Trial Design Considerations in Developing Pediatric Master Protocols

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Background

- Up to 40% of pediatric trials fail to establish safety or efficacy and result in a labeled indication for pediatric use

- Trial Design Challenges
  - Inappropriate endpoints
  - Placebo effects
  - Feasible designs for small populations

Objectives

- Review efficacy/response endpoints measured in pediatric clinical trials since 2007, and highlight issues that should be resolved prior to a master protocol
- Discuss placebo considerations in pediatric trials
- Hypothesize trial designs that may be amenable to the use of a master protocol in the pediatric population

Endpoints in Pediatric Efficacy Trials

- Efficacy endpoints that are well-defined, reliable, and interpretable are critical to trial success
- The use of inappropriate or unvalidated endpoints in pediatric trials has led to trial failure
- Endpoints used in adult trials may not always be suitable for pediatrics
- Characteristics of the endpoint may influence trial outcome

Survey of Endpoints in Pediatric Efficacy Trials (FDAAA 2007 – 2012 & FDASIA 2012 – present)**

	FDAAA	FDASIA	Total
Total Trials	133	103	236
Total Unique Drugs	83	68	138

Trial Outcome	FDAAA (%)	FDASIA (%)	Total (%)
Success	75.9	77.7	76.7
Failure	24.1	22.3	23.3

*Inconclusive trials were considered to have failed

Label Outcome	FDAAA (%)	FDASIA (%)	Total (%)
Approved	83.5	74.8	79.7
Not approved	16.5	25.2	20.3

*Drugs approved in a subset of the full age range studied were considered to have been approved

**Represents preliminary data

Label Outcome by Therapeutic Area**

**Represents preliminary data

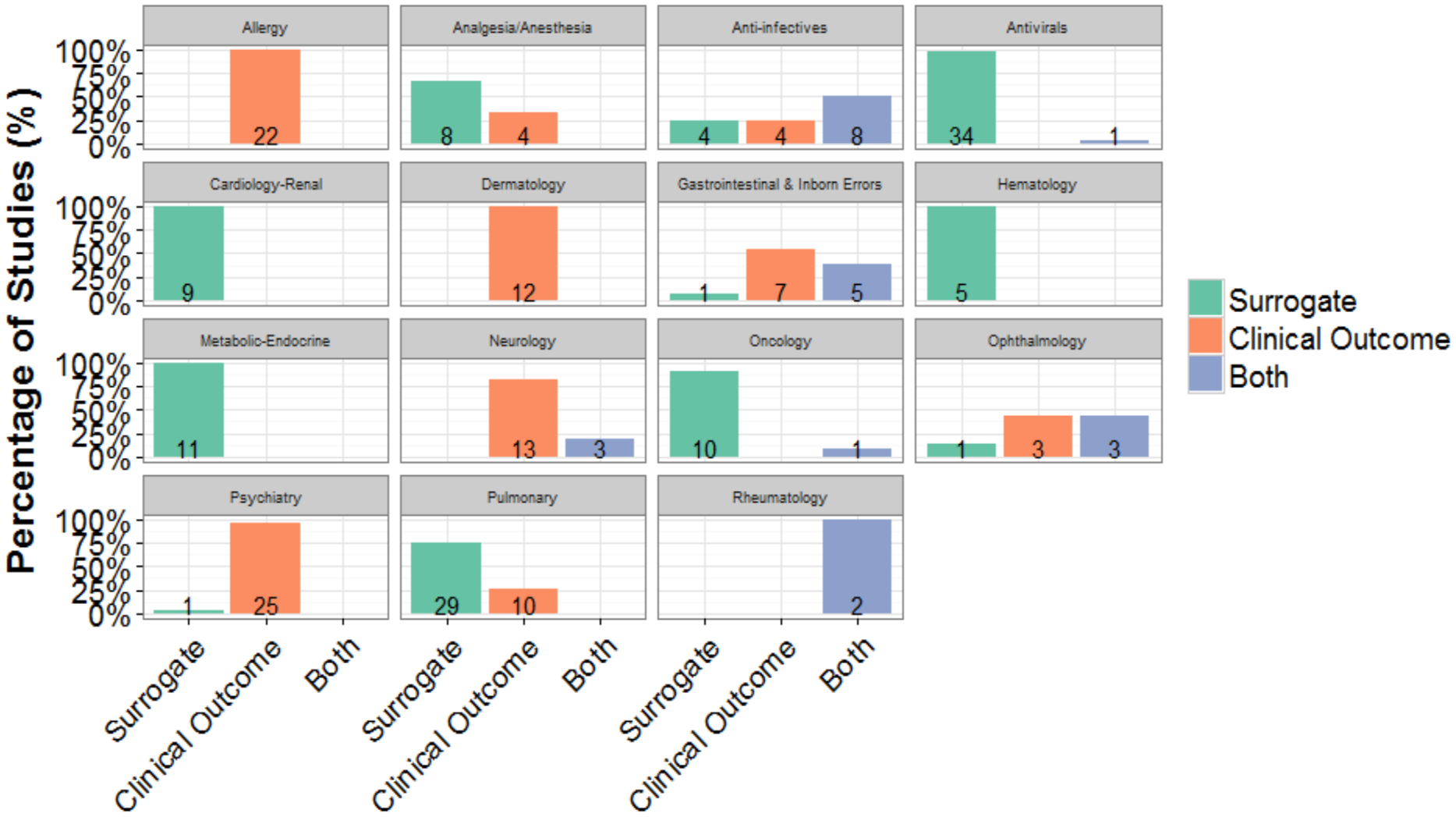
Endpoint Characteristics**

Endpoint Type	FDAAA (%)	FDASIA (%)	Total (%)
Subjective	43.6	41.7	42.8
Objective	46.6	52.4	49.2
Both	9.8	5.8	8.1

Endpoint Type	FDAAA (%)	FDASIA (%)	Total (%)
Clinical Outcome	46.6	36.9	42.4
Surrogate	42.9	54.4	47.9
Both	10.5	8.7	9.7

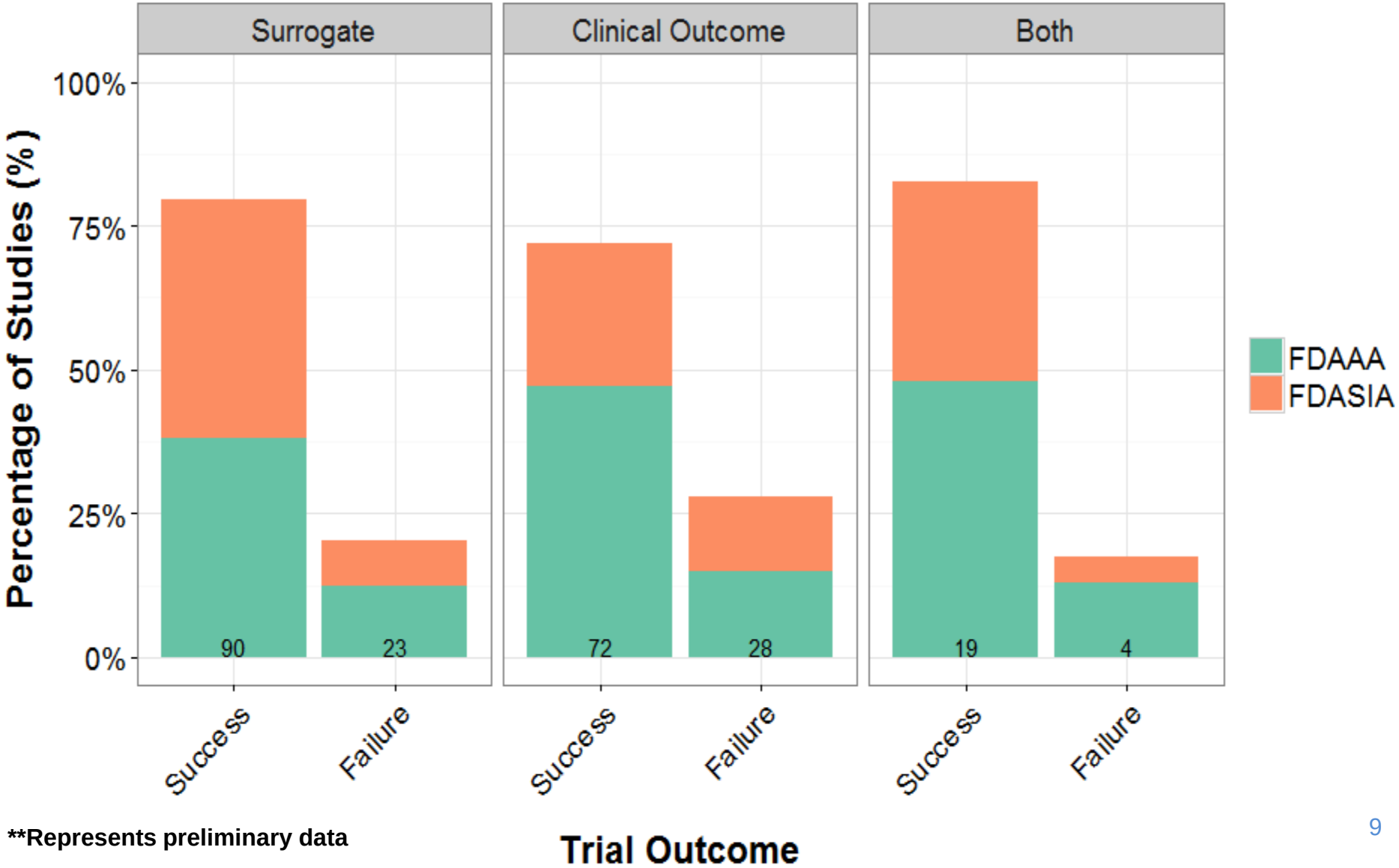
****Represents preliminary data**

Study Endpoint Type by Therapeutic Area**



**Represents preliminary data

Trial Outcome by Endpoint Type**



**Represents preliminary data

Combined Adult & Pediatric Trials**

- 44 drugs were studied in combined adult & pediatric trials
- Most frequent therapeutic areas:
  - Allergy (e.g. allergic rhinitis)
  - Dermatology (e.g. acne)
  - Pulmonary (e.g. asthma)
  - Oncology (e.g. ALL)
- **When the disease in pediatric patients and adults is the same, this is a reasonable approach for master protocols**

*Trials that enrolled patients less than and greater than 18 years of age were considered combined trials

**Represents preliminary data

Trial Outcome for Combined vs. Separate Studies**

**Represents preliminary data

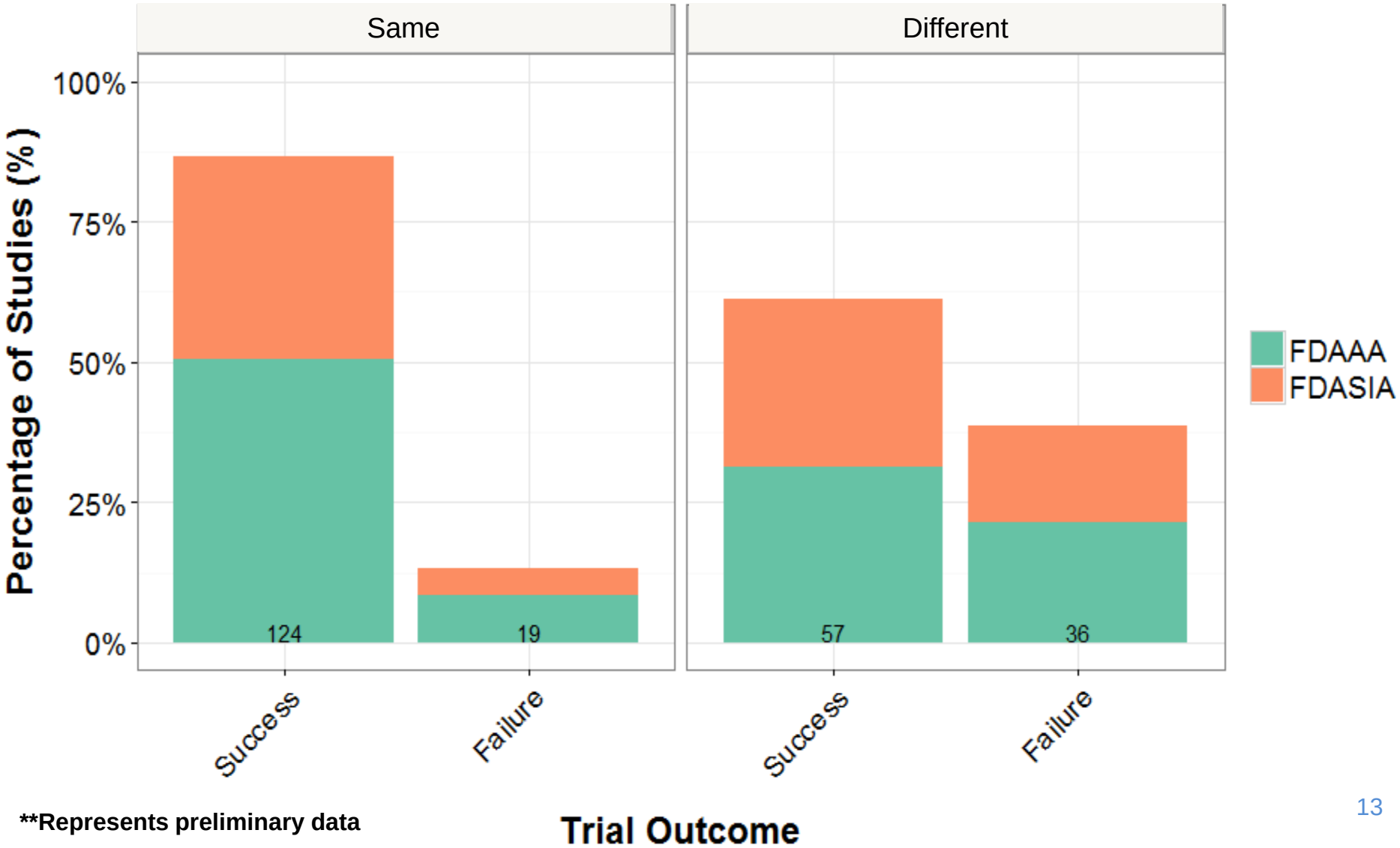
Comparison of Adult and Pediatric Endpoints**

Adult Endpoint	FDAAA (%)	FDASIA (%)	Total (%)
Same as Pediatric	63.2	57.3	60.6
Different than Pediatric	36.8	42.7	39.4

*Endpoints were considered different when the outcome measure was different and/or when the time point of measurement was different

**Represents preliminary data

Trial Outcome by Same Endpoint Used**



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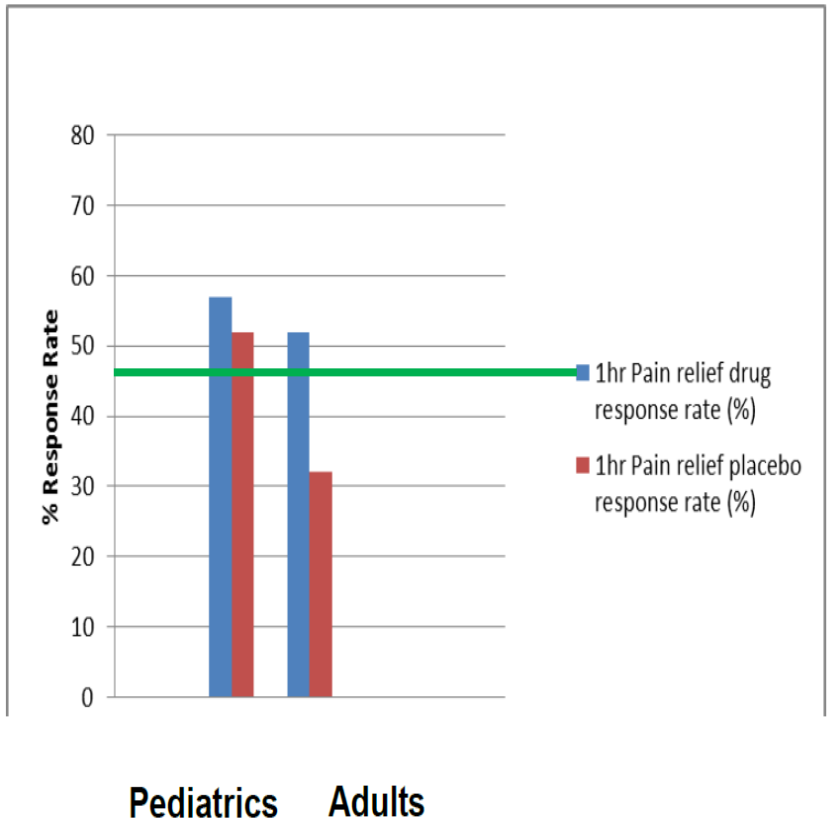
Consistency in Endpoint Selection**

- Total of 66 indications studied across 236 trials
- For 42% (28/66) of the indications, at least 2 or more drugs were studied [median 2.5; range 2-16]
- For 80% (22/28) of the indications, the endpoint and/or time of measurement differed across the various drug trials for that indication
- **Consensus by the sponsors and regulatory agencies on the optimal efficacy endpoint for a given indication is an important step prior to developing a disease-specific master protocol**

**Represents preliminary data

Placebo Use in Pediatric Trials

- There are ethical constraints for the use of placebos in pediatric research
- High placebo responder rates in children have been problematic in previous drug development trials (e.g. MDD, migraine)
- Placebo response in pediatric patients in US may differ from other parts of the world (e.g. Europe)

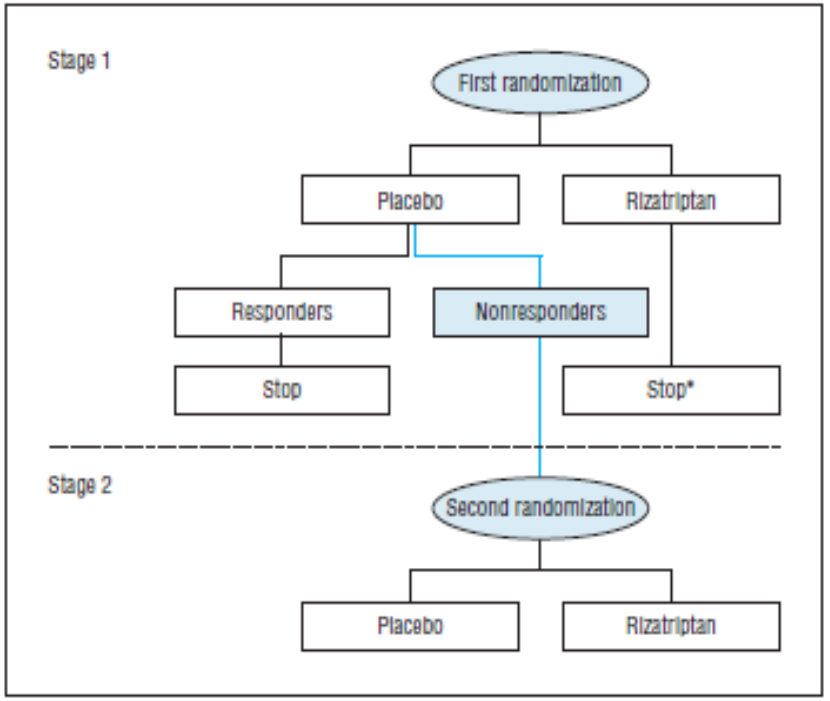


Source: CDER Rounds. Review of Migraine Therapeutics in Adolescents: An Example of Failed Pediatric Trials. HaihaoSun MD, PhD

Placebo Use in Pediatric Trials (cont.)

- Large placebo effects limit the ability to detect effective therapies
- Understanding factors contributing to placebo response is critical
- Strategies for reducing placebo response rates should be considered

Two-Stage Double-Randomization Design



*Sun H, Bastings E, Temeck J, et al. Migraine Therapeutics in Adolescents: A Systematic Analysis and Historic Perspectives of Triptan Trials in Adolescents. *JAMA* Pediatr. 2013;167(3):243-249

Trials Designs Appropriate for Small Patient Populations

- Many trial designs may be amenable to master protocols
- Selection of designs that are feasible and efficient in pediatrics is key (due to small populations, recruitment challenges, etc.)
- Examples of randomized, comparative trial designs with potential for master protocols:
  - Parallel
  - Cross-over
  - Randomized withdrawal
  - Adaptive

Summary - 1

- **Master protocols have potential for use in pediatric product development – but the details are very specific to the disease process**;
  - Certain therapeutic areas remain problematic for pediatric trial success; so master protocols in these areas may be difficult at this time
  - When endpoints measured in adults vs. pediatrics were different, fewer trials were successful
  - Understanding the disease process and selecting appropriate endpoints are a critical part of planning for master protocols

Summary - 2

- Including pediatric patients and adults in a single master protocols may be a reasonable approach when possible
- Strategies for managing the use of placebo in pediatric clinical trials may require further discussion
- Multiple trial designs for small patient populations have the potential to be amenable to the development of master protocols