



**EU-PEARL**  
EU PATIENT-CENTRIC  
CLINICAL TRIAL PLATFORMS

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# THE USE OF COMPLEX CLINICAL TRIALS: A REGULATORY REVIEW

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Quynh Nguyen, Hue Kästel, Katharina Hees, Benjamin Hofner – Paul-Ehrlich-Institut

19-April-2023

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Views are my own and do not necessarily represent the views of the Paul-Ehrlich-Institut (PEI), the European Medicines Agency (EMA), or any other European National Competent Authority (NCA).





# THE USE OF COMPLEX CLINICAL TRIALS

EXAMPLES OF SYSTEMATIC REVIEWS IN SCIENTIFIC LITERATURE



**ESMO** GOOD SCIENCE  
BETTER MEDICINE  
BEST PRACTICE

Annals of Oncology 28: 34–43, 2017  
doi:10.1093/annonc/mdw413  
Published online 11 October 2016

**SPECIAL ARTICLE**

Statistical controversies in clinical research: basket trials, umbrella trials, and other master protocols: a review and examples

L. A. Renfro\* and D. J. Sargent

Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, USA

\*Correspondence to: Dr Lindsay A. Renfro, Division of Biomedical Statistics and Informatics, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA. Tel: +1 507 255 3202; E-mail: renfro.lindsay@mayo.edu

N=12 examples

Park et al. *Trials* (2019) 20:572  
<https://doi.org/10.1186/s13063-019-3664-1>

**REVIEW** Open Access

Systematic review of basket trials, umbrella trials, and platform trials: a landscape analysis of master protocols

Jay J. H Park<sup>1,2</sup>, Ellie Siden<sup>2</sup>, Michael J. Zoratti<sup>3</sup>, Louis Dron<sup>2</sup>, Ofir Harari<sup>2</sup>, Joel Singer<sup>4,5</sup>, Richard T. Lester<sup>1</sup>, Kristian Thorlund<sup>2,3,6</sup> and Edward J. Mills<sup>2,3,6\*</sup>

Check for updates

N=83 studies

Clinical Therapeutics/Volume 42, Number 7, 2020

**The Evolution of Master Protocol Clinical Trial Designs: A Systematic Literature Review**

Elias Laurin Meyer, MSc<sup>1</sup>; Peter Mesenbrink, PhD<sup>2</sup>; Cornelia Dunger-Baldauf, PhD<sup>3</sup>; Hans-Jürgen Fülle, MD PhD<sup>3</sup>; Ekkehard Glimm, PhD<sup>3</sup>; Yuhan Li, M.S.<sup>2</sup>; Martin Posch, PhD<sup>1</sup>; and Franz König, PhD<sup>1</sup>

<sup>1</sup>Center for Medical Statistics, Informatics, and Intelligent Systems, Medical University of Vienna, Vienna, Austria; <sup>2</sup>Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; and <sup>3</sup>Novartis Pharma AG, Basel, Switzerland

N=50 studies

Complement existing literature reviews by regulatory review of complex clinical trials in scientific advices



# SYSTEMATIC REVIEW OF SCIENTIFIC ADVICES

- Scientific Advice (ScA) database (12-10-2022): > 50 000 documents
- Screening for complex clinical trials: Automatic and manual screening
- **Final extraction: 158 documents - 28 ScA procedures - 27 studies**

## **Extracted content (125 items):**

- General scientific advice details: date, no. of questions, scope of questions
- Complex clinical trials details: basket, umbrella, matrix, platform, master protocol
- Operational features: indication(s), treatment arm(s), control arm(s), randomisation and blinding, sample size
- Analyses: primary analysis, interim analysis, multiplicity control
- Regulatory assessment and comments



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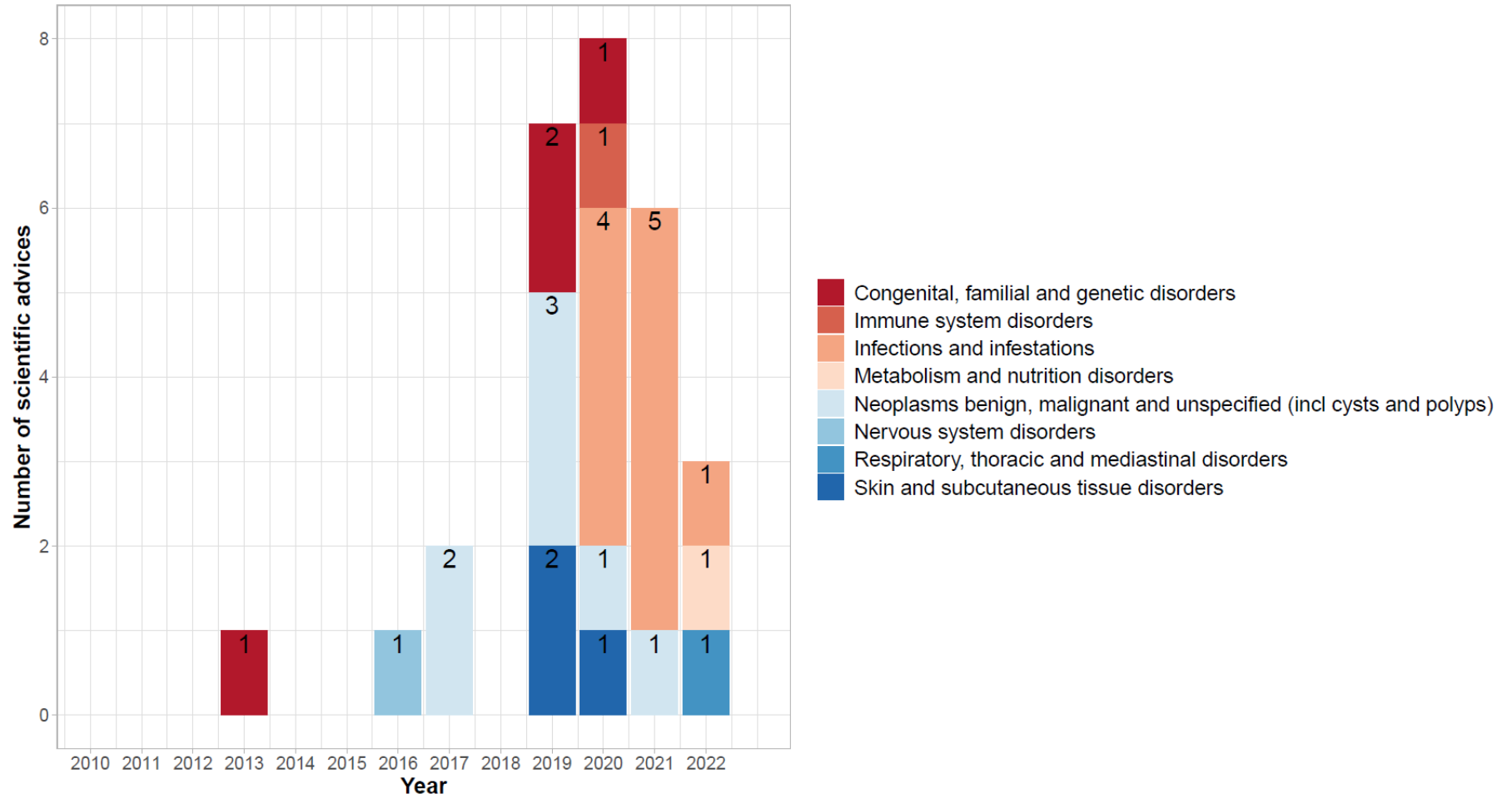
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- Analyses: primary analysis, interim analysis, **multiplicity control**
- **Regulatory assessment and comments**

Preliminary results of the extraction focussing on multiplicity control

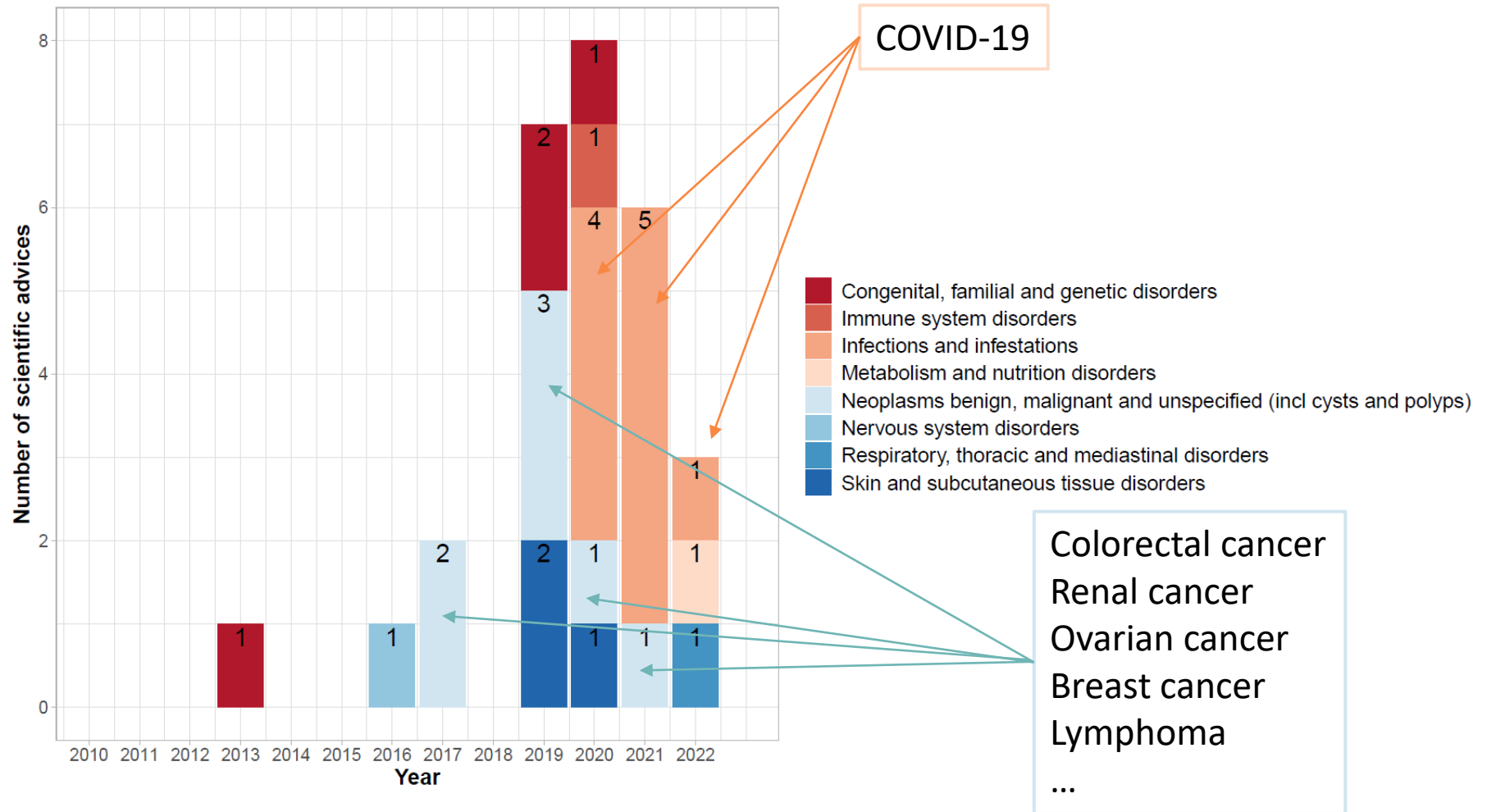


# TIMEFRAME OF SCIENTIFIC ADVICES BY DISEASE GROUPS





# TIMEFRAME OF SCIENTIFIC ADVICES BY DISEASE GROUPS



Increased use of complex clinical trials, mainly oncology and recently COVID-19



# DETAILS ON STUDIES

	All unique studies N = 27 n (%)
<b>Phase of study</b>	
I/II	3 (11.11)
II	6 (22.22)
II/III	4 (14.81)
III	10 (37.04)
Other	4 (14.81)
<b>Status of clinical study as of scientific advice</b>	
Recruiting	8 (29.63)
Planned	17 (62.96)
Not yet recruiting	1 (3.7)
Not mentioned	1 (3.7)
<b>Type of study</b>	
Exploratory	4 (14.81)
Confirmatory	18 (66.67)
Multiple	1 (3.7)
Not mentioned	4 (14.81)







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# DEFINITION OF COMPLEX CLINICAL TRIALS

## EXAMPLES OF DEFINITIONS IN LITERATURE

Type of Trial	Objective
Umbrella	To study multiple targeted therapies in the context of a single disease
Basket	To study a single targeted therapy in the context of multiple diseases or disease subtypes
Platform	To study multiple targeted therapies in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm

Woodcock & LaVange: Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both, 201

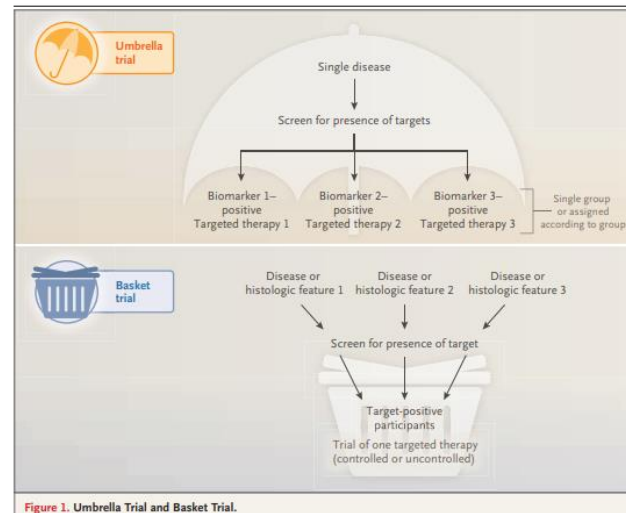


Figure 1. Umbrella Trial and Basket Trial.

Common examples of complex clinical trial designs are basket, umbrella, and platform trials. These designs are more commonly used in oncology, but they may be applied in other therapeutic areas if there is a good rationale and the design is appropriately justified. Basket trials generally investigate the safety/efficacy/effect of an IMP or combination of IMPs across a variety of populations. Umbrella trials investigate the safety/efficacy/effects of several IMPs in a single population. Whereas platform trials may test several IMPs in one or multiple populations in a highly dynamic design.

CTFG: Recommendation Paper on the Initiation and conduct of Complex Clinical Trials, 2019

### DEFINITIONS

While the different definitions of umbrella and basket trials available in the literature are often articulated along the same principles, some important discrepancies in the vocabulary exist,<sup>2,18-22</sup> and currently no generally accepted language for these types of studies is available. For example, the National Cancer Institute's Molecular Analysis for Therapy Choice (NCI Match) trial has been labeled as basket trial by some authors,<sup>2</sup> while others have classified it as an umbrella trial.<sup>19</sup>

Collignon et al.: Current Statistical Considerations and Regulatory Perspectives on the Planning of confirmatory Basket, Umbrella, and Platform Trials, 2020

### Matrix Trial

This term describes a trial that is **both** an **Umbrella Trial** (testing multiple therapies) and a **Basket Trial**, including analyses in multiple disease sub-types. Many **Platform Trials** are Matrix Trials with the additional feature that as the trial progresses and treatments leave the trial, new treatments may enter, and the trial does not have an initially fixed duration or sample size.

EU-PEARL: D2.1 Report on Terminology and Scenarios for Platform Trials and Master Protocols, 2020



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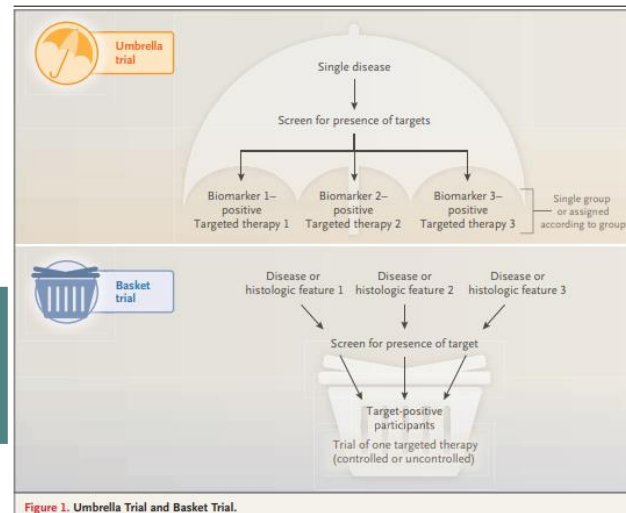


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Several definitions slightly differ in the literature

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EU-PEARL: D2.1 Report on Terminology and Scenarios for Platform Trials and Master Protocols, 2020



# DEFINITION OF COMPLEX CLINICAL TRIALS FOR EXTRACTION

- **Basket trial:**

Study **one** treatment in **multiple** indications/diseases or disease subtypes

- **Umbrella trial:**

Study **multiple** treatments in **one** indication/disease

- **Matrix trial:**

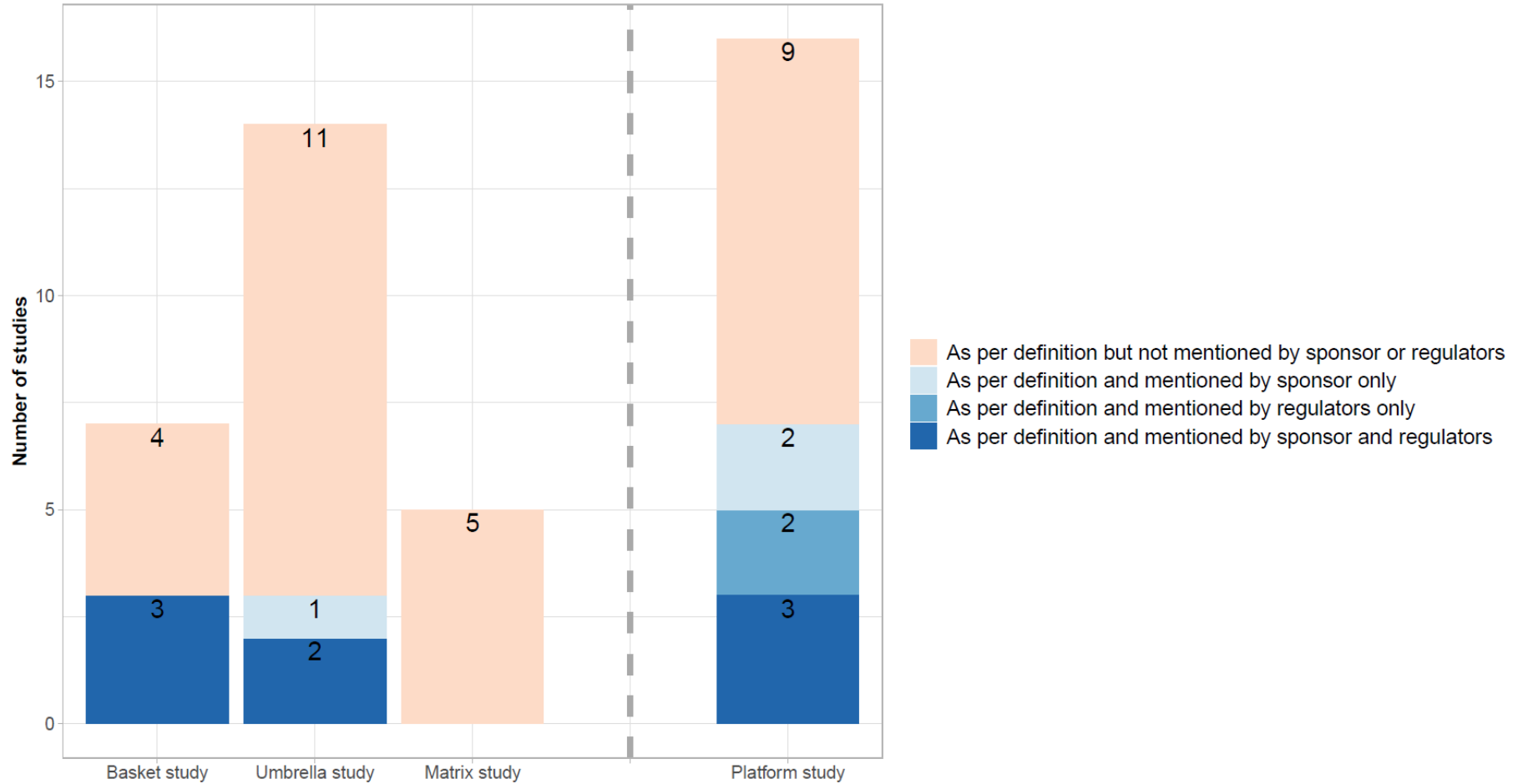
Study **multiple** treatments in **multiple** indications/diseases

- **Platform trial:**

**Basket/Umbrella/Matrix** trial with flexible addition and dropping of arms/substudies possible



# COMPLEX CLINICAL TRIALS



Majority of trials were not defined as basket, umbrella, matrix or platform trial



# MULTIPLICITY ISSUES IN COMPLEX CLINICAL TRIALS

Potential aspects to consider for multiplicity control:

- Dependent test statistics due to the use of common control
- Dependent hypotheses due to the use of e.g. similar treatments
- Special trial situations e.g. orphan or rare diseases
- Confirmatory or exploratory trials

...





# MULTIPLICITY ISSUES IN COMPLEX CLINICAL TRIALS

Potential aspects to consider for multiplicity control:

- Dependent test statistics due to the use of common control -> Simulations
- Dependent hypotheses due to the use of e.g. similar treatments -> ScA extractions
- Special trial situations e.g. orphan or rare diseases
- Confirmatory or exploratory trials

...



# SIMULATION ON COMMON CONTROLS

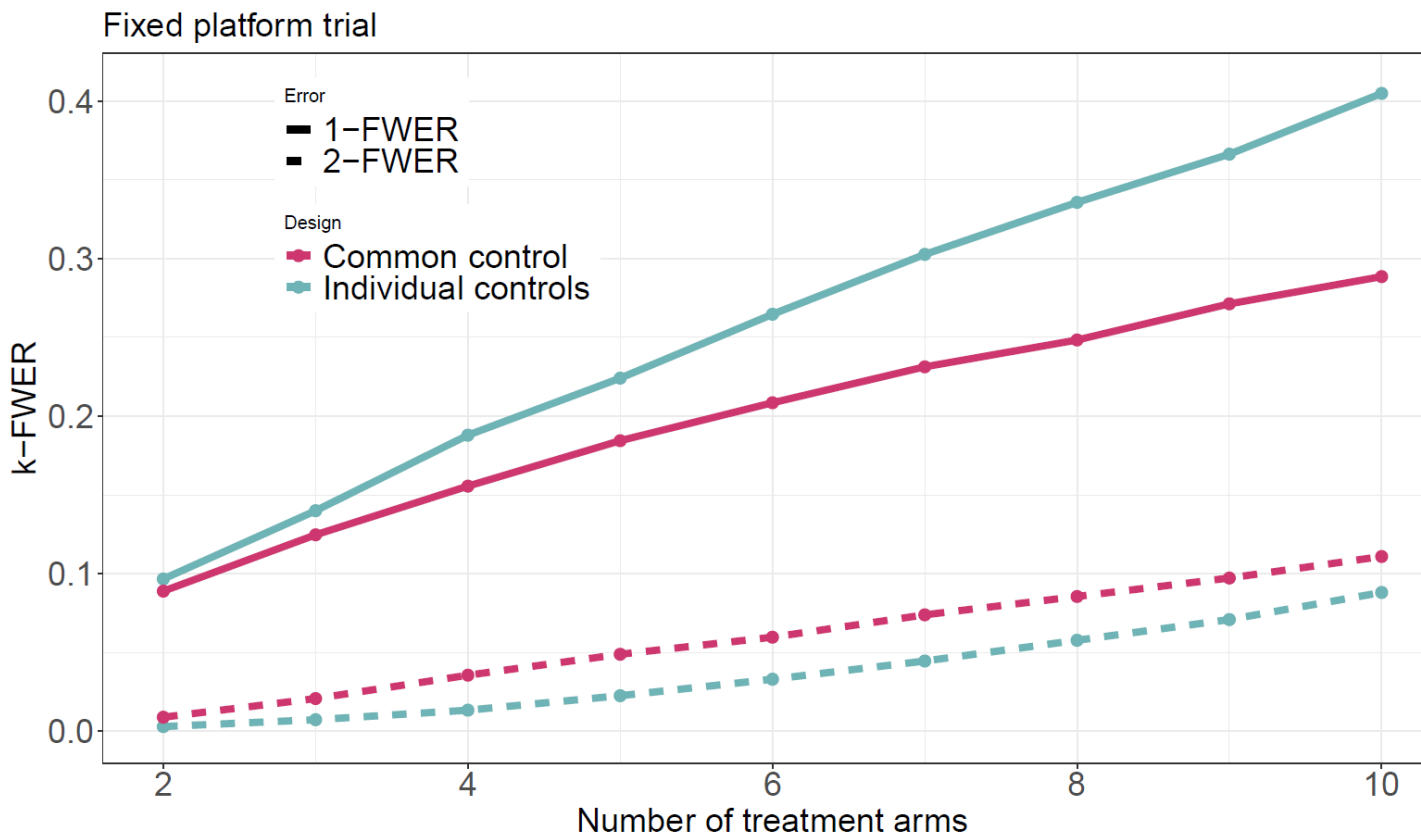
Simulation to compare the use of common controls vs. individual controls

- Error rates
- Power with and without multiplicity control





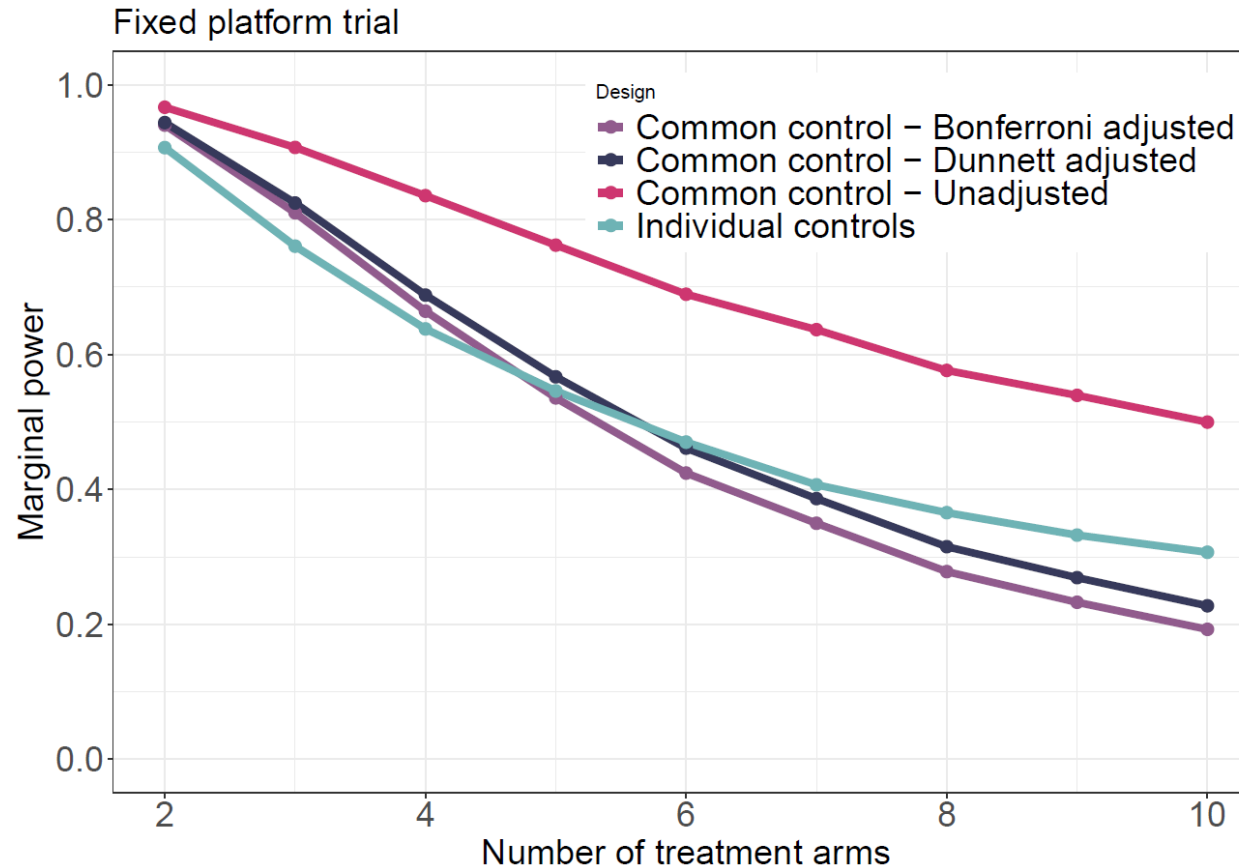
# COMMON CONTROL – ERROR RATES



1-FWER smaller with common control, while 2-FWER higher with common control



# COMMON CONTROL - MARGINAL POWER



With large number of arms, adjustment becomes „too strict“ and common control loses advantage over individual controls



# MULTIPLICITY CONTROL IN SCIENTIFIC ADVICES

- Reason for and against adjustments
- Multiplicity control vs. type of treatment





# MULTIPLICITY CONTROL IN SCA

REASON FOR MULTIPLICITY CONTROL

## Only 3 studies planned for adjustment

- All studies were confirmatory
- All studies used a shared control

## Reason for adjustment

- N=3: Use of shared control
- N=1: Use of similar treatment arms
- N=1: Single claim of efficacy

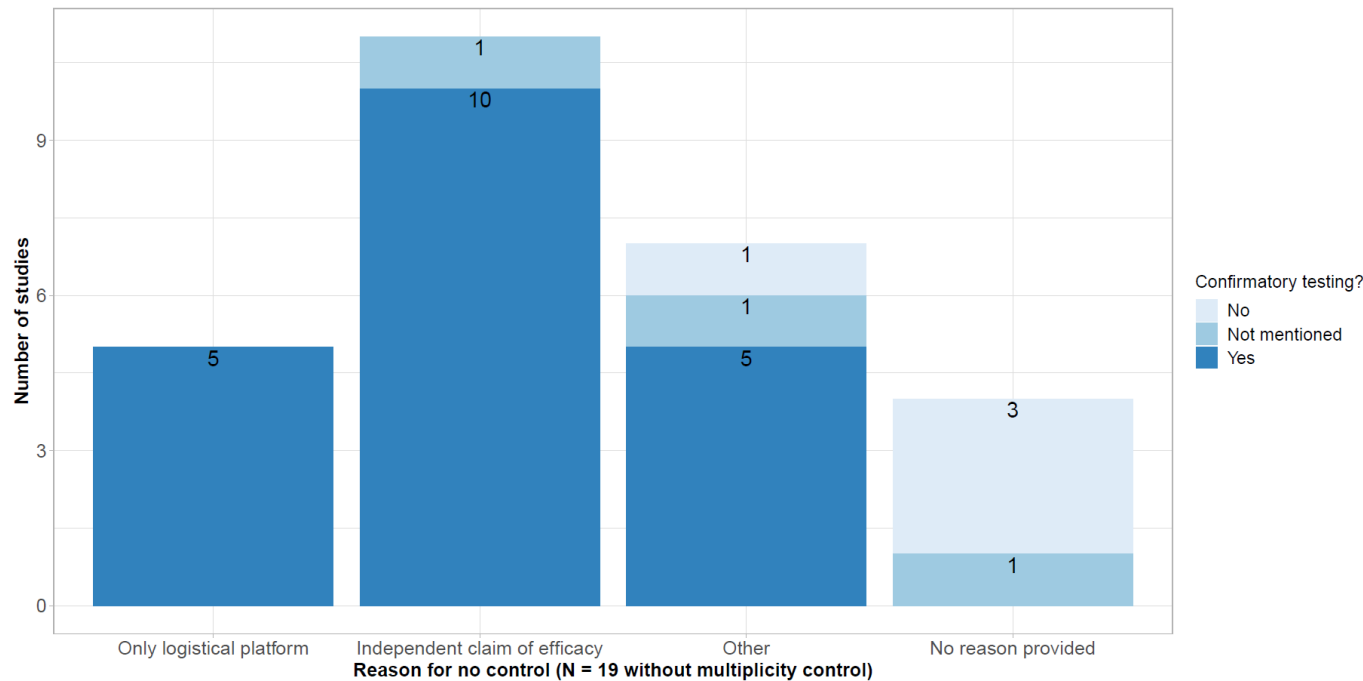
## Comments from regulators:

- N=2: Accepted
- N=1: Accepted with concern  
Type I error control via simulation but analytical solution preferred



# MULTIPLICITY CONTROL IN SCA

## REASON AGAINST MULTIPLICITY CONTROL



### 10 studies without comments from regulators

- N=8: non-confirmatory, not mentioned if confirmatory, confirmatory but only one test is performed
- N=2: confirmatory (basket trial, umbrella/platform trial)

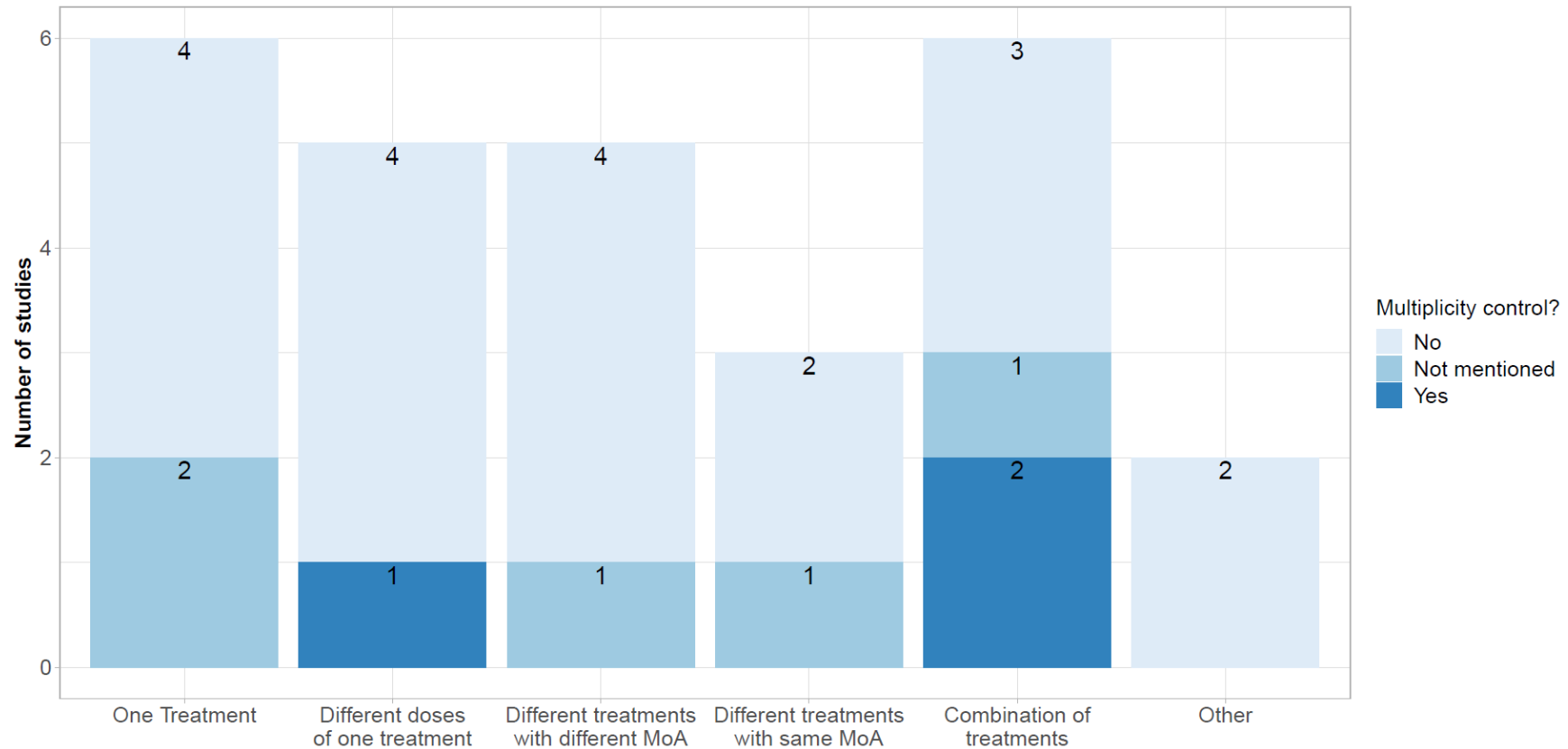
### 9 studies with comments from regulators

- N=5: Basket trials, Acceptance of independent cohorts -> no adjustment required
- N=4: Umbrella/platform, Acceptance but with the following conditions/concerns:
  - Risk of false-positive rate due to multiple testing
  - Similar MoA leading to dependent treatment arms

Though majority of trials were confirmatory, no adjustment is proposed by sponsors



# MULTIPLICITY CONTROL IN SCA BY TYPE OF TREATMENT



In majority of studies no multiplicity adjustment was proposed, though several doses of the same treatment or similar treatments were used



# MULTIPLICITY CONTROL IN SCA BY TYPE OF TREATMENT

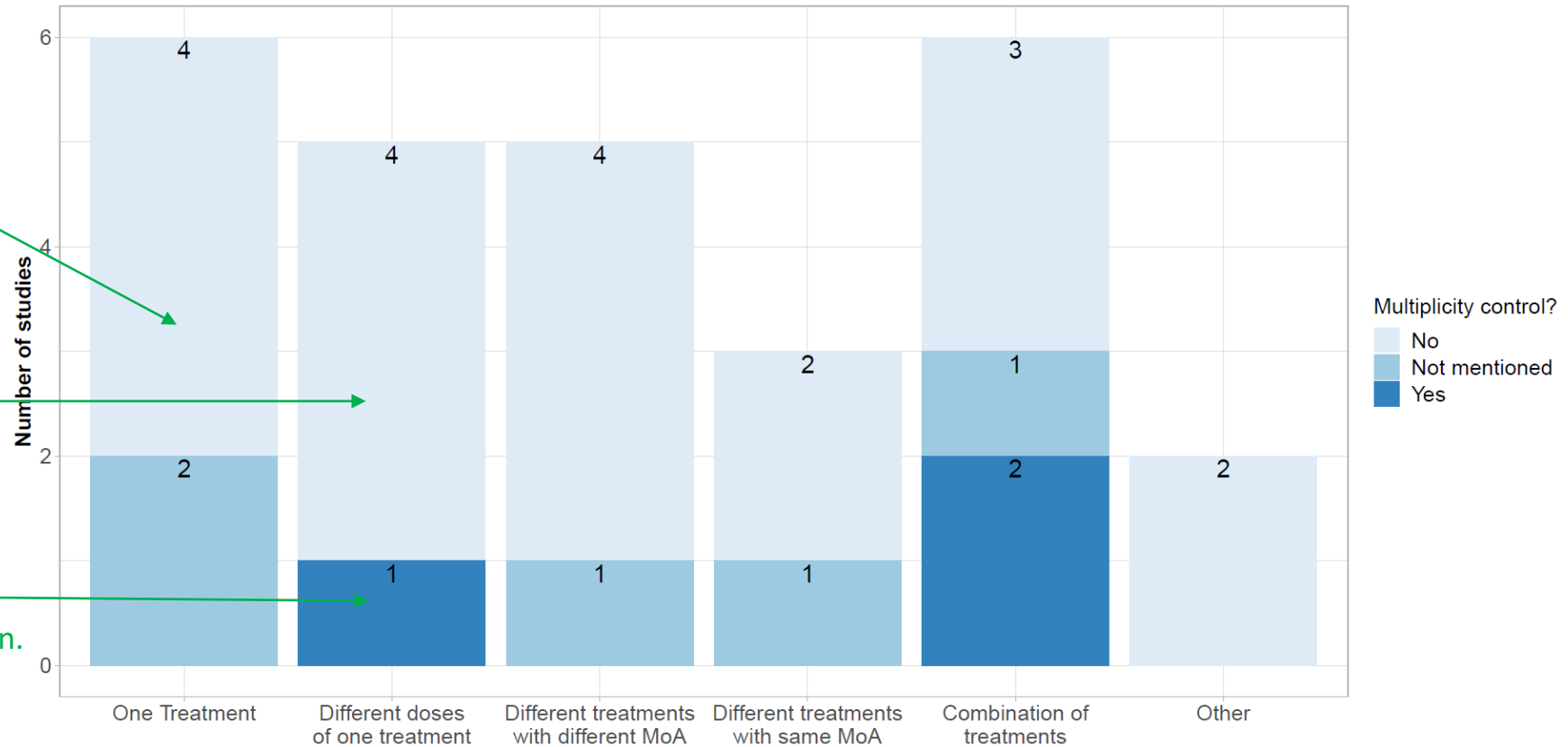
CONCERNS/CONDITIONS BY REGULATORS



Basket trials:  
Independence of cohorts

Basket trials, Matrix:  
One test only

Umbrella:  
Different routes of admin.



**Regulatory comments:**

Accepted

Accepted with concerns

Concerns



# MULTIPLICITY CONTROL IN SCA BY TYPE OF TREATMENT

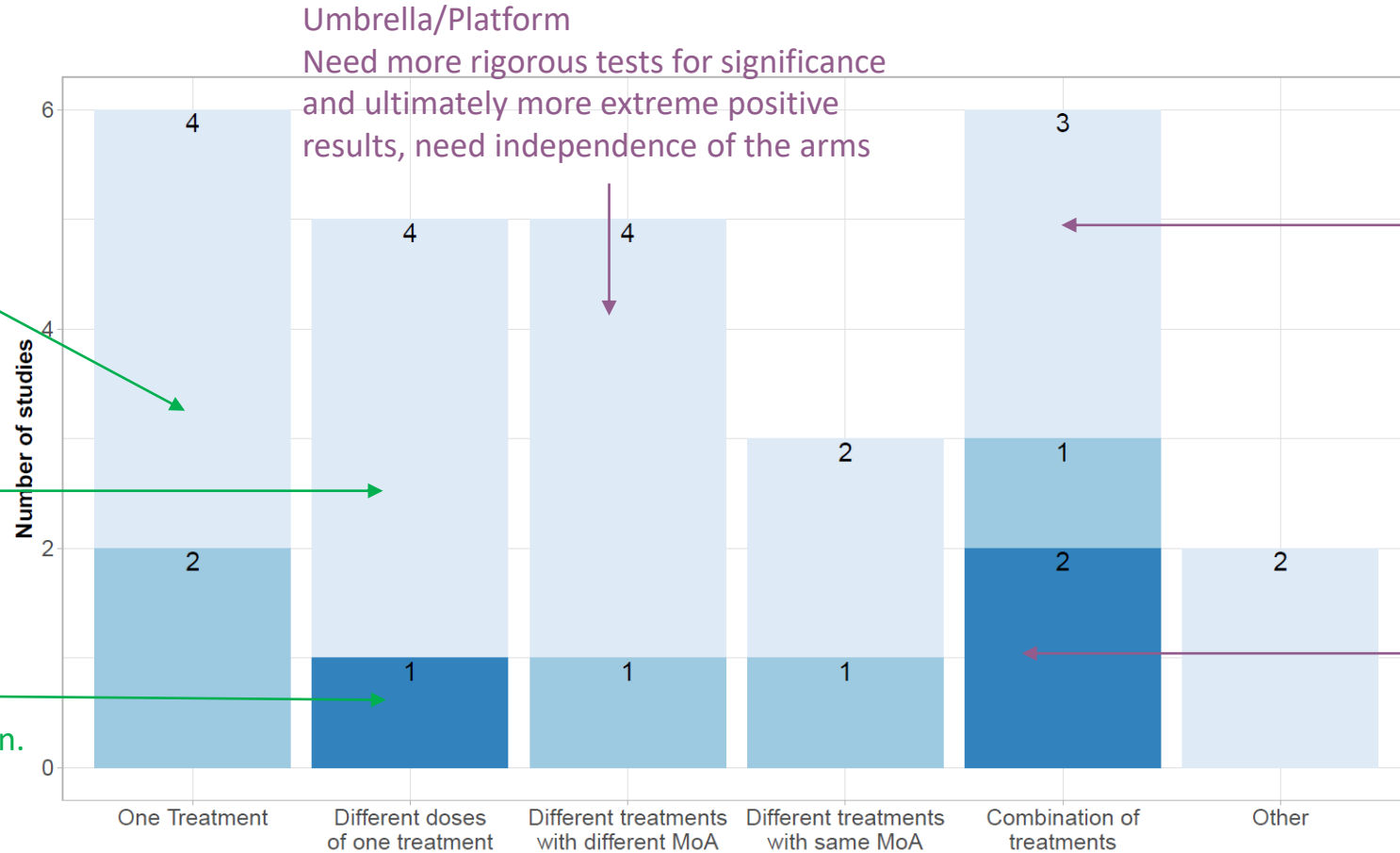
CONCERNS/CONDITIONS BY REGULATORS



Basket trials:  
Independence of cohorts

Basket trials, Matrix:  
One test only

Umbrella:  
Different routes of admin.



Umbrella/Platform  
Need more rigorous tests for significance  
and ultimately more extreme positive  
results, need independence of the arms

Umbrella, Matrix/Platform, Basket:  
One test only, need independence of  
cohorts

Multiplicity control?

- No
- Not mentioned
- Yes

Umbrella/Platform, Matrix/Platform:  
Analytical proof of type I error  
control preferred

**Regulatory comments:**

Accepted

Accepted with concerns

Concerns





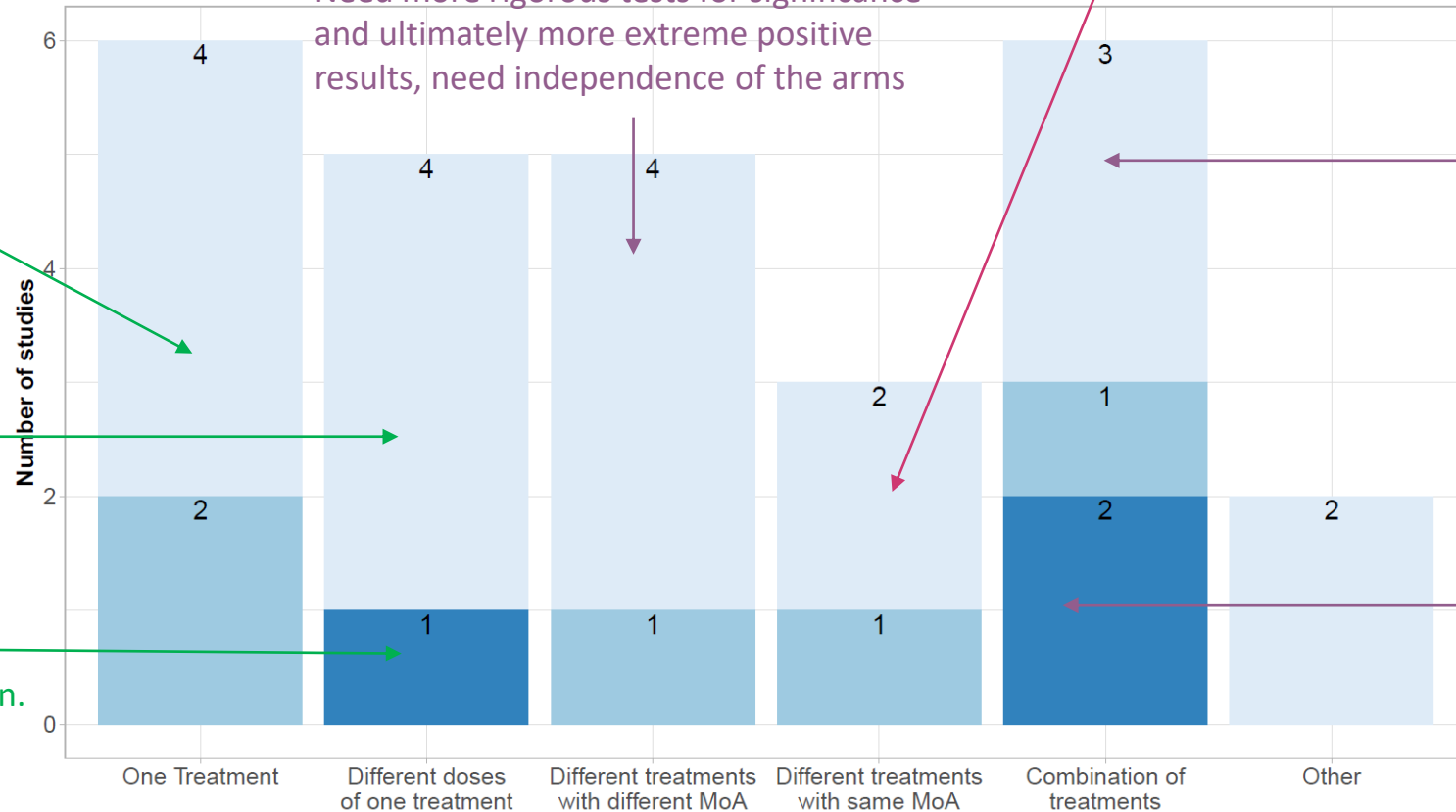
# MULTIPLICITY CONTROL IN SCA BY TYPE OF TREATMENT

CONCERNS/CONDITIONS BY REGULATORS

Basket trials:  
Independence of cohorts

Basket trials, Matrix:  
One test only

Umbrella:  
Different routes of admin.



Umbrella/Platform  
Need more rigorous tests for significance and ultimately more extreme positive results, need independence of the arms

Umbrella/Platform  
Need for type I error control, address risk of false-positive

Umbrella, Matrix/Platform, Basket:  
One test only, need independence of cohorts

Multiplicity control?

- No
- Not mentioned
- Yes

Umbrella/Platform, Matrix/Platform:  
Analytical proof of type I error control preferred

**Regulatory comments:**

Accepted

Accepted with concerns

Concerns



# SUMMARY AND LIMITATIONS



## Findings of complex clinical trials in ScA aligned with literature

- Increased use of complex clinical trials
- No multiplicity control often justified by independence of arms
  - Through „independent“ populations
  - Through „independent“ treatments
  - Usually „accepted“ by regulators in Scientific Advices
- Multiplicity control most likely needed if dependency exists:
  - Similar treatments or combination of treatments
  - Use of shared control

## Complex clinical trials in ScA limited as compared to literature reviews

- No ScA requested for certain trials (e.g. exploratory)
- Trials may not be labelled as complex clinical trial
- Incomplete database as only products where PEI was responsible were included, e.g. monoclonal antibodies, vaccines, and advanced therapy medicinal products (ATMPs)\*

\*Full list of medicinal products that are in the responsibility of PEI: <https://www.pei.de/EN/institute/official-duties/duties-node.html>



# BACKUP

- Detailed definition of complex clinical trials for ScA
- PEI Database details





# DEFINITION OF COMPLEX CLINICAL TRIALS FOR SCA EXTRACTION

- **Basket trial: Study one therapy in multiple indications/diseases or disease subtypes**
  - Target population: different disease or subtype of a disease, presence of certain biomarkers
  - Same treatment is studied across all target populations
  - Can be in substudies
  - Indications are studied in individual cohorts/arms but with the same treatment
- **Umbrella trial: Study multiple treatments in one indication/disease**
  - In each arm/substudy, patients receive corresponding investigational treatment
  - Can be a single study or substudies
  - Treatments are studied in individual cohort/arms but throughout same indication
- **Matrix trial: Multiple indications/diseases, multiple treatments**
  - Several indications and several treatments
  - Each indication has a different treatment
  - Exclusive from umbrella/basket trial
- **Platform trial: Multi-arm trial with flexible addition and dropping of arms/substudies possible**
  - Not a separate category but a specific form of basket, umbrella or matrix trials
  - Substudies/arms can potentially be added or stopped dynamically during the course of the trial



# PEI DATABASE DETAILS

## Timeframe of scientific advices

- First document from 1999
- < 2017: incomplete database
- 2017-2020: full database
- > 2020: only ScA with PEI-Coordinatorship

