Alternative approaches & Trial Considerations

Academic Perspective

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Disclosures

Consultancies/honoraria (<$10,000): AbbVie, AlfaSigma, Amgen, Astra Zeneca Biogen, Boehringer, Bristol-Myers Squibb, Celgene, Eli Lilly, EMD Serono, GlaxoSmithKline, F. Hoffmann-La Roche, Johnson & Johnson, Merck, Novartis, Pfizer and UCB. The Cincinnati Children's Hospital, where HBR works as a full-time public employee, has received contributions (>$10,000 each) from the following industries in the past 3 years: Bristol-Myers Squibb, F. Hoffmann-La Roche, Janssen, Novartis, and Pfizer. This funding has been reinvested for the research activities of the hospital in a fully independent manner, without any commitment to third parties.

Overview

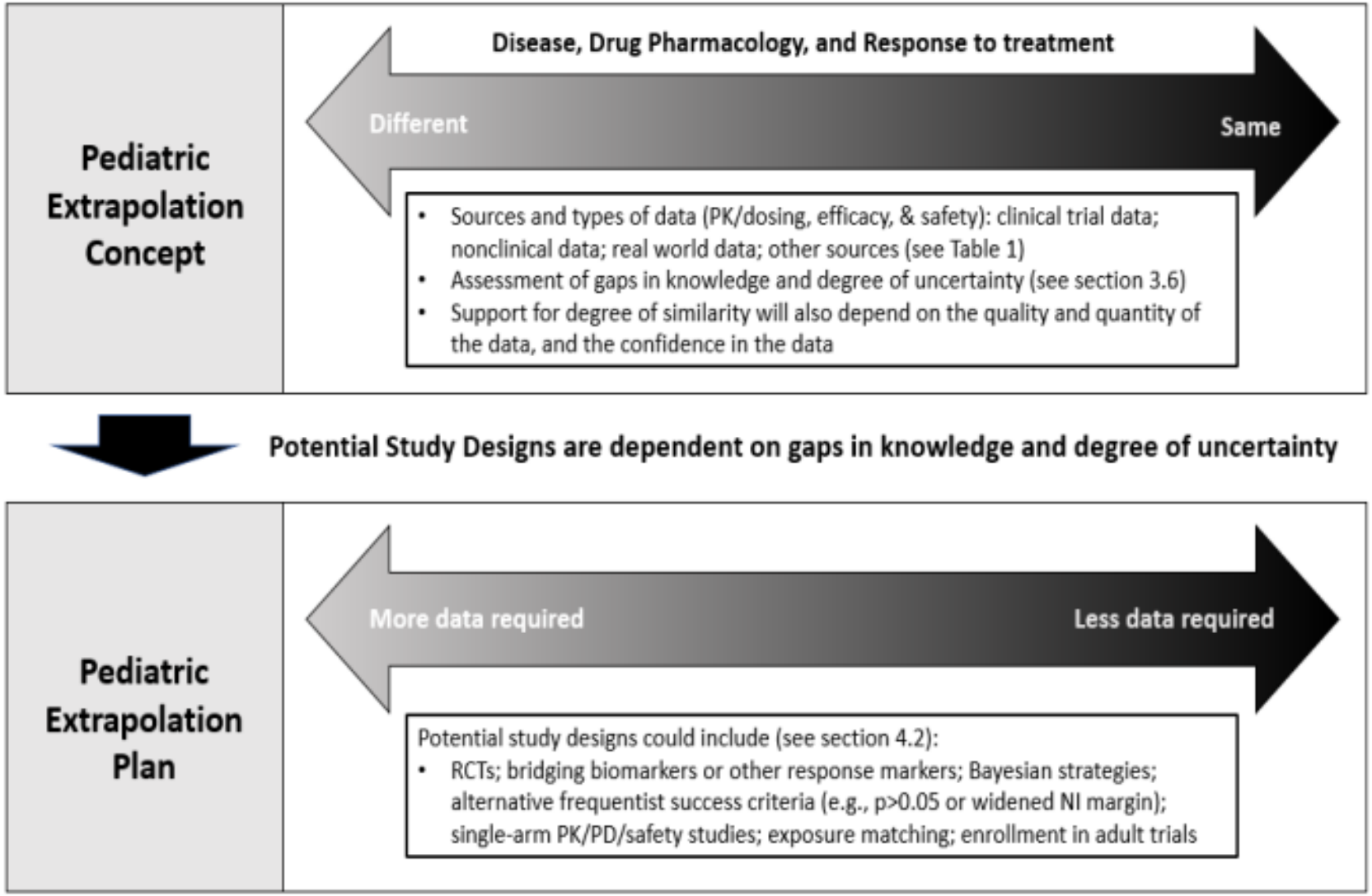
- Regulatory Focus
  - Designs
  - Timing
  - Waiver & Deferrals
- Industry Focus
  - Eligibility criteria (washout, concurrent and prior medications)
  - Post study access

Children vs Adults

- Maturation of organ system
- Impact of growth & development
- Pediatric preparation of medication
- Same classification criteria
- Same response measures
- Same disease activity/ damage
- Same treatment guidelines

Pediatric Extrapolation

E11A Pediatric Extrapolation Guidance for Industry
2024; Drug approval using data from adults to fill important pediatric knowledge gap



MOA that might impact growth and development

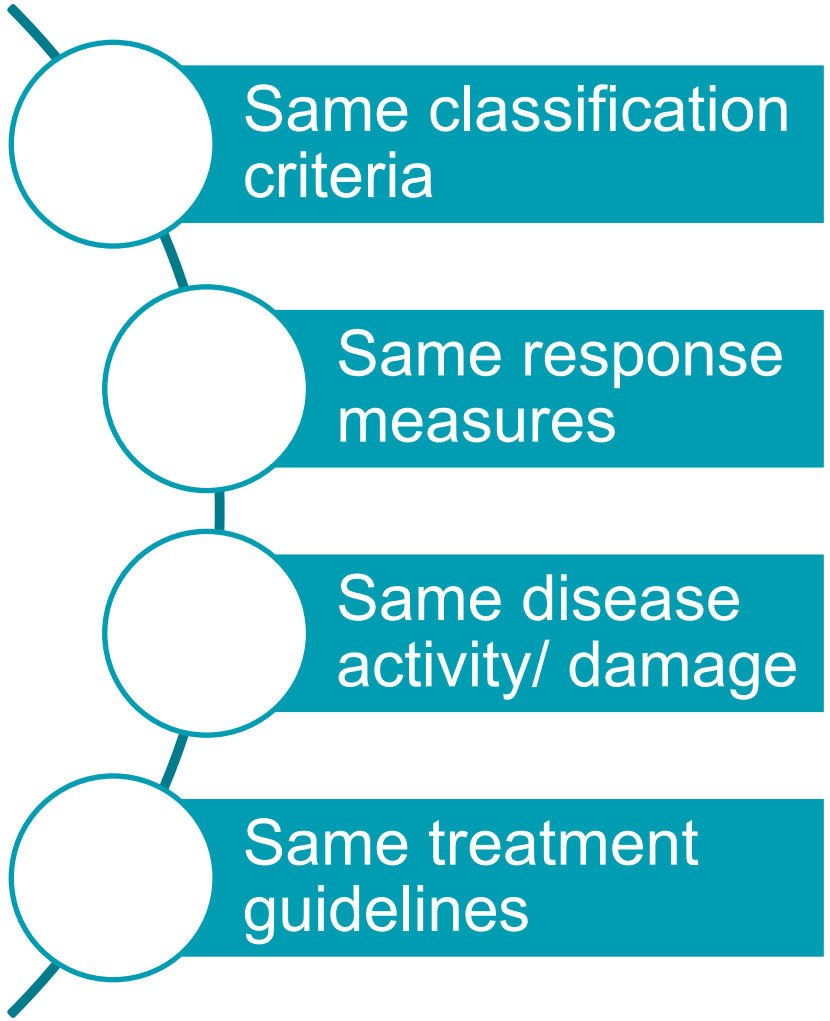
"E11A Pediatric Extrapolation

How do we expect medications to be different when a patient turns 18 years ?

26th Amendment to the U.S. Constitution – 7/5/1971

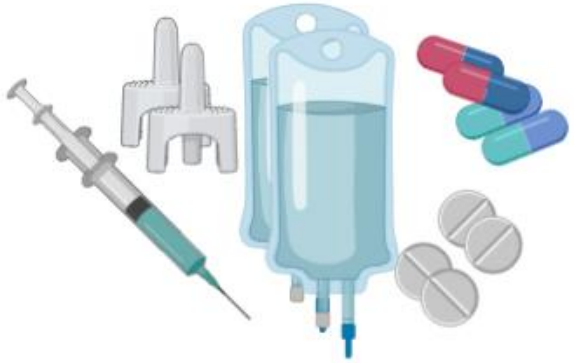
Open label PK/PD Study

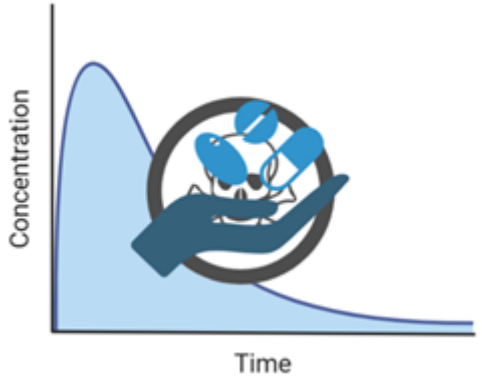
- Placebo/SOC arm only, if needed for medications for which there are scientific reasons
  - e.g. MOA of influence growth, development, fertility



Circumvent Late Start of cSLE Studies

- **Avoid deferrals of pediatric studies until Phase 3 program in adults is (almost) completed**
  - Potential exception: safety concerns based on MOA of medication
  - Especially for medication receiving Breakthrough Designation for adult SLE
- **Seemingly late alignment of FDA and EMA opinions contributes to delays**
  - Early agreement on PSP would be helpful
  - Avoid large number of PIP modifications
- **Early development of pediatric formulation**





Timely Steps to Identify Suitable Medication Dosage for Smaller Patients

- **Sub-analyses of adult SLE trials**
  - Medication response in adults with childhood-onset SLE
  - Medication response in adults with multiorgan involvement (as is common with cSLE)
  - Medication response by weight, body surface area, age (in adults)
- **PK/PD/initial safety in adolescents during Phase 2-3 trials in adult SLE**
  - Adolescents in **extra OL cohort** of adult trials at pediatric centers
- **Avoid staggered enrollment and/or interruption of cSLE trial**
  - Unless there is specific safety concern based on MOA of medication

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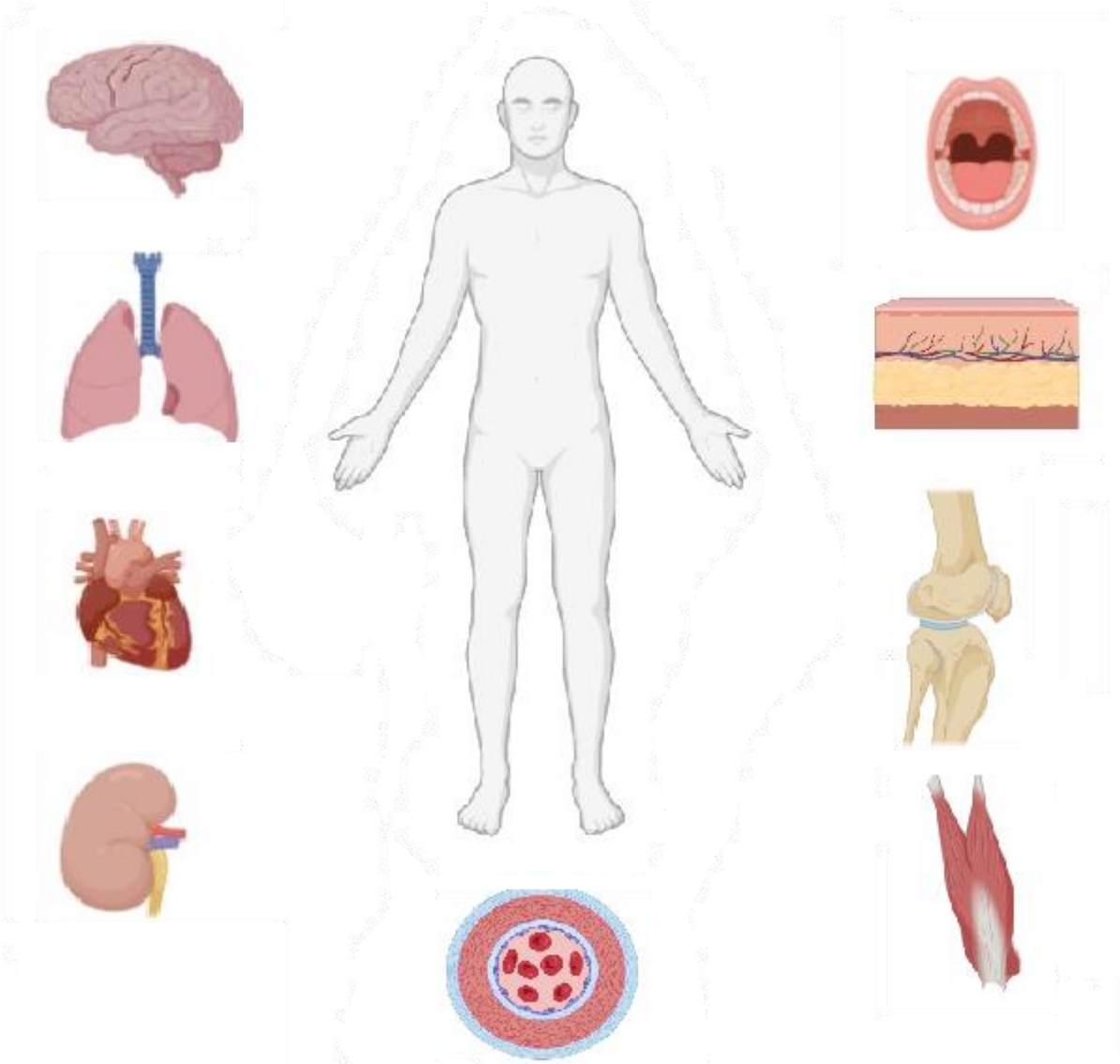
Avoid Organs-specific Sub-studies



- Physiologic function of organs in children 5+ years is generally comparable to that of adults
- Oversampling for certain organ involvement if deemed important based on MOA

Multiorgan disease is common
- 37% of cSLE patients have LN
- 25% of LN patients have NPSLE

Eligibility Criteria from Adult Studies Need Careful Review prior to Adoption in cSLE Trials

- **Prior medication exposure (beyond failure to respond to medication with same MOA) should not be restricted**
- **Rationale for prohibited concurrent drugs should be based on potential drug-drug interactions**
  - e.g. MTX but not leflunomide allowed
- **Washout periods should have scientific rationale / safety concerns**
  - “Spill-over” effects in subanalyses
- **No required minimum disease duration**

Randomized Controlled Withdrawal Trials

Pros

- Active drug for all during time of active disease at baseline
- Patients with flare|non-response are discontinued from the Part 1
- Randomization only of responders
- Minor to moderate flare during Part 2 triggers re-start of active drug
- Placebo (or active comparator) exposure – less time off drug

Cons

- No direct measure of efficacy
- Extrapolation from adult data from DB parallel design is less straight forward
- Poorly suited for drug with long HL
- Flare - clinical vs serological only

Open-label “wash-in” Part 1	Blinded Efficacy in Part 2

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Mild - Moderate Flares Rarely Result in Damage

Association of HDAS with longitudinal SLE outcomes				
		Descriptive statistics by HDAS Number (column %)		Association of ever experiencing HDAS with longitudinal SLE outcome* OR (95% CI; p value)
Longitudinal parameter	**No**	**HDAS (n=161)**	**HDAS (n=125)**	
AMS in highest quartile (AMS ≥4.3)		9 (5.6)	59 (47.2)	11.7 (5.1 to 26.6; <0.001)†
SFI flare occurrence				
No of mild/moderate flares in highest quartile (≥7)		9 (5.6)	60 (48.0)	17.3 (7.4 to 40.5; <0.001)
No of severe flares in highest quartile (≥3)		6 (3.7)	50 (40.0)	14.9 (6.0 to 36.9; <0.001)
SDI damage accrual				
Accrued damage during observation period		45 (28.0)	66 (52.8)	2.3 (1.3 to 3.9; 0.003)

The association between HDAS (but not flares !) and overall damage accrual remained significant after adjusting for renal disease activity during the observation period

Kandane-Rathnayake R, Lupus Science & Medicine 2025; Koehlmeyer R LSM 2020

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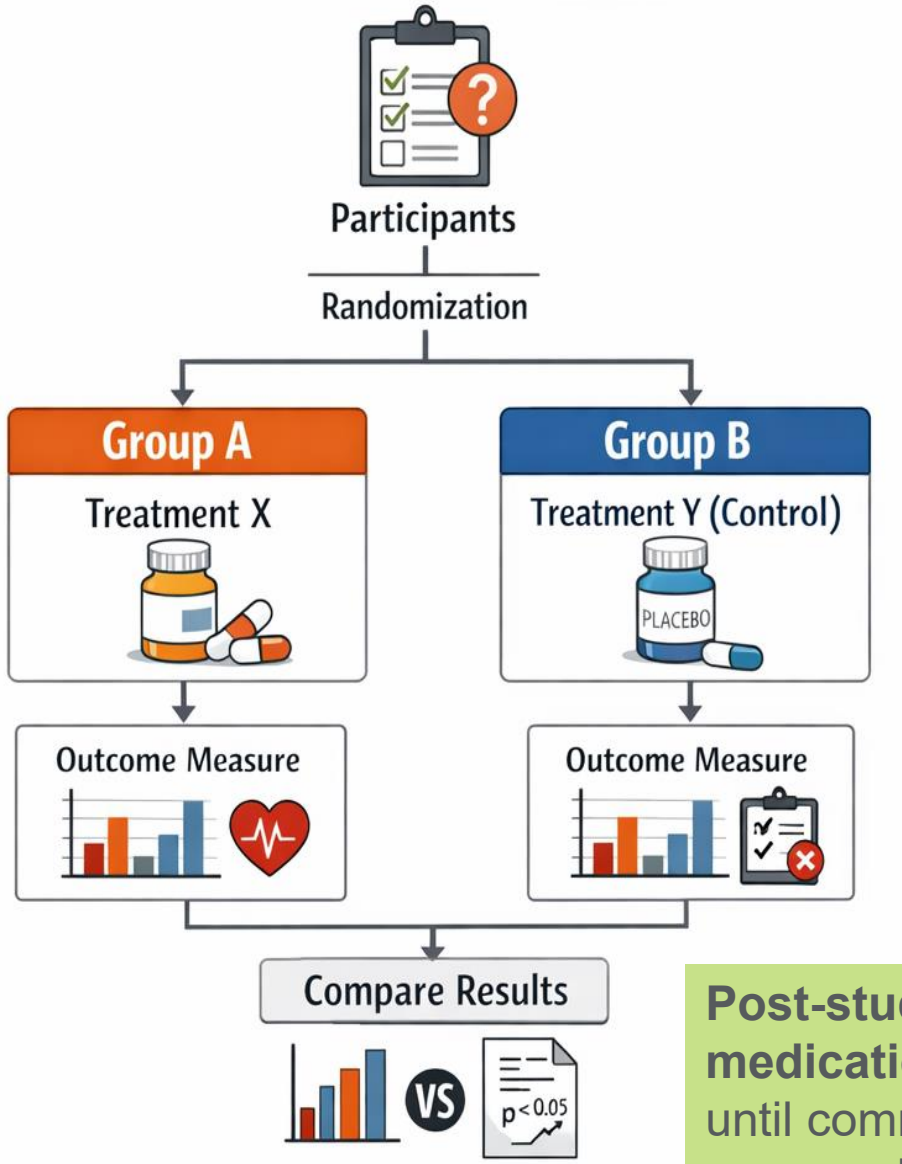
Randomized Parallel Design Study

Unequal randomization can increase sample size but unlikely influences family interest in the study



Early escape arm for cSLE flare or lack of improvement

-continue in long-term extension (LTE) study to get OL effectiveness / safety data

Limit the burden of study participation

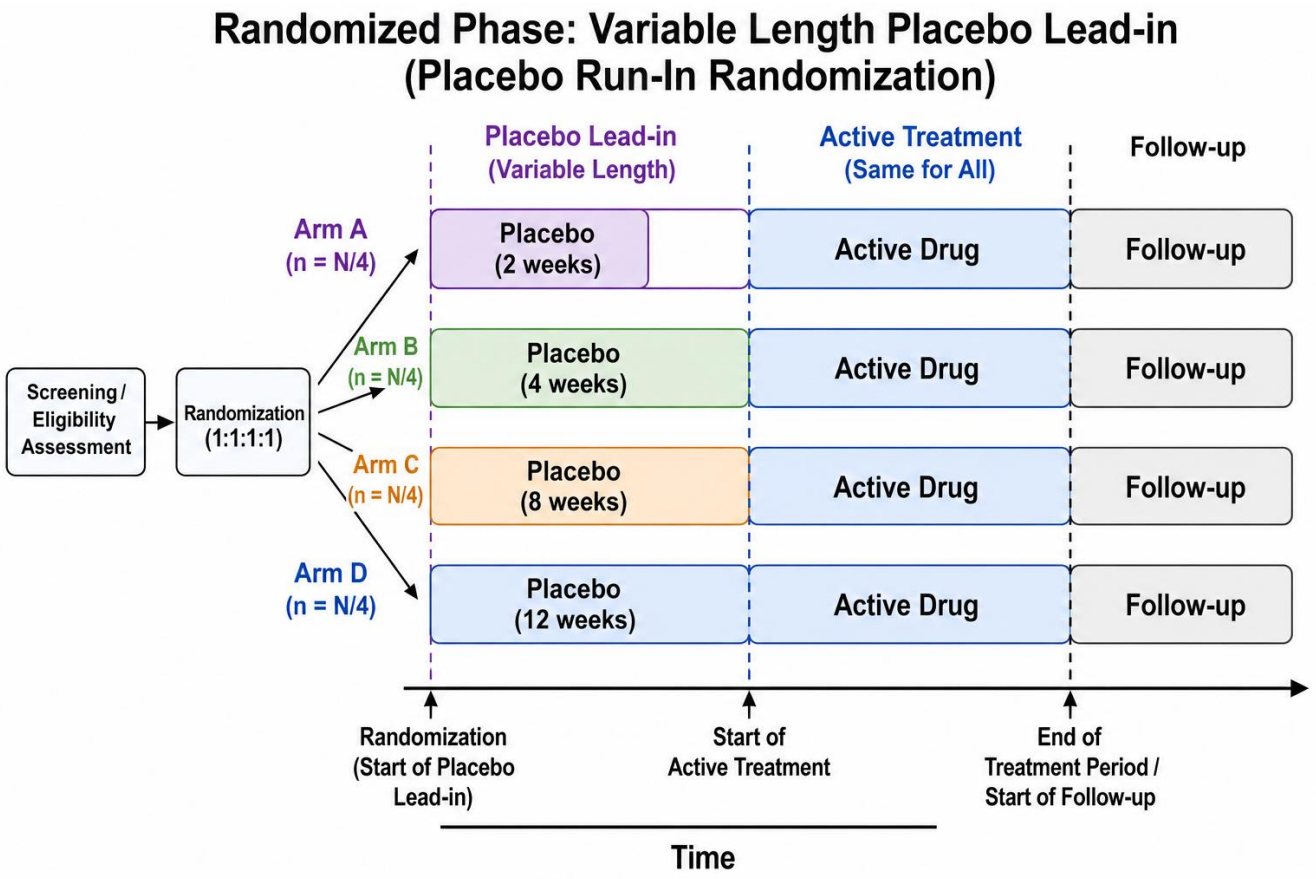
Length/timing of visits, CV screening, number of PRO, central labs, financial, different portals/platforms/devices by various vendors & do not change them during the study

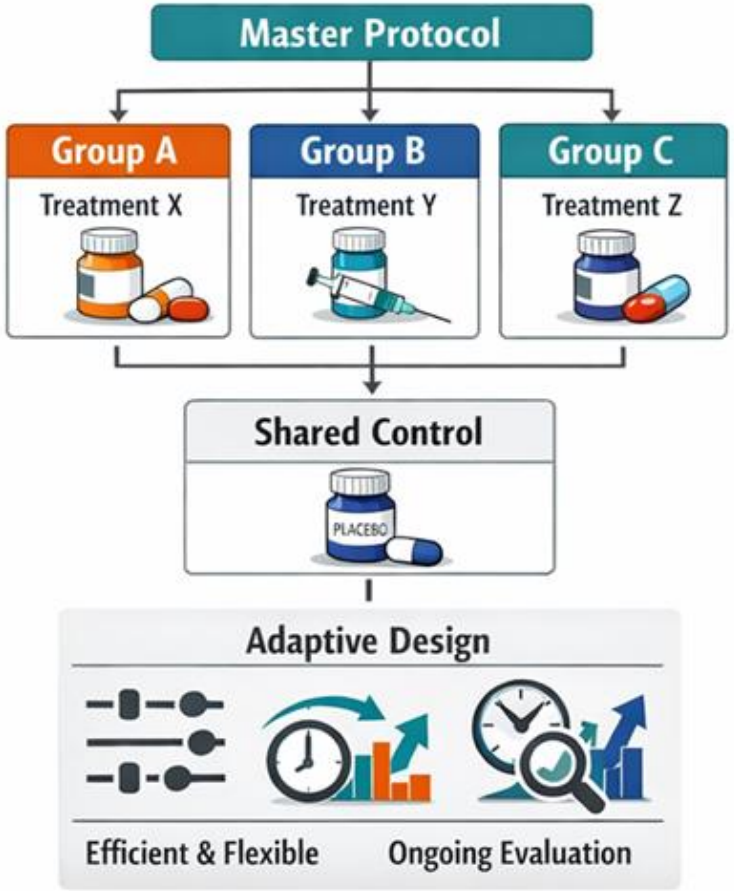
Post-study access (LTE) to study medication considered effective in patients until commercially available drug can be accessed – **NO INDIVIDUAL INDs !**

Other designs

~~N-of-1 studies~~
~~Cross-over studies~~

Platform trial
Phase-in trials





Take Home Points

1. Limit deferrals of pediatric studies start of enrollment while adult phase 3 program is still ongoing
2. Omit placebo exposure in children, unless scientifically justified based on MOA of medication
3. Washout periods and prohibited prior | concurrent medications must have scientific rationale based on safety concerns
4. Limit the burden of study participation (families, sites)
   - Ensure easy post-study access to study medication for all participants who cannot access medication deemed helpful at affordable cost