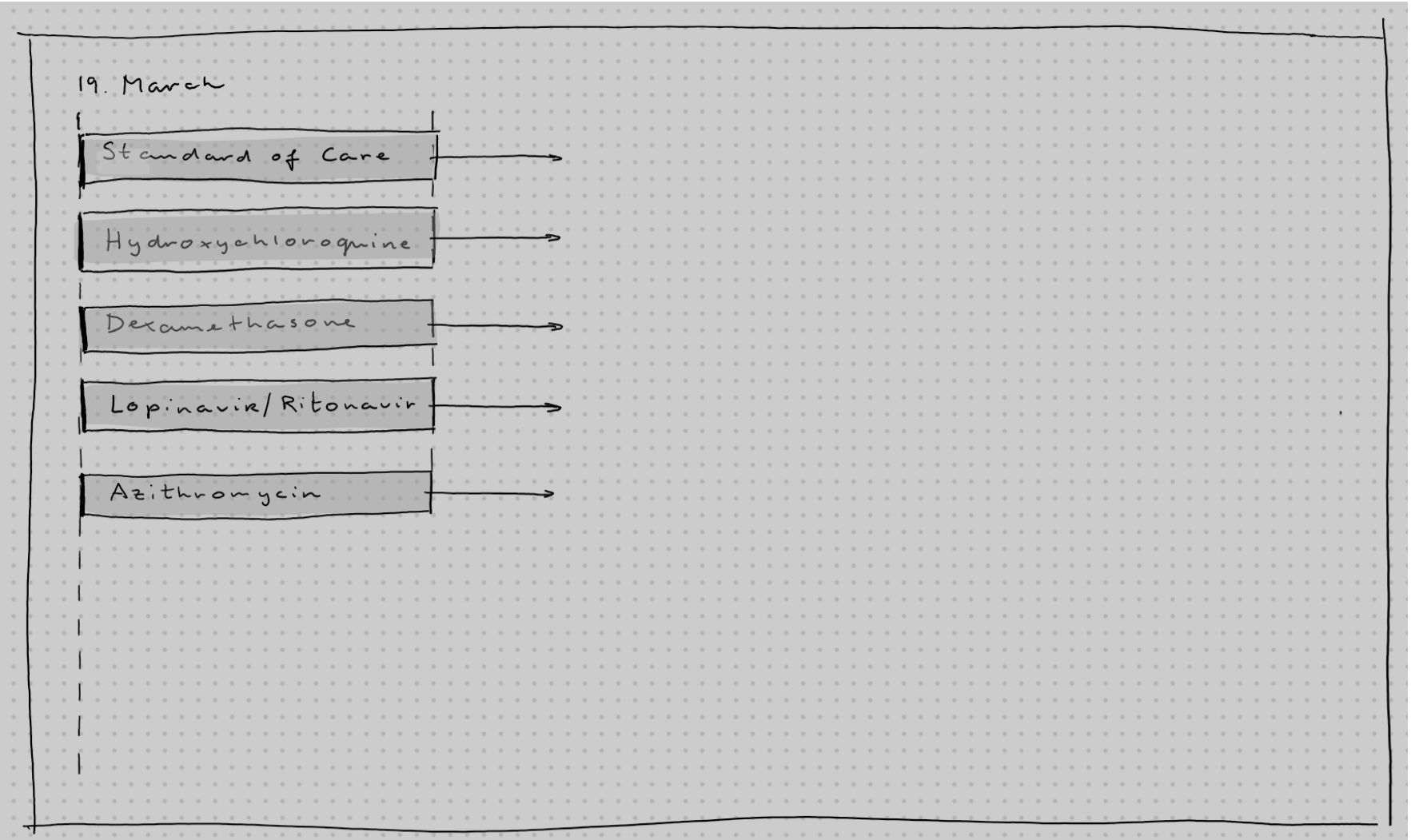
- Other treatment arms irrelevant for making decision about a particular treatment
  $\Rightarrow$ Do not adjust
- When testing different subgroups, doses, ...
  $\Rightarrow$ Consider adjusting

Bretz & König (2020)

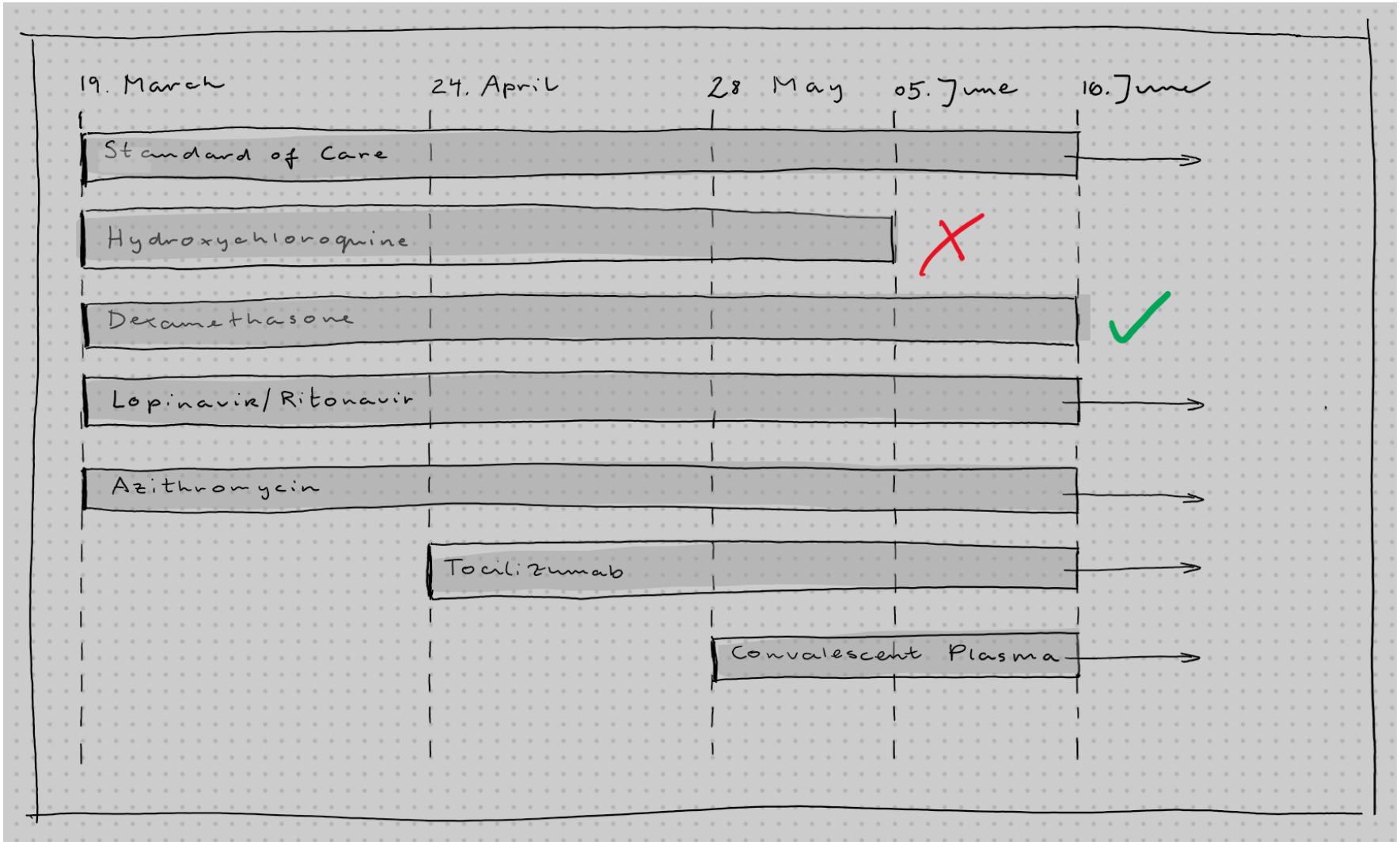
- Not all null hypothesis are simultaneously true (weak control)
- Multiple hypotheses are often tested for a single submission (e.g. Basket trial)
  $\Rightarrow$ Adjust in confirmatory setting

Need to understand risk of false decisions

A platform trial (RECOVERY)



RECOVERY


19. March
24. April
28 May
05. June
10. June
Standard of Care
Hydroxychloroquine
Dexamethasone
Lopinavir/Ritonavir
Azithromycin
Tocilizumab
Convalescent Plasma

What you probably didn't know

- Initial design of RECOVERY set to control FWER using methods discussed in previous lecture
- At the time not clear how to do so when adding arms

Sampling scheme (2 stage)

In stage 1 we recruit patients to all of the treatments

We then conduct an interim analysis to choose which treatments to continue recruiting from

At interim analysis j

- if $Z_{k,j} < l_j$: treatment k is dropped from trial.
- if $Z_{k,j} > u_j$: can reject H_k and stop trial.

Family-wise error rate (Magirr et al, 2012)

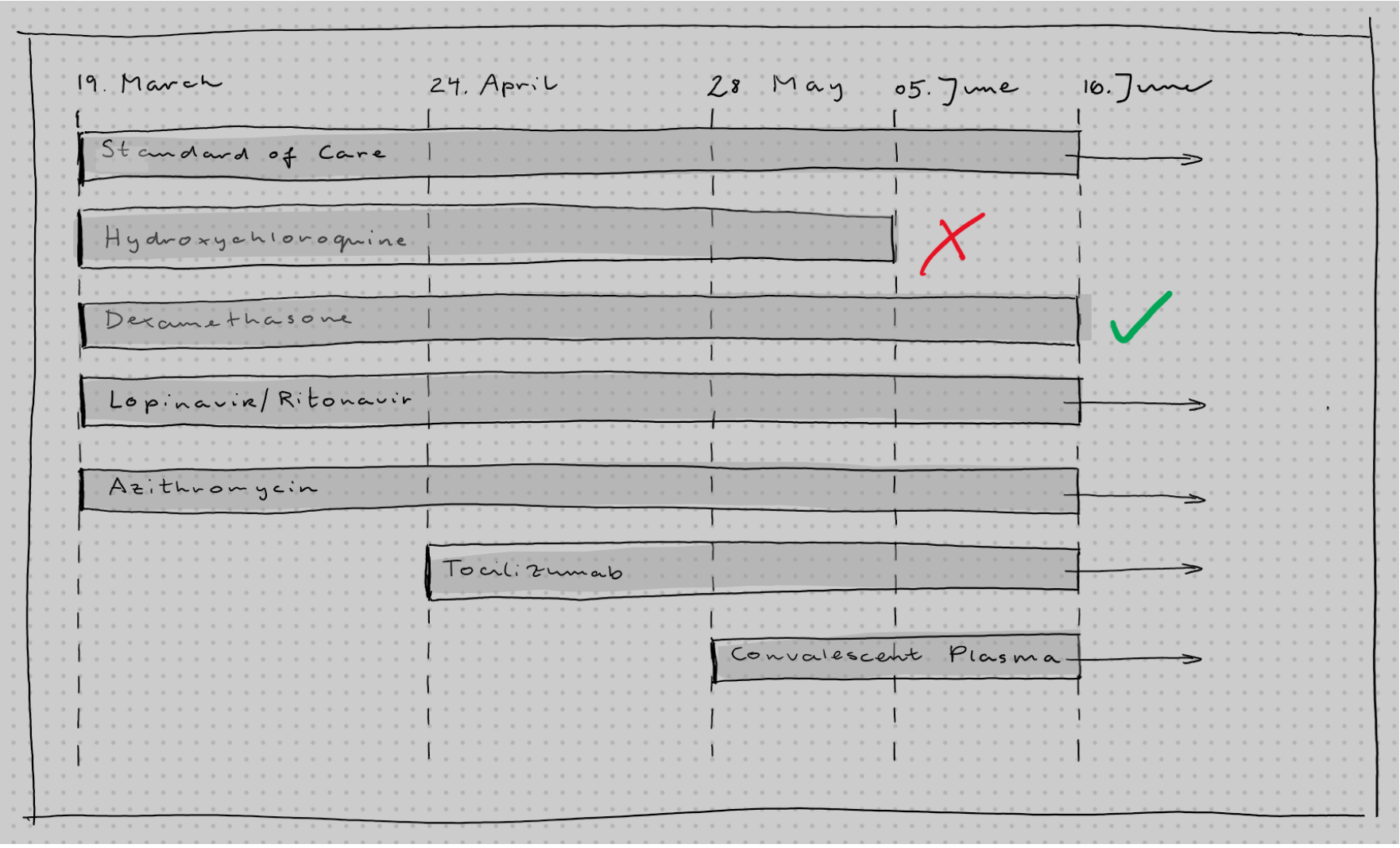
Issue: J-stage trial with K arms $\Rightarrow$ up to $K * J$ tests.

Fact: Strong control of FWER $\Leftrightarrow$ Weak control of FWER.

Problem: Test statistics are correlated.

Solution: Condition on the vector of sample means on control.

Multi-arm platform trials



Pre-planned adding (Greenstreet et al., 2021)

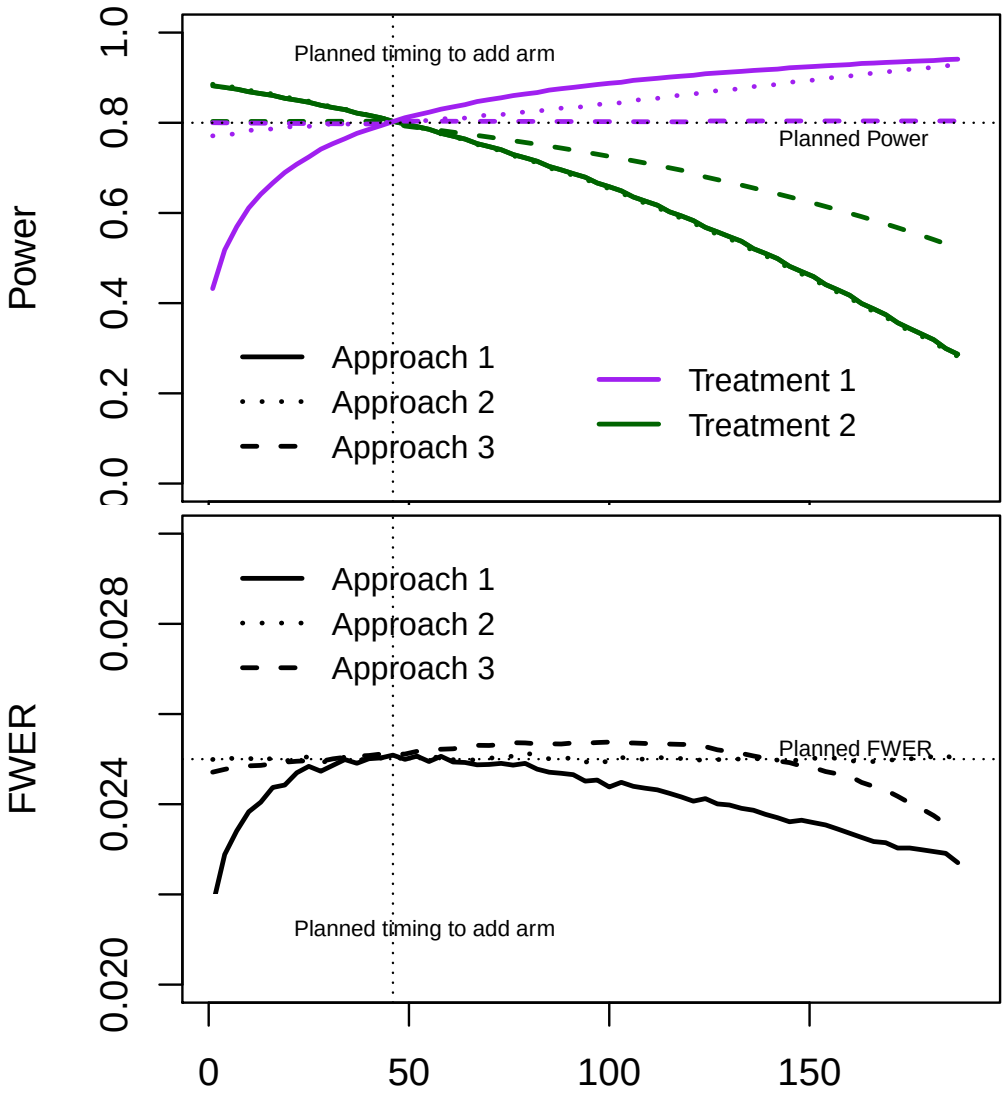
- Timing of adding an arm is known
- Same control group and endpoint
- Allocation ratio pre and post adding fixed (but possibly different)

Pre-planned adding (Greenstreet et al., 2021)

- Timing of adding an arm is known
- Same control group and endpoint
- Allocation ratio pre and post adding fixed (but possibly different)

$\Rightarrow$ Same ideas as before can be used to find design

Incorrect timing



When the second active treatment is added

A1: Move interim to when treatment is added but keep boundaries

A2: Move interim to when treatment is added and update boundaries

A3: Keep interim

Pre-planned adaptive tests

Advantages of pre-planned adaptive tests

1. Sufficient statistics
2. Sample size calculations
3. Confidence intervals always consistent with test decision

Pre-planned adaptive tests

Advantages of pre-planned adaptive tests

1. Sufficient statistics
2. Sample size calculations
3. Confidence intervals always consistent with test decision

BUT arm adding and treatment selection is typically more complex than a pre-planned rule.

Conditional error (König et al, 2008)

- The conditional error, $A(Y)$, is the maximal probability of rejecting $\mathcal{H}$ with the original test, conditional on the interim data Y
- $B(Y)$ is the conditional error for a new test following an unplanned adaption.
- If $B(Y) \leq A(Y)$ the new test controls the FWER.
- Can be used to account for ad-hoc design changes

Flexible adding (Burnett et al., 2022)

Initial design:

- $J = 3$, $K = 2$
- $n = 10$ patients per arm per stage
- Triangular bounds

Modification:

- At first interim
- add 2 arms

Operating characteristics

	$\boldsymbol{\theta}$	$P(\boldsymbol{R})$	$\mathbb{E}_{\boldsymbol{\theta}}(N)$	$\mathbb{P}_{\boldsymbol{\theta}}(R_1)$	$\mathbb{P}_{\boldsymbol{\theta}}(R_2)$	$\mathbb{P}_{\boldsymbol{\theta}}(R_3)$	$\mathbb{P}_{\boldsymbol{\theta}}(R_4)$
2 trials	$(0,0,0,0)$	0.08	87	0.03	0.03	0.03	0.03
	$(\delta,0,0,0)$	0.98	87	0.93	0.02	0.03	0.03
	$(\delta,0,\delta,0)$	0.98	86	0.93	0.02	0.82	0.04
	$(\delta,\delta,\delta,\delta)$	0.98	84	0.81	0.81	0.77	0.77
Start new	$(0,0,0,0)$	0.05	62 (+30)	0.02	0.02	0.02	0.02
	$(\delta,0,0,0)$	0.76	63 (+30)	0.75	0.01	0.01	0.01
	$(\delta,0,\delta,0)$	0.89	62 (+30)	0.67	0.02	0.67	0.02
	$(\delta,\delta,\delta,\delta)$	0.95	63 (+30)	0.64	0.64	0.64	0.64
Cond Error	$(0,0,0,0)$	0.05	78	0.03	0.02	0.01	0.01
	$(\delta,0,0,0)$	0.92	71	0.91	0.00	0.01	0.01
	$(\delta,0,\delta,0)$	0.95	71	0.86	0.01	0.64	0.03
	$(\delta,\delta,\delta,\delta)$	0.98	76	0.77	0.77	0.61	0.61

Table: R_i is the event that we reject H_{0i}, $\boldsymbol{R}$ is the event to reject at least one H_{0i}, $E_{\boldsymbol{\theta}}(N)$ is the expected sample size.

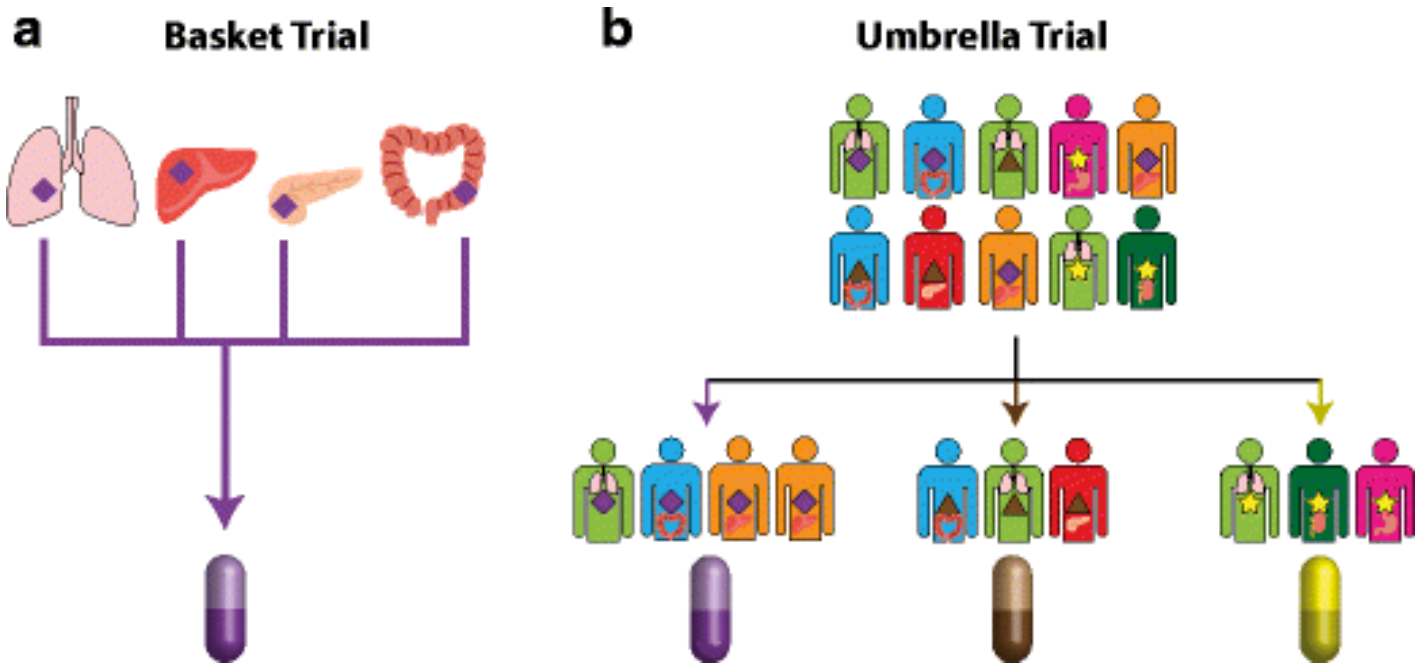
Risk of wrong decision

- FWER is only one way to understand risk of wrong decisions
- Online FDR been explored in Robertson et al. (2023)
- Specific metrics have been suggested (e.g. Cui et al., 2023)

Umbrella and Basket trials

Basket Trials Single treatment and single biomarker, different histologies placed in baskets

Umbrella Trials Single histology, multiple biomarkers each matched to treatments

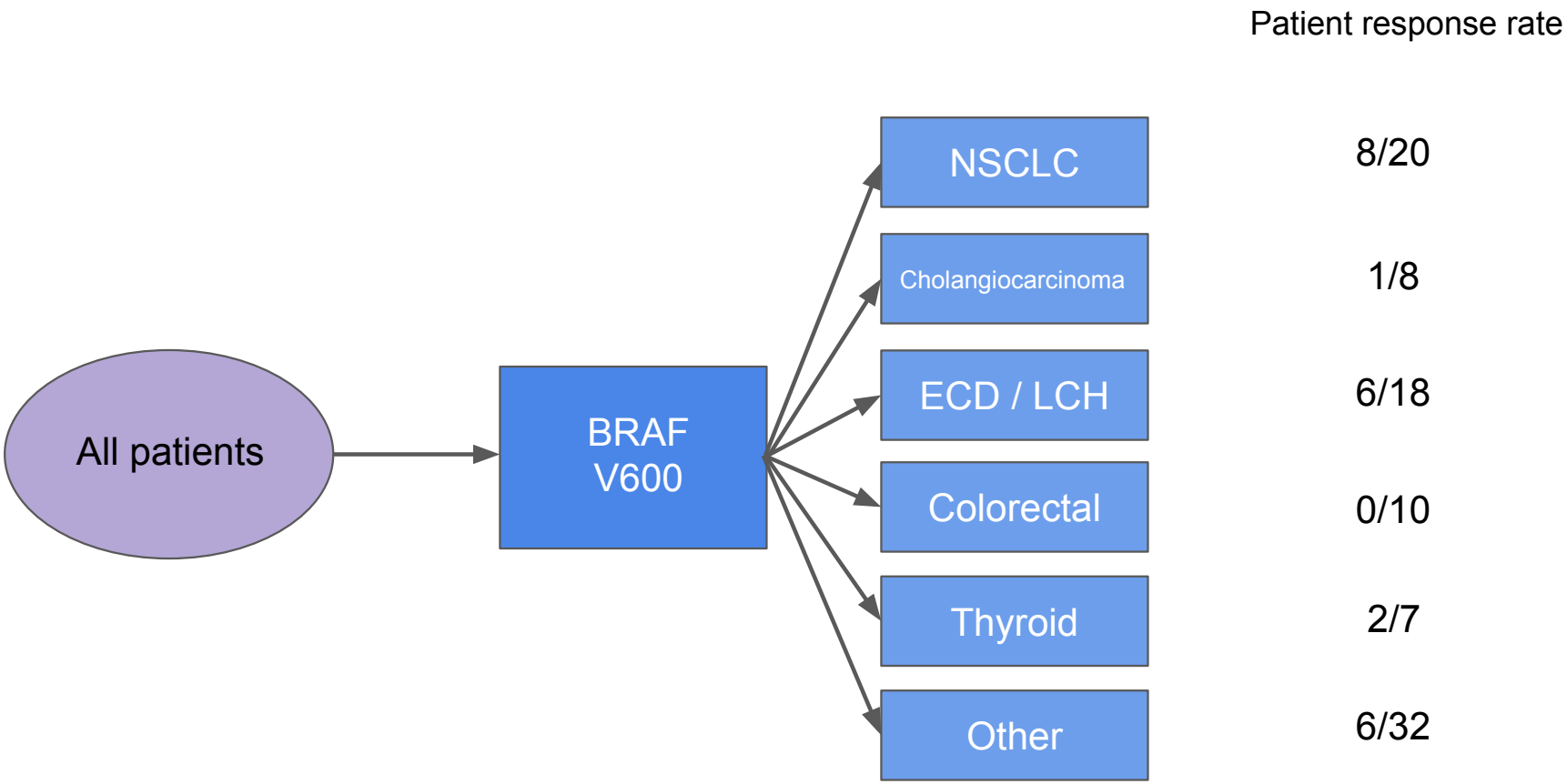


From Bui and Kummar (2018)

Basket trials in oncology – An example

Hyman *et al.* (2015) reported a recent basket trial, which has been designed to evaluate the efficacy of vemurafenib in BRAF-V600.

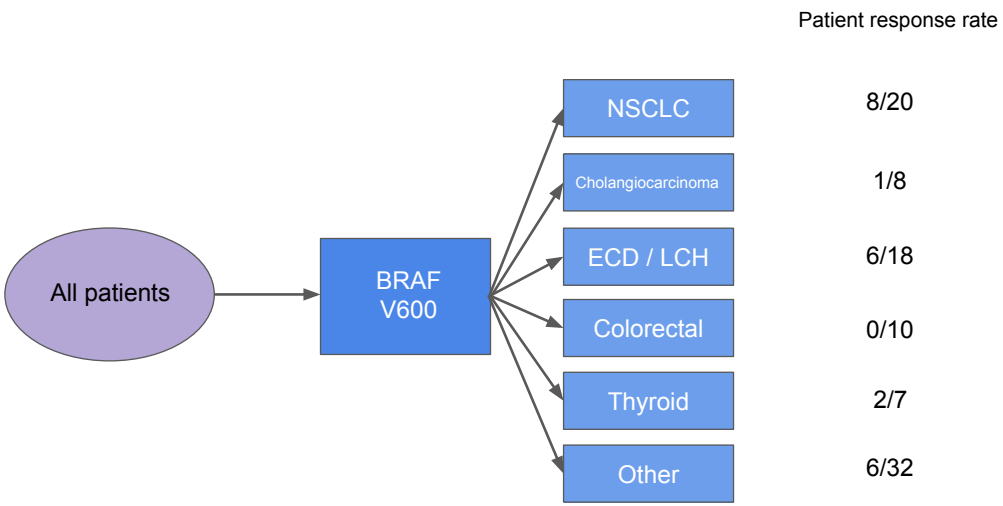
A total of 122 patients with BRAF-V600 mutations were enrolled, of which 95 entered the 6 modules.



Borrowing of information between modules

With the **common genomic mutation** targeted by the investigational drug, one may expect:

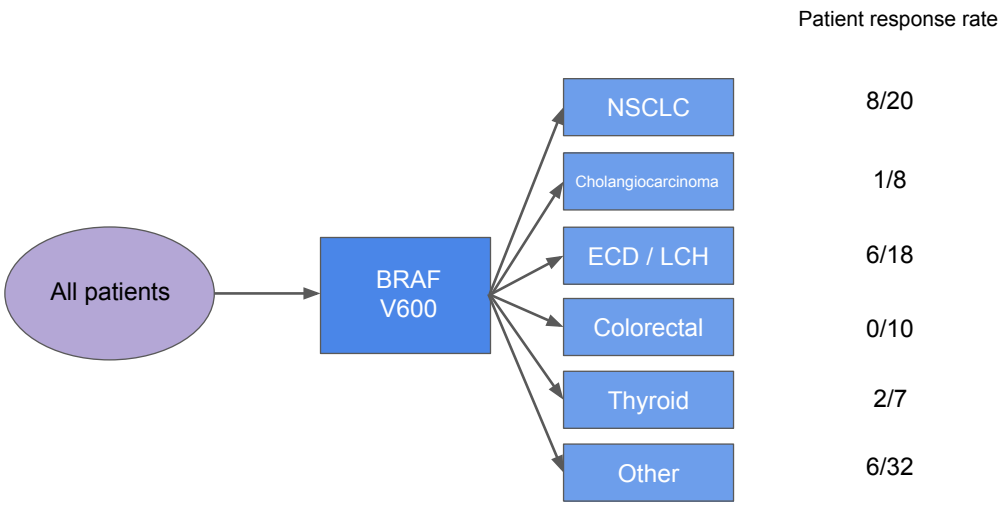
... some patient subgroups may **respond to the treatment similarly**.



Borrowing of information between modules

With the **common genomic mutation** targeted by the investigational drug, one may expect:

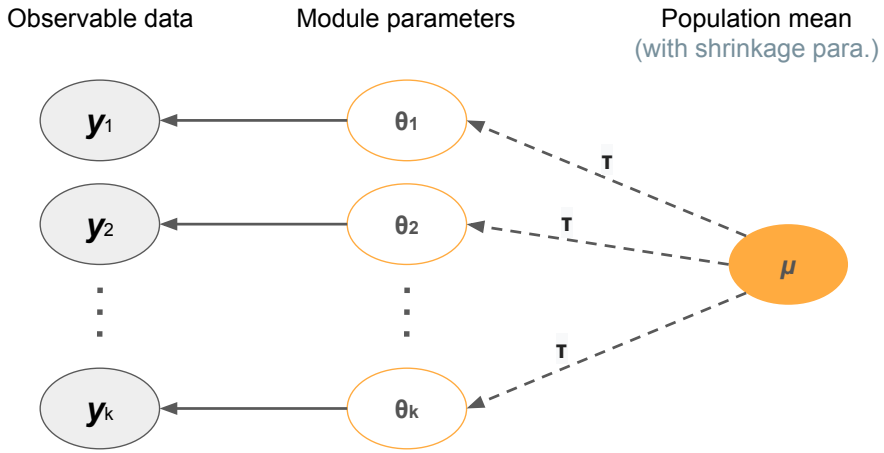
... some patient subgroups may **respond to the treatment similarly**.



Potential analysis strategies:

- Stand-alone analyses
- Complete pooling
- Borrowing of information

Bayesian hierarchical models

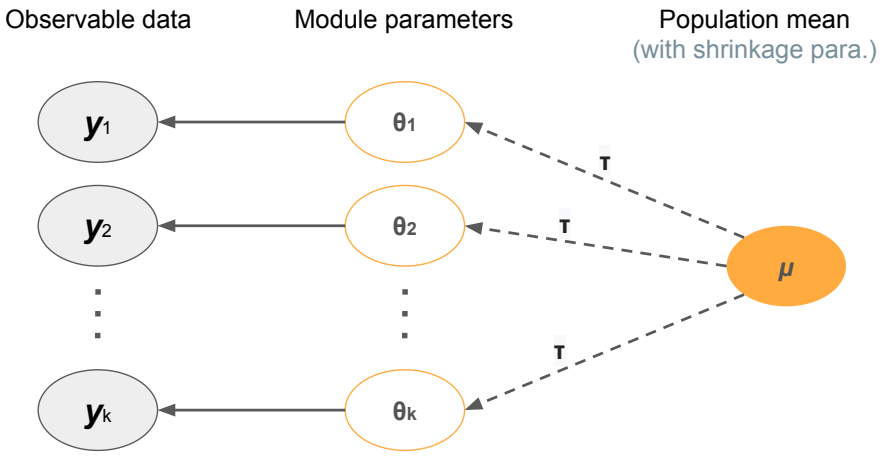


A hierarchical model for binomial data:

$$y_i|p_i, n_i \sim \text{Binomial}(p_i, n_i)$$
$$\text{logit}(p_i) = \theta_i$$
$$\theta_i|\mu, \tau \sim N(\mu, \tau^2)$$
$$i = 1, \ldots, k.$$

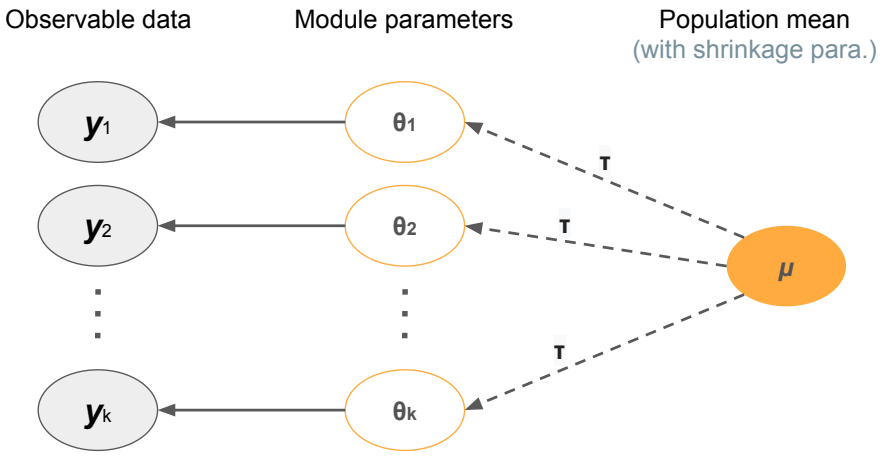
- Hierarchical modelling assumes **exchangeability** (similarity) of the θ_is
- The degree of borrowing is determined by τ:
  $\tau = 0 \rightarrow$ complete pooling of data from other modules;
  $\tau = \infty \rightarrow$ no borrowing.
- Very restrictive to suppose all θ_is will be shrunk towards one population mean

Relaxing the exchangeability assumption – EXNEX



$$y_i|p_i, n_i \sim \text{Binomial}(p_i, n_i)$$
$$\text{logit}(p_i) = \theta_i$$
$$\theta_i|\mu, \tau \sim N(\mu, \tau^2)$$
$$i = 1, \ldots, k.$$

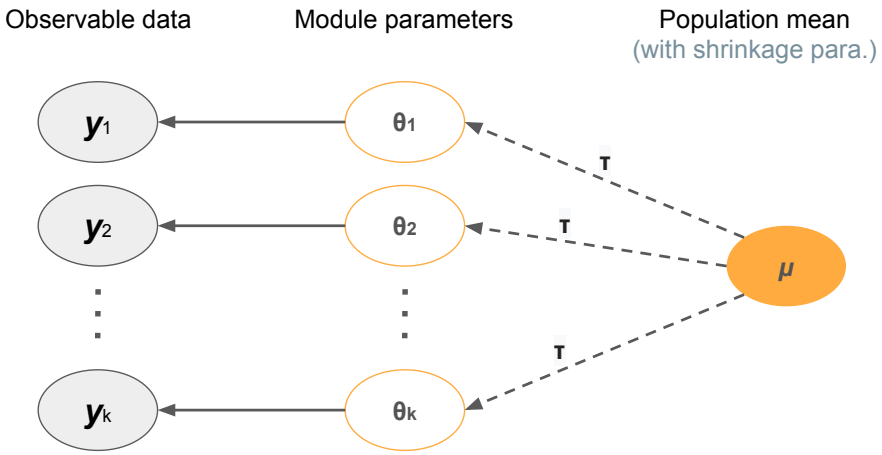
Relaxing the exchangeability assumption – EXNEX



$$y_i|p_i, n_i \sim \text{Binomial}(p_i, n_i)$$
$$\text{logit}(p_i) = \theta_i$$
$$\theta_i|\mu, \tau \sim N(\mu, \tau^2)$$
$$i = 1, \ldots, k.$$

... with probability of 1!

Relaxing the exchangeability assumption – EXNEX

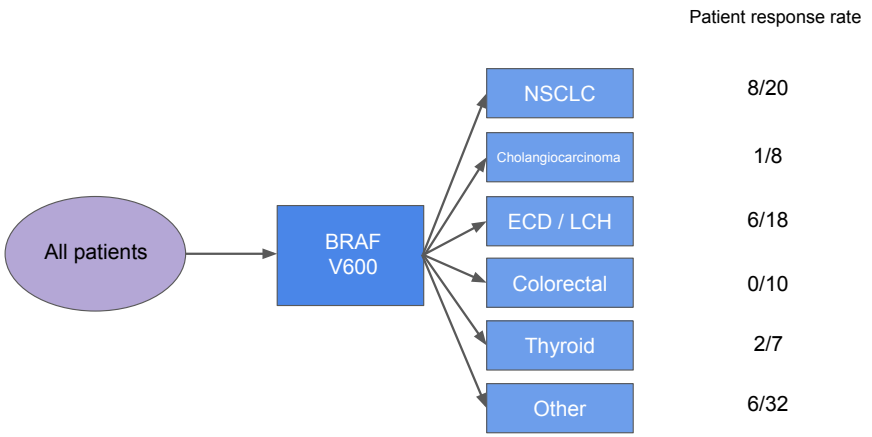


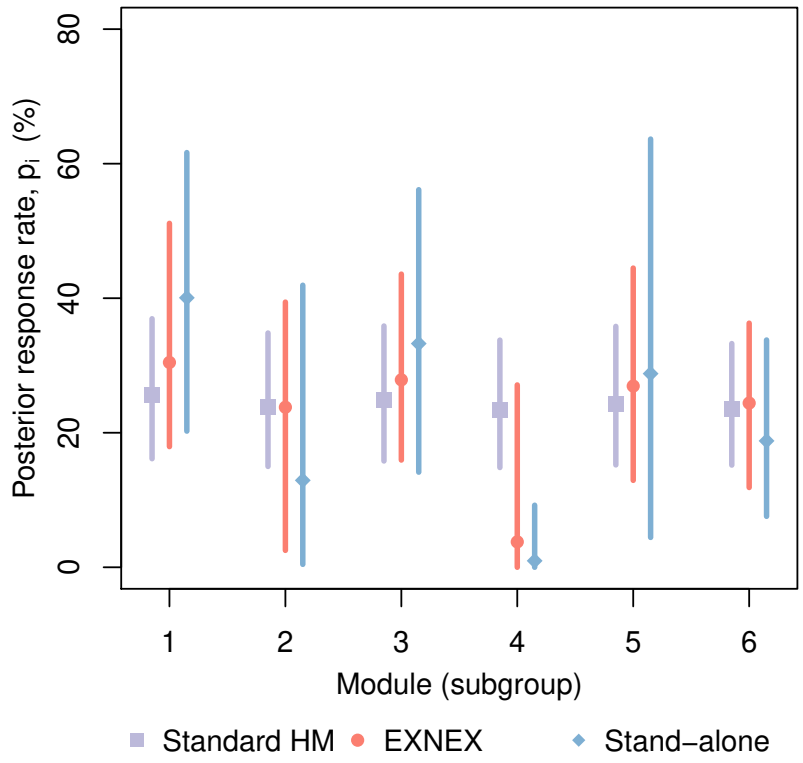
$$y_i|p_i, n_i \sim \text{Binomial}(p_i, n_i)$$
$$\text{logit}(p_i) = \theta_i$$
$$\theta_i|\mu, \tau \sim N(\mu, \tau^2)$$
$$i = 1, \ldots, k.$$

... with probability of 1!

- Neuenschwander *et al.* (2016) propose an extension to allow for **non-exchangeability**
  - EX: $\theta_i|\mu, \tau \sim N(\mu, \tau^2)$ with probability of w_i
  - NEX: $\theta_i \sim N(m_i, s_i^2)$ with probability of $1 - w_i$

Comparing different analysis models





Discussion

- In adaptive platform trials understanding risk of incorrect decisions is key
- Information borrowing a key feature of Basket and Umbrella trials
  - Should consistently be incorporated from design (Zheng et al, 2023) to analysis e.g. Zheng & Wason (2022)
- No one-size fits all solution for Master protocols, but case by case considerations necessary