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Design of PK/PD Studies

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Background

Pediatric studies in infectious diseases

Main area of experience: TB, HIV, malaria and other parasites

Characteristics: High pediatric disease burden; Combination therapy; Comorbidities; Often in low-resource environment; Often poorly understood exposure-efficacy/safety in adults

New combinations (TB-HIV)
Different levels of drug resistance
Bridging to new populations (Asian, African, South America)
New target exposures adults (rifampicin)
New treatment schedules (dose, frequency)
New indications (prophylaxis)
New formulations (fixed dose combinations)
New drugs (bedaquiline, delamanid)

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This presentation

- Illustrating pediatric trial design components of a new agent
  - Trial focusing on PK information to achieve exposure similarity with adults and generation a safety data base
  - Model-informed design for model-based analysis
  - Sequential de-escalation of age-cohorts
  - Basic case with options & extensions

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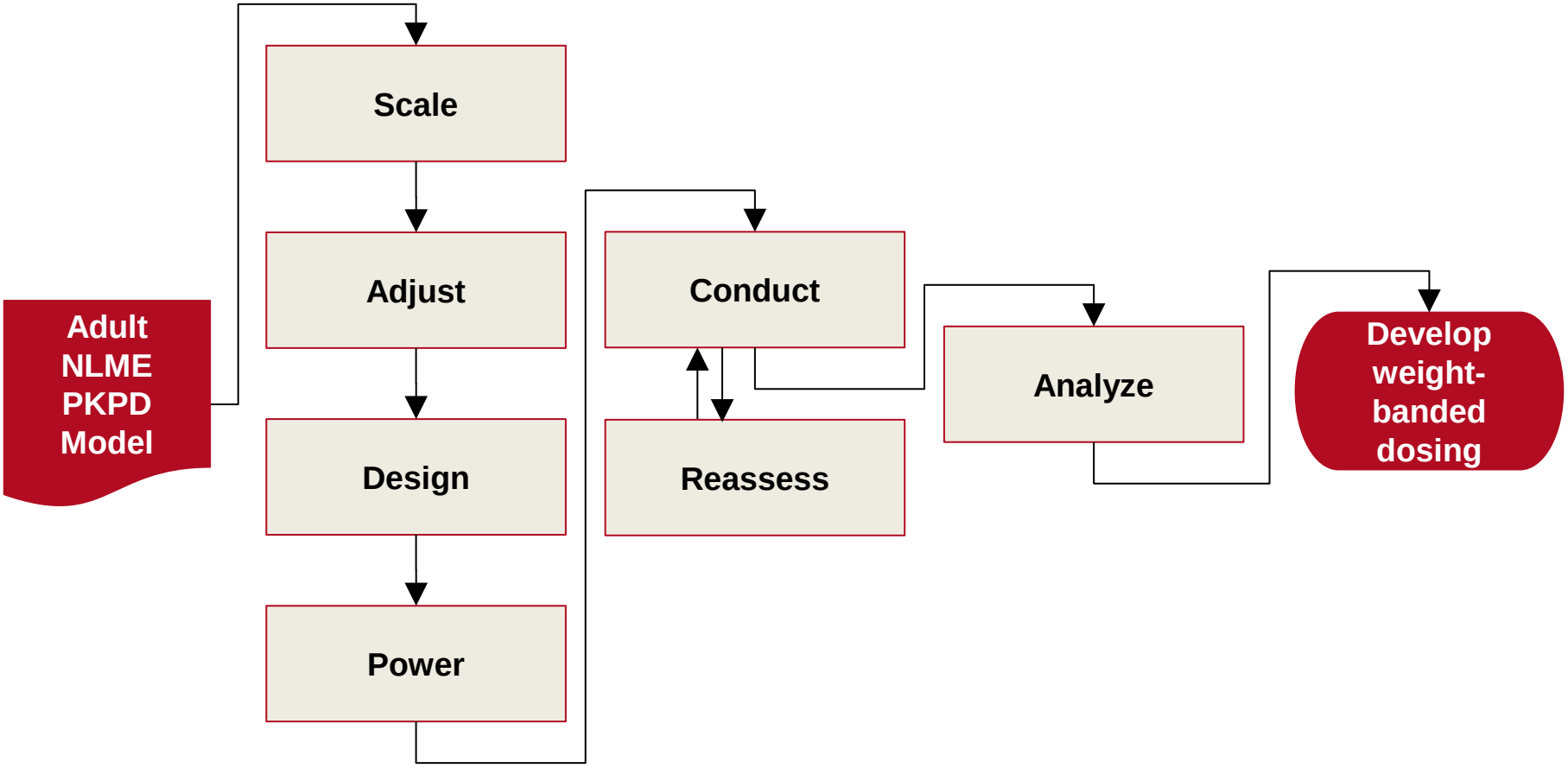
Workflow

for pediatric studies



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Workflow

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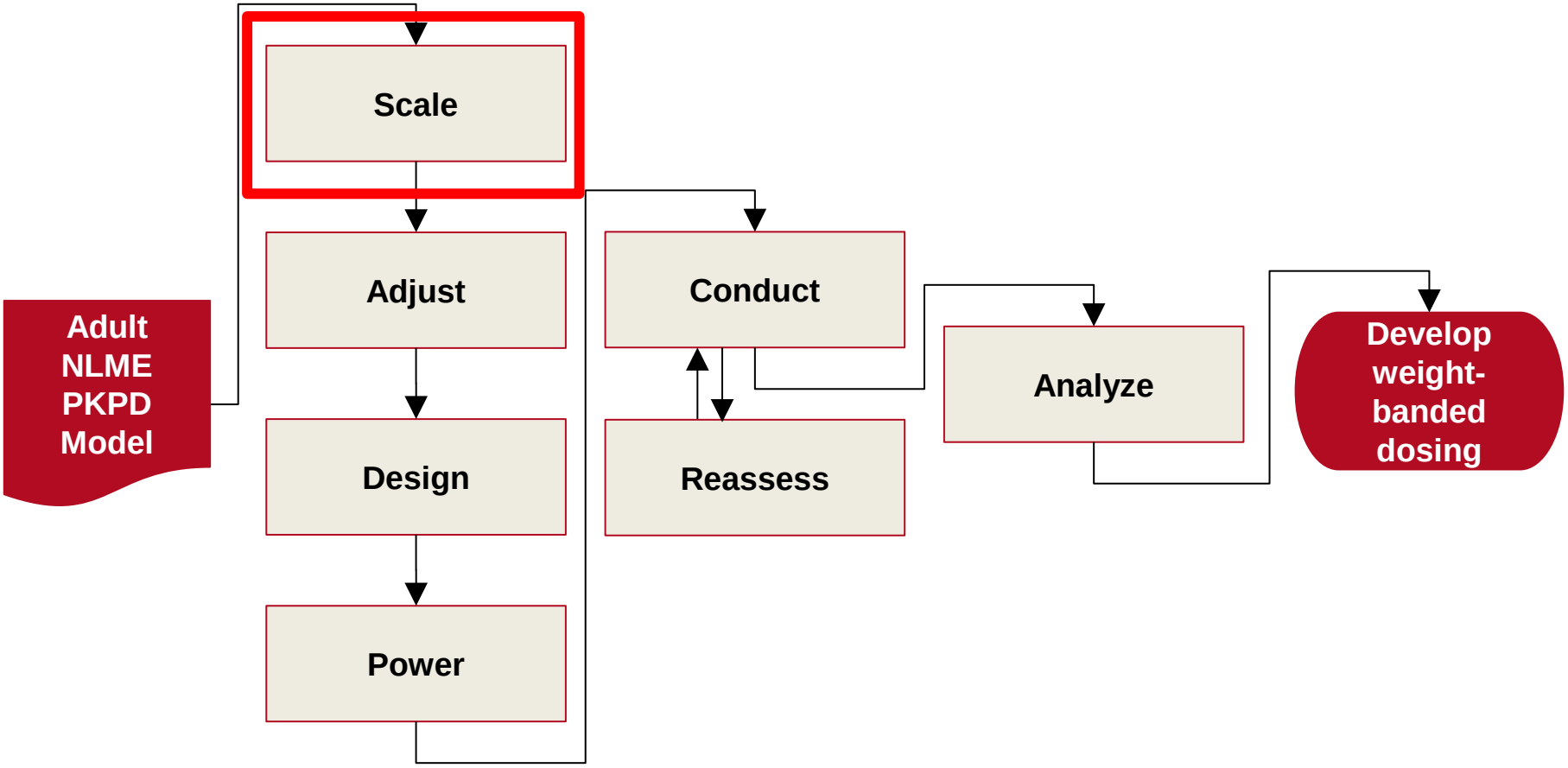

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Scale

PKPD model from adults to children

Steps in basic PK scaling:

1. Determine size model based on allometry
2. Use maturation function based on known route of elimination if age-range includes <2 years
3. Add formulation effects and organ function model if needed in study population

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Scale

PKPD model from adults to children

- Pharmacokinetics: allometry & maturation functions [1,2]

$$V_{typ} = V_{std} \cdot \frac{BW}{70}$$

$$CL_{typ} = CL_{std} \cdot \left(\frac{BW}{70} \right)^{0.75} \cdot MF \cdot OF$$

BW: body weight
MF: maturation function
OF: organ function

- MF: empirical function to describe age-related increase apart from size

$$MF = \frac{PCA^{s}}{PCA_{50}^{s} + PCA^{s}}$$

PCA: Postconceptual age
PCA_{50}: PCA with 50% maturity
s: Hill coefficient

Renally cleared: Rhodin et al. [3]

Metabolized: Johnson et al. [4]

[1] Tod et al. “Facilitation of Drug Evaluation in Children by Population Methods and Modelling.” J Pharm Med 2008;22
[2] Anderson & Holford. "Mechanism-Based Concepts of Size and Maturity in Pharmacokinetics." Annu. Rev. Pharmacol. Toxicol. 2008. 48:303–32
[3] Rhodin et al. "Human renal function maturation: a quantitative description using weight and postmenstrual age." Pediatr Nephrol (2009) 24:67–76
[4] Johnson et al. Prediction of the clearance of eleven drugs and associated variability in neonates, infants and children. Clin Pharmacokinet 45(9):931-956 (2006)

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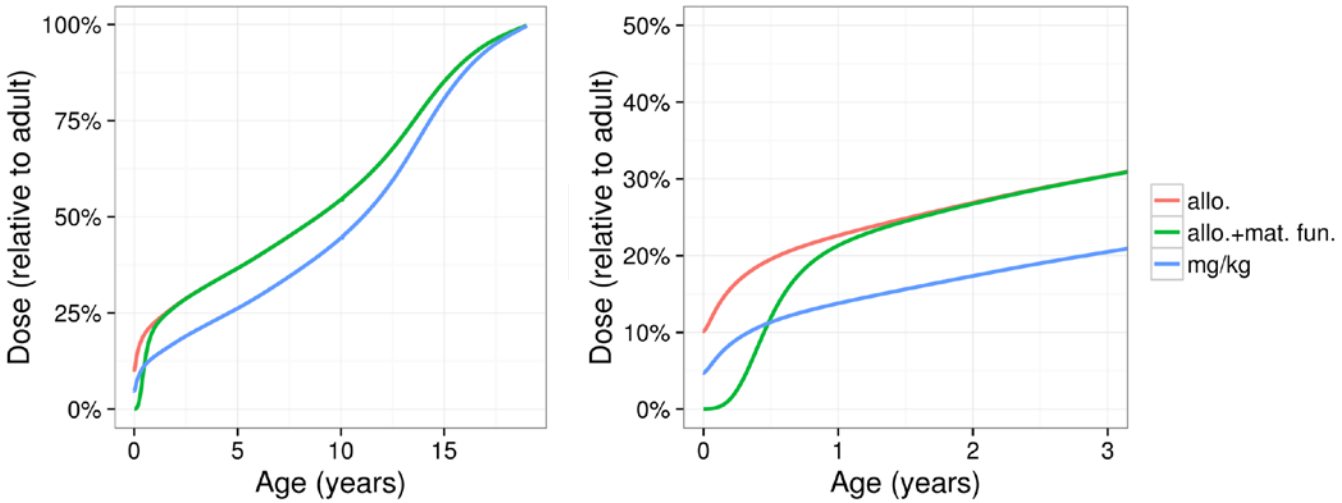
Scale

PKPD model from adults to children

Example: Comparison of scaling approaches for vancomycin (main elimination by glomerular filtration)[1,2]



[1] *Parameter value from*:

Anderson et al. “Vancomycin pharmacokinetics in preterm neonates and the prediction of adult clearance.” Br J Clin Pharmacol 2007; 63 (1): 75-84

[2] *Growth data from*:

WHO Multicentre Growth Reference Study Group. "WHO Child Growth Standards based on length/height, weight and age". Acta Paediatr, Suppl. 2006, 450, 76-85.

de Onis M et al. "Development of a WHO growth reference for school-aged children and adolescents" Bull WHO, 2007;85:660-7.

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Scale

PKPD model from adults to children

- Other PK aspects:
  - Absorption (pH, motility, …)
  - Binding proteins
  - Body composition
- PBPK models
  - Integrating multiple developmental/size/disease differences
- Disease
  - Same infecting organisms
  - Differences in disease manifestation
- PD aspects:
  - Exposure-response often missing in adults but assumed similar

[1] Kearns et al. "Developmental Pharmacology — Drug Disposition, Action, and Therapy in Infants and Children." N Engl J Med. 2003 Sep 18;349(12):1157-67.

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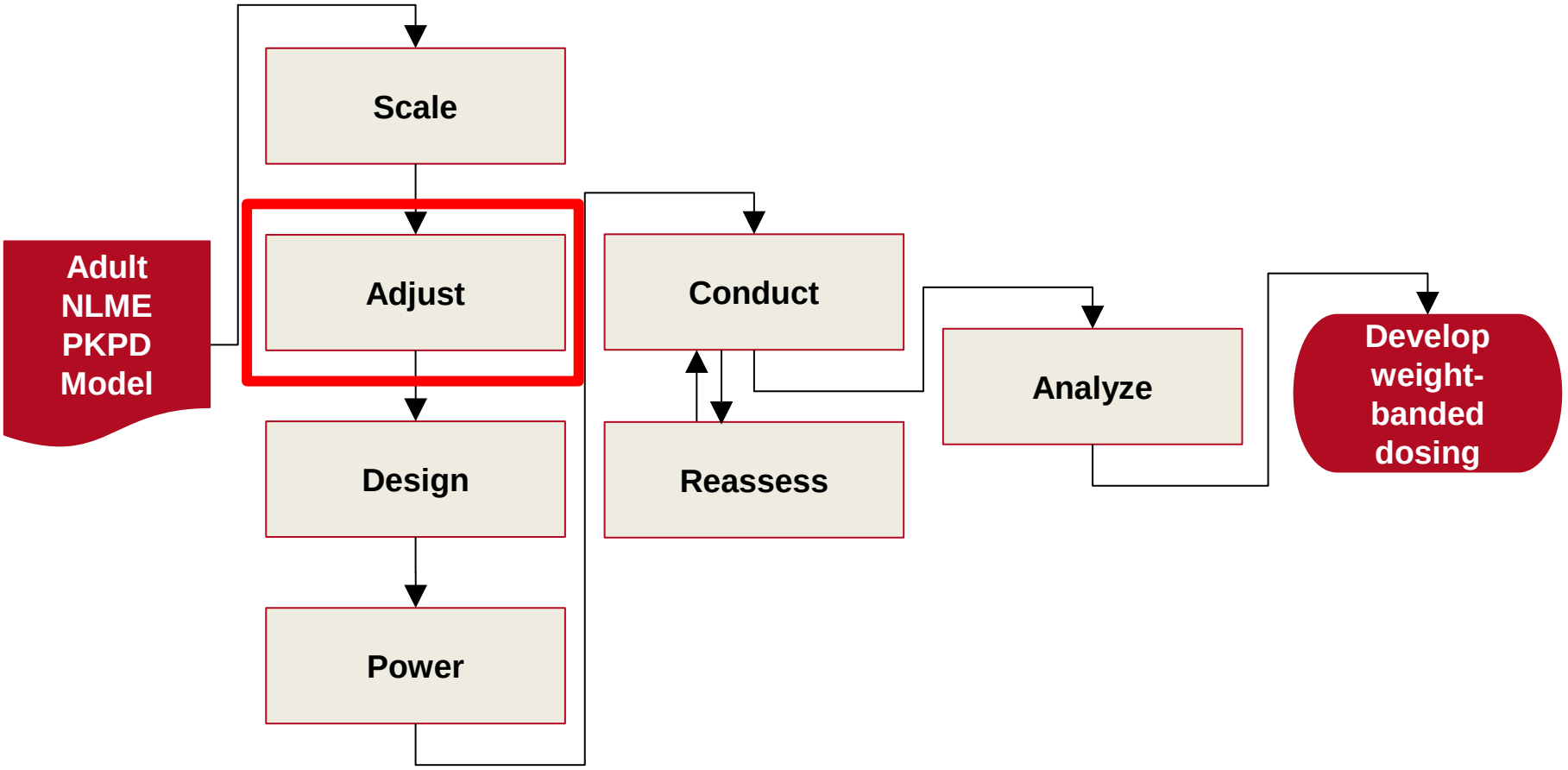
Workflow

for pediatric studies



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Adjust

Dose adjustment to target exposure/effect

- Target adult exposure on standard doses
  - Homogeneous exposure across and within cohorts is the typical goal
- Define target
  - Which exposure metric(s), at what time, from what source (trial results, model-based analysis, preclinical)
- Generally only discrete set of doses/formulations available
  - Expected variability in exposure similar to adults acceptable
- Conflict:
  - Successful achievement of target exposure with low variability will result in minimal information about exposure-response
  - Learning will focus on efficacy/safety at adult exposure not on learning about exposure-response and possible differences compared to adults

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Adjust

Dose adjustment to target exposure/effect

Methodology:

1. Simulate exposure/effects using
   - Available doses
   - Scaled PK(PD) model
   - Relevant age-weight distribution
     - Growth curves (WHO, CDC)
     - Empirical in-house data bases
2. Check predicted results with clinical team
3. Adjust dosing per cohort if needed
4. Repeat if necessary

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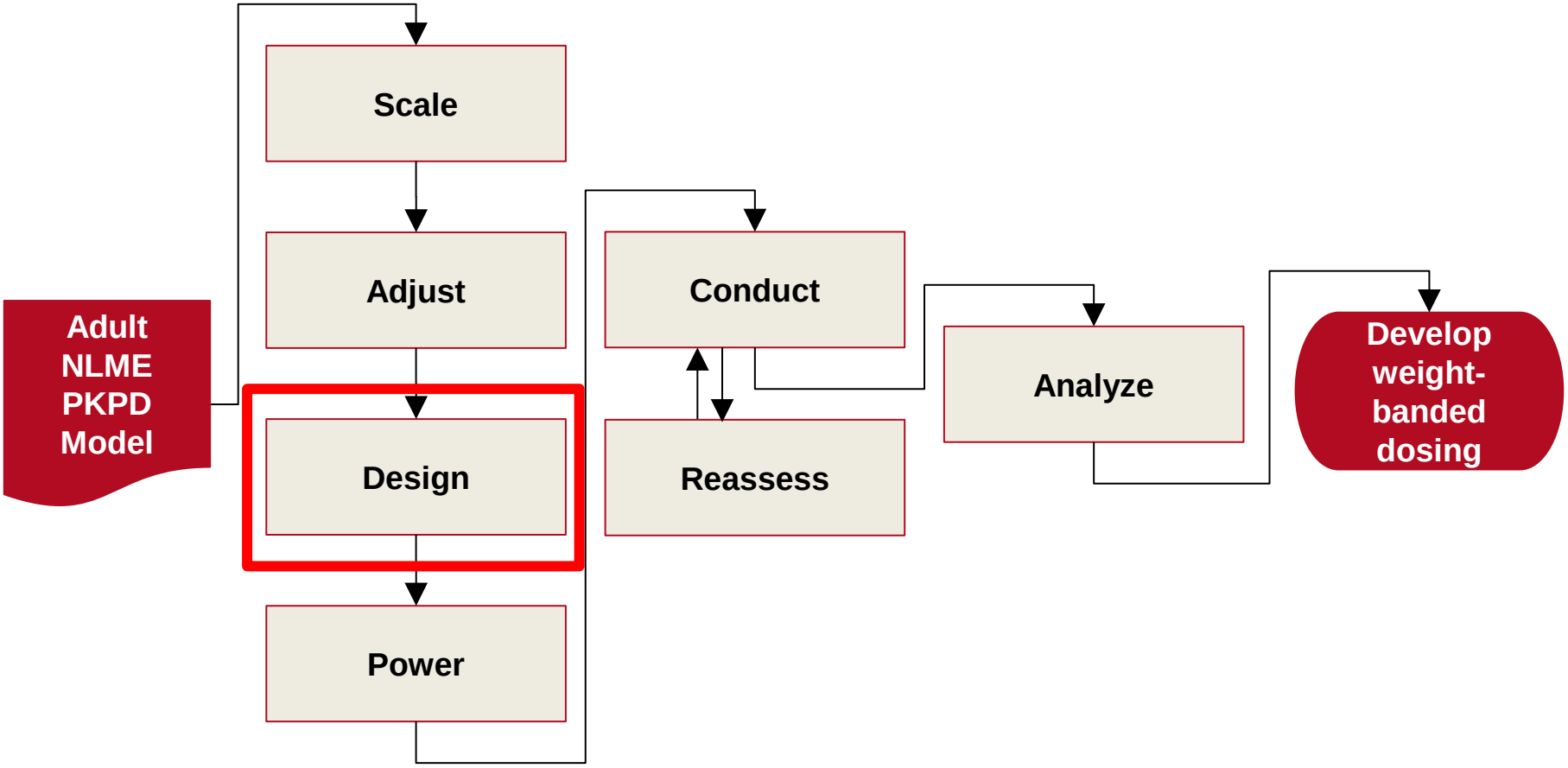
Study dose vs dosing recommendations

- Final dose recommendations may differ from studied doses for a number of reasons:
  - Study dosing is mainly age-banded, dosing preferably weight-banded
  - Final pediatric PK model (on which dosing is based) differ from prior PK model(s)
  - Exposure-response found to be different
  - Formulation changes between study doses and dosing recommendations
    - Fixed dose combinations
    - Dedicated pediatric formulations

Workflow

for pediatric studies



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Design

- Many constraints in study design:
  - Ethical
  - Practical
  - Cost
  - …
- Study design important for expected data quality:
  - Scope of model
  - Model identifiability
  - Parameter precision

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Design

- Large set of design parameters:
  - Dosing strategy modifications
    - Within-subject variation favourable for characterising nonlinear PK and exposure-response
  - What to observe
    - Total and/or unbound concentration, matrix
    - Parent and/or metabolites
    - Biomarkers, Safety, Efficacy
  - Observations
    - Number, timing, difference in times between subjects
    - Importance of design increases with sparsity per individual
  - Covariates to collect
  - …

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Design

Methodology:

1. Determine set of ethically attractive and clinically feasible candidate designs
2. Perform clinical trial simulations (CTS) for candidate designs using scaled model & planned doses
   - intended analysis method (estimation method)
3. Evaluate performance of designs using multiple metrics (model identifiability, parameter precision, convenience, study costs, …)

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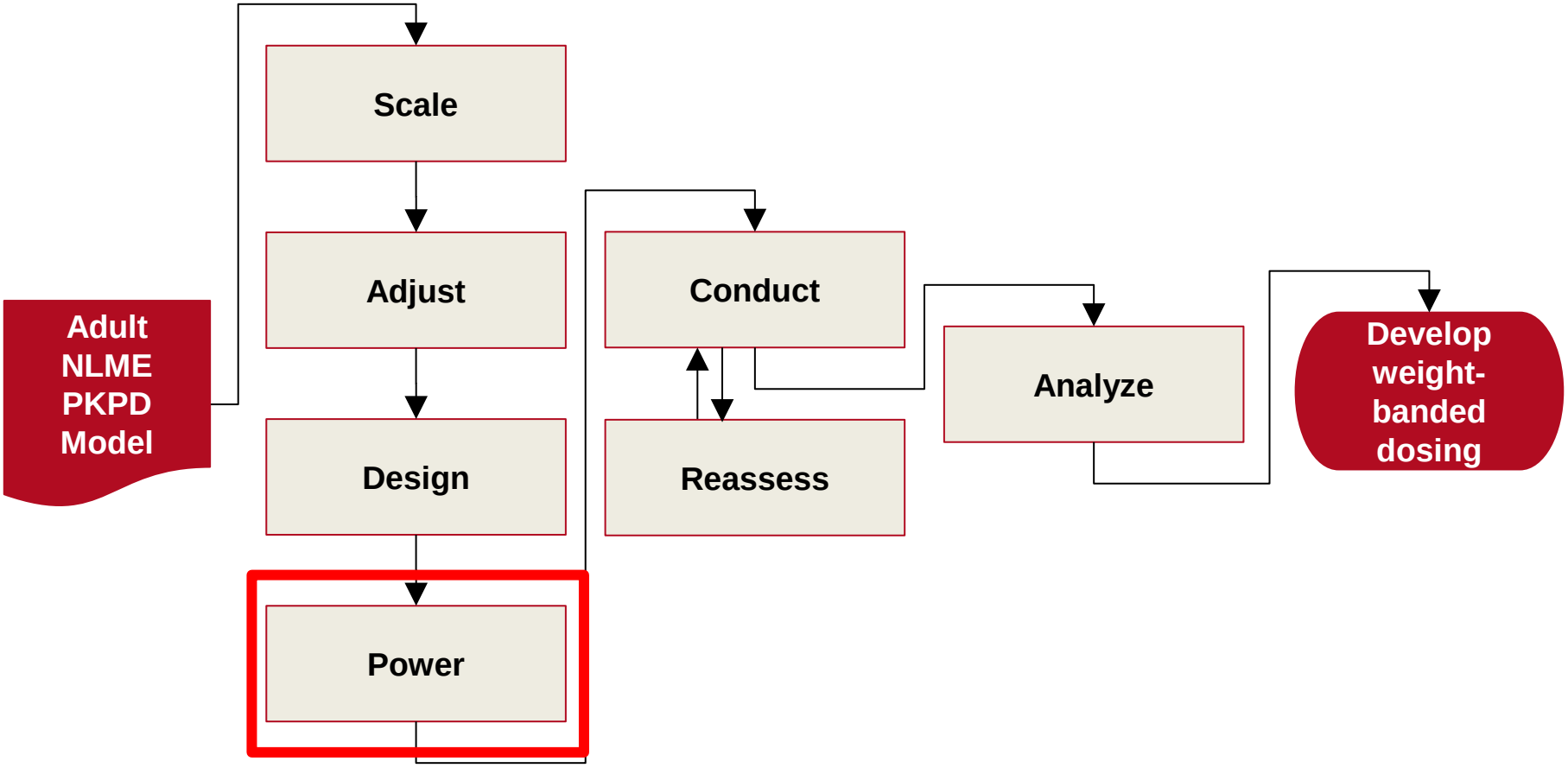
Workflow

for pediatric studies



Power

study for required parameter precision

- Sample size needs to be chosen to fulfill precision criteria:
  ".. target a 95% CI within 60% and 140% of the geometric mean estimates of clearance and volume of distribution … in each pediatric sub-group with at least 80% power." [1]

- Considerations:
  - Choice of PK parameters
  - "*within 60% and 140% of the geometric mean*"
  - Estimation of CIs
  - CIs at which ages/weights
  - Use of prior information in analysis

[1] Yaning Wang et al. "Clarification on precision criteria to derive sample size when designing pediatric pharmacokinetic studies." J Clin Pharmacol 2012;52:1601-1606

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Power

Parameter considerations

- CL
  - Relates mainly to $C_{average}$ and C_{min}
  - More complex with non-linear elimination
- V
  - Determines fluctuations, not $C_{average}$
  - With distribution, multiple V terms, differently related to C_{max} and C_{min}
- Ka
  - Rate of absorption related to C_{max}

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Power

Prior information

- What prior adult information/data is to be used in the analysis of pediatric data?
  - No use of prior information/data in analysis
  - Assumption of same structural PK model
  - Prior information from adults based on assumption of continuity (parameter values for children approach those of adults as age increases)
  - Prior information on selected or all parameters
  - Full or partial use of the adult information

Power

Estimating parameter precision: 95% CIs

- Asymptotic covariance martrix
  - –Suggested approach in Wang et al.
  - –Assumes symmetry in imprecision around point estimates
- Case Bootstrap
  - –Gold standard in large studies
  - –Underestimates interindividual variability in small studies
- Sampling-Importance-Resampling
  - –Promising new method [1]
- Likelihood profiling
  - –Appropriate for mapping CIs, but difficult to implement in powering

[1] Dosne et al. "Application of Sampling Importance Resampling to estimate parameter uncertainty distributions." PAGE 22 (2013) Abstr 2907 [www.page-meeting.org/?abstract=2907]

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Power

What weights to calculate CIs for

- Median weights in each age cohort
  - –According to CDC suggested by Wang et al.
  - –Disease population specific median weight

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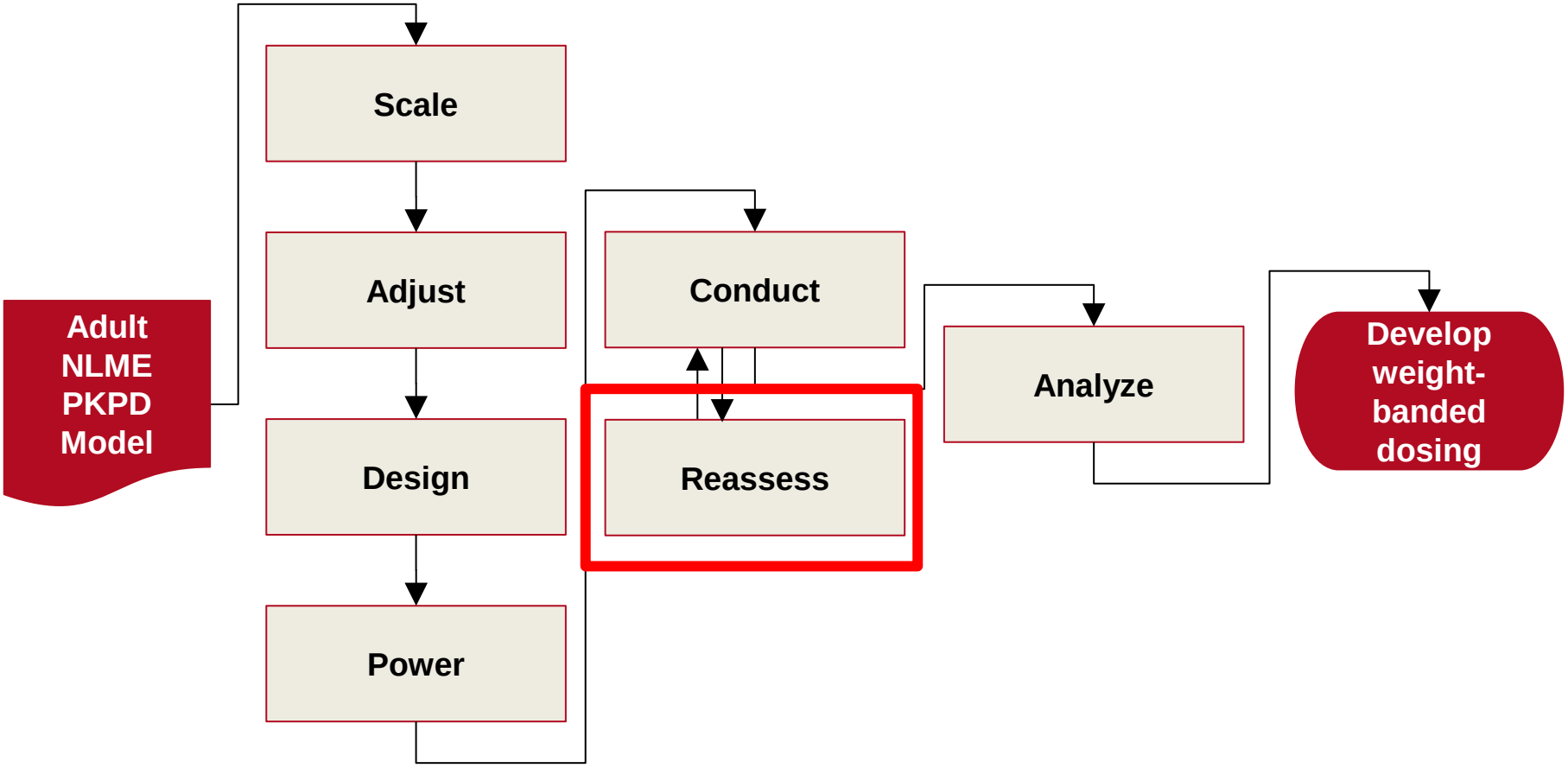
Workflow

for pediatric studies



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Reassessment

after each cohort

- To assess exposure
  - Is exposure sufficiently similar to target to provide relevant safety information?
- To assess agreement with expected data information
  - Was the data as informative as expected?
  - Study additional subjects
- To determine doses for next (younger) cohort
  - Update PKPD model with new data
  - Reassess planned doses

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Reassessment

after the first X patients of a cohort

- It may be too late to learn about study (PK) problems after an entire cohort been studied

- Assess agreement with target exposure
- If necessary,
  - Update PKPD model
  - Propose new doses

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Reassessment

after each patient

- Assess agreement with target exposure/response
- If outside desired range,
  - Calculate individual PKPD parameters
  - Propose new doses or treatment interruption

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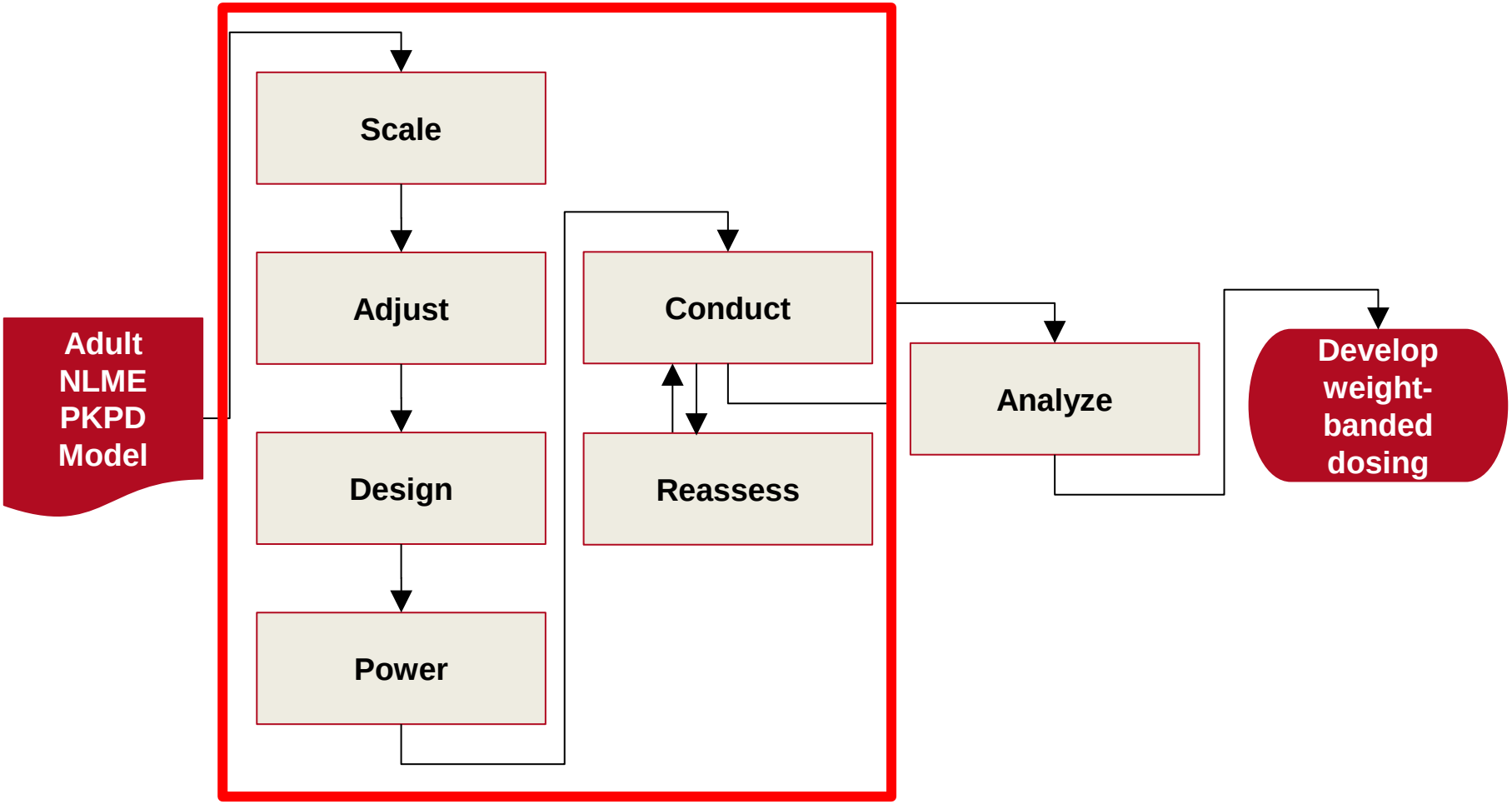
Workflow

for pediatric studies



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Extensions & alternatives

to the proposed workflow

Scale & Adjust:

- Utilize model/parameter uncertainty from adults

Design & Power:

- Use optimal design methodology
  - Maximize overall parameter precision using D-optimality
  - Maximize precision for specific parameters using Ds-optimality
  - Use global optimal design with parameter uncertainty from adult model
  - Power study using Fisher information matrix

CTS for verification

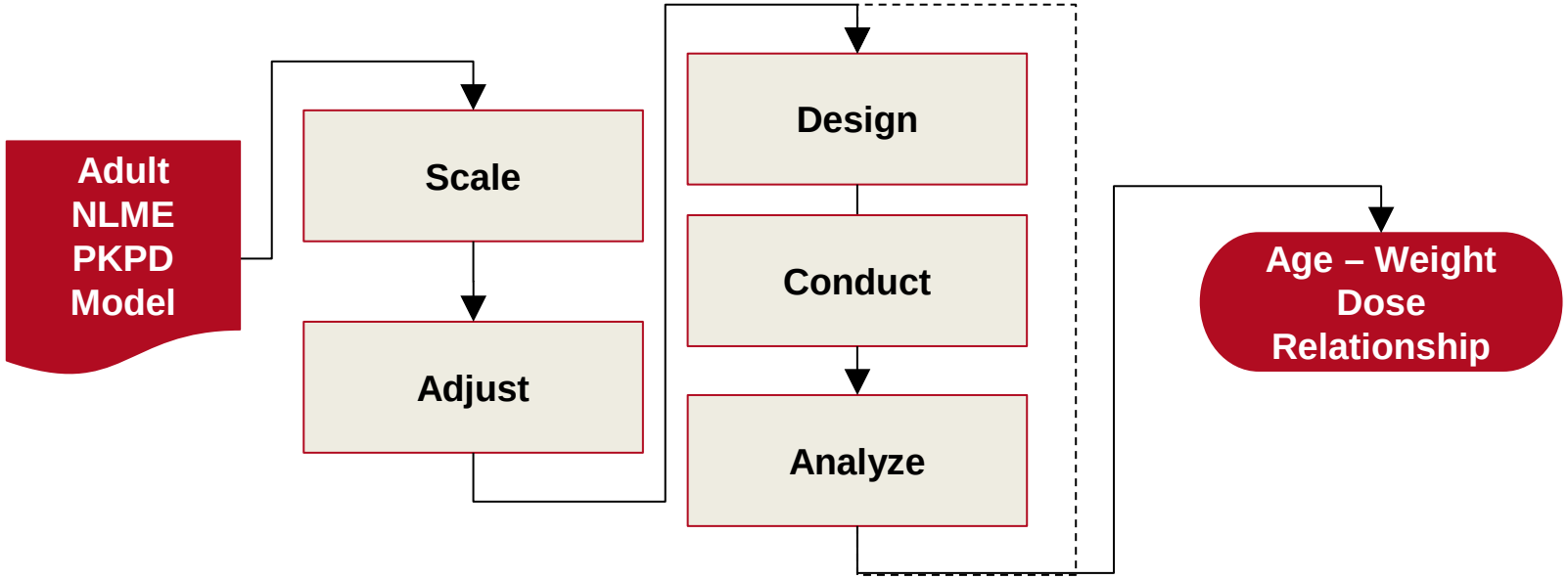
Extensions & alternatives

to the proposed workflow

Reassess & Analyze:

Model-based adaptive optimal design with automatic stopping [1]

- Interim analysis after every cohort
- Update of design for next cohort
- Stopping if precision is sufficient



[1] Strömberg and Hooker. "Simulated model based adaptive optimal design of adult to children bridging study using FDA stopping criteria." PAGE 24 (2015) Abstr 3614 [www.page-meeting.org/?abstract=3614]

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Summary

- Model-informed study design for model-based analysis is a multi-step procedure, each step has many options and potential for further development
- Multiple pharmacometric tools available to guide planning and analysis of pediatric trials. Extensions to 'basic' workflow can reduce assumptions and increase robustness
- Extrapolations:
  - Assumption that target exposure is the same as in adults
  - Assume that safety at recommended doses are similar to that of study doses

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Acknowledgements

Sebastian Ueckert, UU

Elin Svensson, UU

Thomas Dorlo, UU

Martin Bergstrand, UU

Andrew Hooker, UU

Paolo Denti, Univ of Cape Town

Helen McIlleron, Univ of Cape Town

Anneke Hesseling, Stellenbosch University

Joel Tärning, Mahidol-Oxford

Kelly Dooley, John's Hopkins

Rada Savic, UCSF