Pediatric Trial Design & Endpoint Considerations

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Goal

- Review efficacy/response endpoints measured in pediatric clinical trials submitted to the FDA, and describe critical endpoint attributes that may influence trial outcome

Background

- Approximately 25 - 40% of pediatric trials fail to establish safety or efficacy and result in a labeled indication for pediatric use
  - BUT, the situation is improving through an understanding of pediatric study design issues
- Contributing Factors to Trial Failure (Failed Pediatric Drug Development Trials, *Clin Pharmacol Ther* 2015; 98(3):245-251)
  - Dosing (to be addressed in the afternoon session)
  - Differences between adults and pediatrics
  - Trial design
- Trial Design Challenges
  - Feasible designs for small populations
  - Placebo effect
  - Appropriate endpoints (particularly adults vs. pediatrics)

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
  - e.g. differences in the disease; developmentally inappropriate; infeasible sample size
- Attributes of the endpoint may influence trial outcome

Objectives

- Survey primary efficacy endpoints measured in pediatric drug development trials submitted to the FDA
- Characterize endpoints as subjective or objective
- Compare pediatric and adult endpoints
- Relate endpoint attributes to trial and label outcome

Methods

- Surveyed pivotal efficacy and PK/PD pediatric trials submitted under:
  - FDAAA (2007 -2012)
  - FDASIA (2012 – July 2016)
- Extracted data from FDA-authored reviews
- Endpoints were categorized as:
  - subjective vs. objective vs. both
  - same vs. different than the adult endpoint
- Trial outcomes were categorized as:
  - success vs. failure
- Label outcomes were categorized as:
  - approved vs. not approved

Pediatric Efficacy/Response Trials

	FDAAA, N	FDASIA, N	Total, N
Total Trials	133	101	234
Total Unique Drugs	83	55	138

Trial Outcome	FDAAA, N (%)	FDASIA, N (%)	Total, N (%)
Success	99 (75.6)	80 (77.7)	179 (76.5)
Failure	32 (24.4)	23 (22.3)	55 (23.5)

Label Outcome	FDAAA, N (%)	FDASIA, N (%)	Total, N (%)
Approved	109 (83.2)	77 (74.8)	186 (79.5)
Not approved	22 (16.8)	26 (25.2)	48 (20.5)

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

Breakdown of Pediatric Trials

- 52 different indications; 197 distinct endpoints
- Most frequently studied areas: pulmonary (16%), antiviral (14%), allergy (12%)
- Most studied drug class: antivirals (21 different drug products)

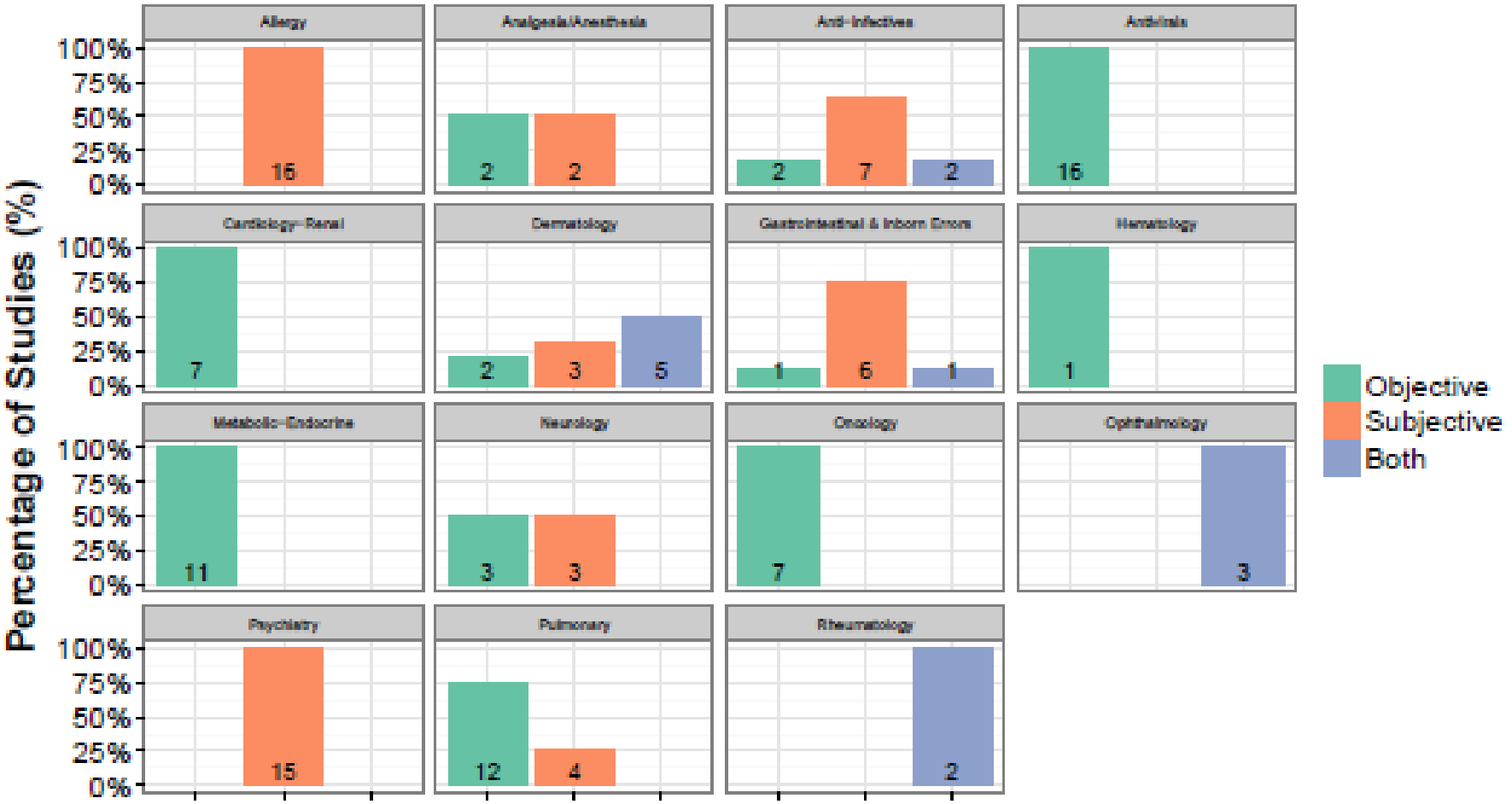
Label Outcome by Therapeutic Area

Endpoint Attributes - 1

Endpoint Type	FDAAA, N (%)	FDASIA, N (%)	Total, N (%)
Objective	62 (47.3)	52 (50.5)	114 (48.7)
Subjective	55 (42.0)	44 (42.7)	99 (42.3)
Both	14 (10.7)	7 (6.8)	21 (9.0)

Endpoint Type	Successful, N (%)	Failed, N (%)	Total, N	P-value
Objective	91 (79.8)	23 (20.2)	114	<0.05
Subjective	68 (68.7.)	31 (31.3)	99	
Both	20 (95.2)	1 (4.8)	21	

Study Endpoint Type by Therapeutic Area

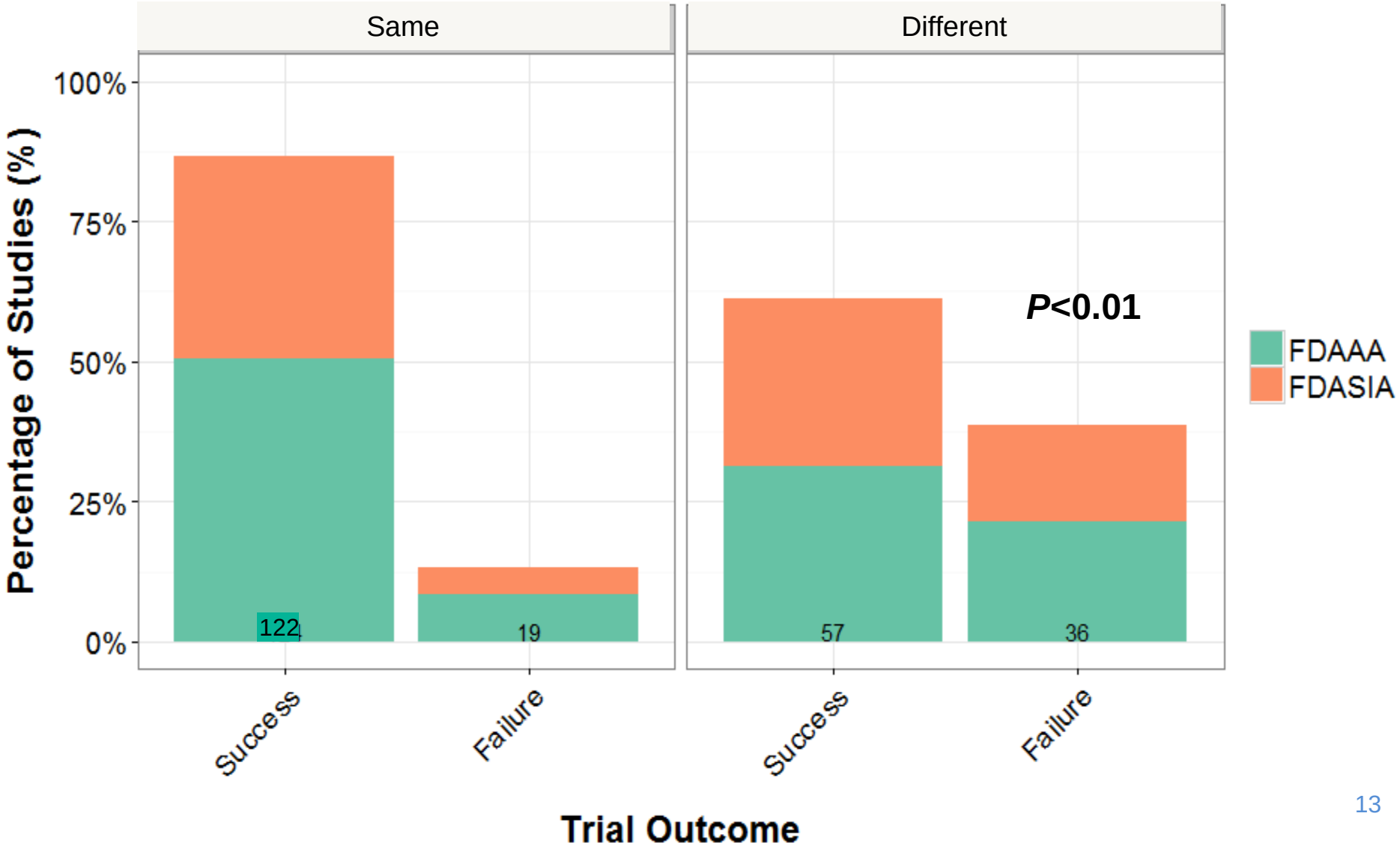


Endpoint Attributes - 2

Endpoint Type	FDAAA, N (%)	FDASIA, N (%)	Total, N (%)	P-value
Pediatric Same as Adults	84 (64.1)	57 (55.3)	141 (60.3)	<0.01
Pediatric Different than Adults	47 (35.9)	46 (44.7)	93 (39.7)	

- Most frequent therapeutic areas where pediatric & adult endpoints were:
  - the same = dermatology, anti-infective, oncology
  - different = antiviral, psychiatry, gastroenterology

Trial Outcome by Same Endpoint Used



Endpoint Attributes - 3

Type of Difference	N	Successful, N (%)	Failure, N (%)	P-value
Endpoint Measure	32	21 (65.6)	11 (34.4)	<0.01
Timing of Measurement	35	28 (80.0)	7 (20.0)	
Both	26	8 (30.8)	18 (69.2)	

- A higher trial failure rate was observed when:
  - both the endpoint itself & the time point of measurement were different
  - as opposed to when only the endpoint itself or only the time point of measurement was different

Examples – Failed Trials Where the Pediatric & Adult Endpoint Were Not the Same

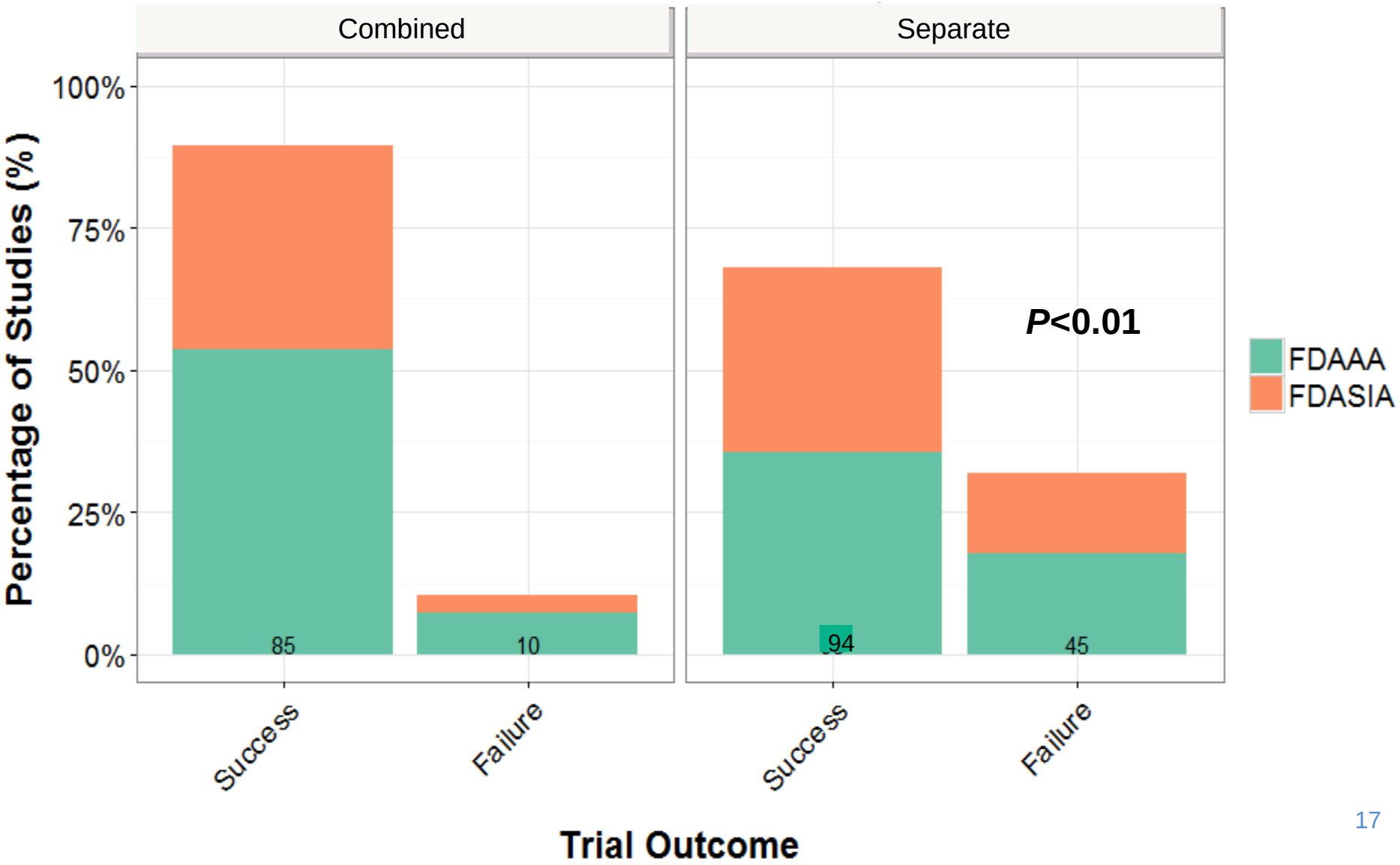
Indication	Ped Age Grp	Ped Endpoint	Time of Measurement	Adult Endpoint	Time of Measurement
PAH	1 - 17 yrs	Percent change in VO2 peak	16 wks	6-minute walk	12 wks
Chronic HBV	2 – 17 yrs	HBV DNA <1000 copies/mL & ALT normalization	48 wks	Histological improvement (biopsy)	48 wks
Bronchospasm	0 - 5 yrs	Daily asthma SS; Ped Asthma Caregiver Assessment	4 wks	FEV1	12 wks
Ppx or Tx of thrombosis (pts w/ HIT)	0 - 16 yrs	aPTT & ACT	2 hrs following every infusion	Death & amputation & new thrombosis	Time to event
Anticoagulation (PTCA or PCI or at risk of HIT)	0 – 16 yrs	ACT	30 days	Death, MI, urgent revascularization, vessel closure	Time to event
PONV	2 – 16 yrs	Complete control (no nausea, vomiting, or rescue meds)	Within 2 hrs following extubation	Complete control (no nausea, vomiting, or rescue meds)	Within 24 hrs after surgery
Ulcerative colitis	5 – 17 yrs	Treatment success defined by PUCAI	6 wks	Treatment success defined by PGA	6 wks

Combined Adult & Pediatric Trials

- 95 (40.6%) trials enrolled both adult & pediatric patients
  - 44 drug products were evaluated in these trials
- Most common therapeutic areas:
  - Allergy (e.g. allergic rhinitis)
  - Dermatology (e.g. acne)
  - Pulmonary (e.g. asthma)
- When the disease in pediatric patients and adults is the same, this is a reasonable approach

*Trials that enrolled patients less than and greater than 17 years of age were considered combined trials

Trial Outcome for Combined vs. Separate Studies



Summary - 1

- Certain therapeutic areas/indications remain problematic for pediatric trial success; investigating the reasons for trial failure is an important step to designing future studies
- **Selection of suitable endpoints for use in pediatric trials is a critical aspect of trial design**
  - When endpoints measured in adults vs. pediatrics were different, fewer trials were successful
    - Understanding the disease process and the endpoint being measured is essential
  - Including both adults and pediatric patients in a single study may be a reasonable approach when possible
  - Using a composite endpoint that includes both subjective and objective components was favorable in this assessment, but must be carefully considered
- **Endpoint selection is just one aspect of trial design; other factors must be considered**

Summary - 2

- Considerable progress has been made since the evaluation of the BPCA studies, when the pediatric trial failure rate was >40%;
  - A better understanding of trial design, endpoints and dosing will allow us to successfully plan for pediatric drug development studies in the future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