Pediatric Clinical Trials

Innovative Trial Designs and Leveraging Existing Data

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The Pediatric Drug Development: Dynamic Physiology & Challenges

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Distinct physiological sub-populations

Increasingly distinct from adult disease and/or ”reference” population
Less historic precedent: e.g., endpoint selection, effect size, variability
More inter-patient and intra-patient variability
Increasing operational challenges: e.g., rare disease, parental involvement

Neonates	Infants & Toddlers	Preschool	School-Age	Adolescents
Birth - 27 days (corrected GA)	28 days - 23 months	2 - 5 years	6 - 11 years	12 - 17 years

Clinical Trial Design Considerations: Not just little adults

Data Generation: the what

Patient Population/Target Indication

- Does the disease exist across all age groups?
- Is the pathophysiology the same across age groups?
- Are there age-specific subtypes?
- Do different diagnostic criteria apply?
- Is the disease course (onset, chronicity, progression, outcome) similar?

Response to Treatment/Endpoint

- Is the exposure-response relationship similar between and target populations?
- Are endpoints objective or subjective?
- Are endpoints validated and responses measurable in the target age group?

Data Generation: the how

- The “participant” is the family unit: caregivers, parents, and the patient
- Is the design feasible?
- How does the prevalence/incidence impact the design?
- Is the design safe for the given participant and family unit? (e.g., degree of monitoring, access to trial staff)?
- Are enrollment methods appropriate for the target patient?

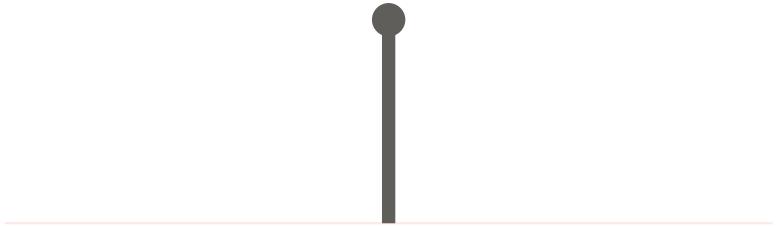
ICH E11A (2024): Extrapolation of safety and efficacy is now a CONTINUUM, not a categorical full/partial/no. Degree of similarity across 1) disease similarity, 2) drug pharmacology, and 3) expected response to treatment must all be considered in trial design

Power & Probability: Tools for Clinical Trial Design and Efficiency

Traditional power

Assumes effect is known and fixed

"If the true effect is exactly 2.0 mmHg, we will detect it 80% of the time with N = 300"

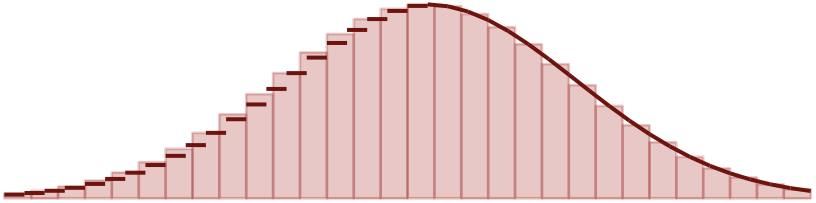


Conditions on a single assumed effect size

Bayesian Probability of Statistical Success

Integrates over uncertain effects

"Given our current belief about the distribution of plausible effects, the trial will succeed X% of the time with N=300"

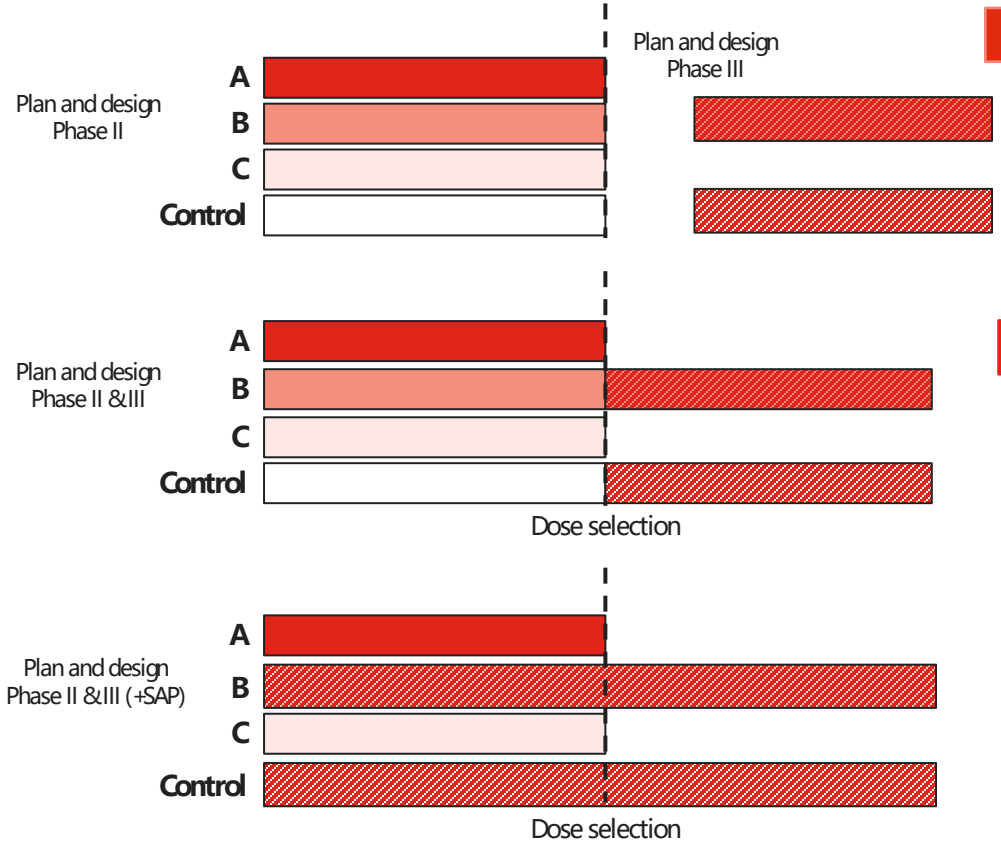


Uncertainty is represented as probability, prior knowledge is formally acknowledged, and both are updated by data

Key insight: **Power = 80% but PrSS = 55% → you are powering on an optimistic effect size**

The gap between power and PrSS reflects uncertainty in the assumed effect size. A well-powered trial can still have low PrSS if the assumed effect is over-estimated.

Adaptive Trial Designs



STANDARD TWO-PHASE TRIAL

Included in confirmatory analysis

Not included in confirmatory analysis

OPERATIONALLY SEAMLESS

Main efficiency: maintains flexibility between phases, administrative time saving, operational efficiencies (drug supply), regulatory time saving

Best fit: neonates-infants, PK and/or dose ranging initial phase

INFERENTIALLY SEAMLESS (Higher Efficiency)

Main efficiency: data from BOTH phases combined in final analysis, which reduces overall sample size

Best fit: rare disease; dose selection/confirmation combined; subgroup enrichment

Control Arms: Pure, Hybrid, and Synthetic Controls

Pure External Control	Hybrid Control Arm	Synthetic Control Arm
No concurrent control arm. Entire comparator derived from historical/real-historical/real-world data (natural history, registries, prior trials, published cohorts).	Concurrent randomized control arm AUGMENTED with external control data. Reduces required concurrent controls while preserving a degree of randomization.	External controls derived, using propensity score methods or causal inference frameworks, to emulate a control arm in the context of the new trial
Best fit:	**Best fit:**	**Best fit:**
Neonates, ultra-rare disease in any age group; conditions where external data is is defensible for safety and feasibility	Infants/Preschool in rare disease; when enrollment is slow but some randomization randomization is required by regulators regulators	Indications and populations where trial data are available and confounding can be controlled

Single Arm Studies in Pediatrics

Critical Pathways and Considerations	1. Scientific Sufficiency: control arm does not meaningfully add to what can be inferred –OR- 2. Ethical/Practical Necessity: feasibility, ethical considerations

Regulatory acceptance is strongest for progressive rare disease, objective endpoints, large expected effect size, well-characterized natural history with stable disease trajectory, no available alternative comparator.

Most accepted single arm trials include an external reference
- Natural history cohort (majority), baseline control, or published literature

Do not favor: subjective endpoint, high placebo response or unstable disease trajectory, available active comparator, poorly documented natural history

Early engagement with regulatory agencies
- Pre-specified efficacy decision criteria justified and aligned

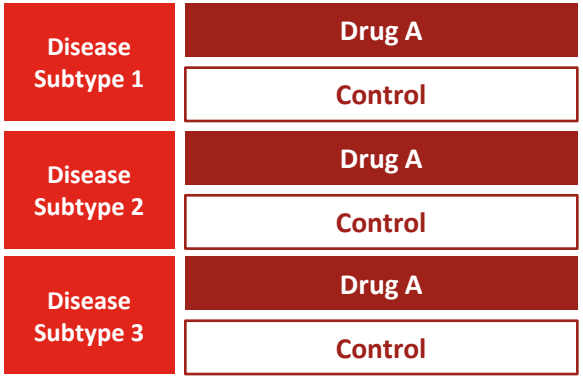
Master Protocols
Platform, Basket, and Umbrella Trials in Pediatrics

Basket Trial

How it works:

Single drug tested across **multiple diseases** or disease subtypes simultaneously.

Most relevant where drug targets a pathway present across multiple indications.

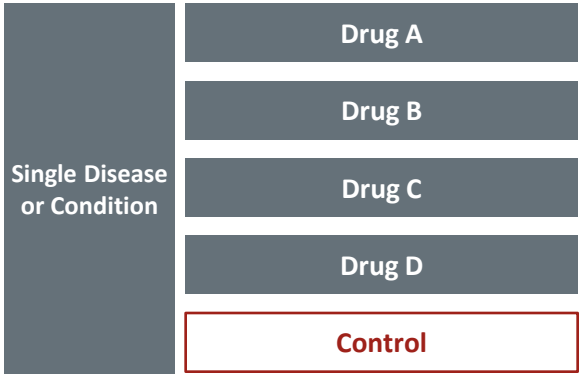


Umbrella Trial

How it works:

Multiple drugs tested for a **single disease**, stratified by biomarker or molecular profile.

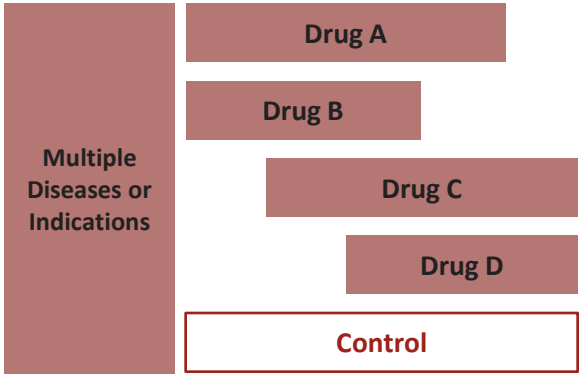
Each arm has its own experimental drug but may have shared eligibility and control arm.



Platform Trial

How it works:

Multiple treatments evaluated across **one or multiple diseases or indications** within a single protocol infrastructure.



The Patient Unit-Centric Considerations

Burden minimization as a design principle

Visits/feasibility
- Location: home visits, telehealth, direct-to-patient drug delivery, local labs/providers
- Frequency: weekend options, larger visit window flexibility, need to have vs nice to have frequency
- Family support: sibling childcare, travel reimbursement
- Electronic consent: multiple caregivers

Assessments
- Non-invasive endpoints: digital technologies, wearables, electronic diary
- PRO by proxy: caregiver/parent
- Developmental milestones
- Remote measurements

Patient voice incorporation early and often

Patients, caregivers, physician input
- Inform design early and throughout development
- Disease-specific/patient-specific insights
- Patient-centric goals and endpoints (e.g., quality of life)

Patient Advocacy/Research Networks
- Spread awareness of trials and aide in recruitment
- Registry connections
- Regulatory engagement

Thank You

Questions & Discussion