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Tuberculosis Scientific Committee
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Using Pharmacokinetic Modelling to Evaluate Novel TB Drugs in Children More Efficiently

Experiences from BDQ CRUSH, P1108 and IMPAACT 2005

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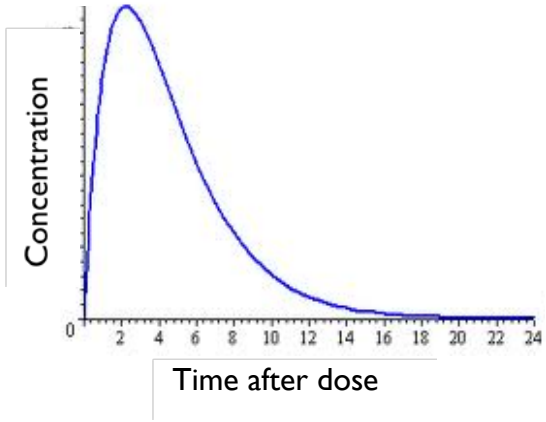
Presentation outline

- Why PK and studies in children?
- Introduction to pharmacokinetic modelling
- Examples
  - IMPAACT 2005
  - P1108 and BDQ CRUSH
- Summary

Why pharmacokinetics?

A drug's **effects** depend on the free **concentration** at the site of action

Absorption
Distribution
Elimination
Metabolism



Relapse free cure

Adverse side effects

Differences between adults and children

- Body size
- Enzyme maturation
- Organ maturation
- Formulation
- Administration route

- Binding proteins
- Body composition

e.g. Andersson and Holford. "Mechanism-Based Concepts of Size and Maturity in Pharmacokinetics." Annu. Rev. Pharmacol. Toxicol. 2008;48:303–32

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Pharmacometrics

- A **multi-disciplinary** field where statistics, mathematics and computational science meet pharmacology, physiology and biology

- Mathematical **models** to characterize, understand, and predict a drug's pharmacokinetic and pharmacodynamic features in **populations**

- **Nonlinear mixed-effects** models describing the **typical** behavior and the stochastic **variability** in a system followed over time

Pharmacokinetic population models

1. Structural model with primary parameters (clearance, volume of distri… …

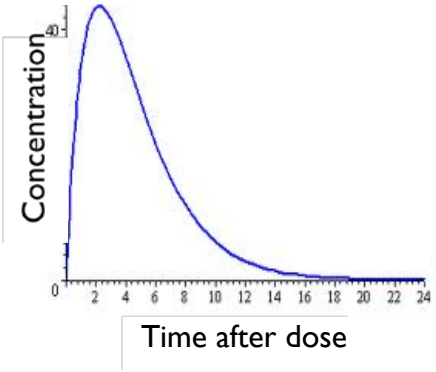
$$\frac{dA1}{dt} = -ka_i * A1$$

$$\frac{dA2}{dt} = ka_i * A1 - \frac{CL_i}{V_i} * A2$$

…ign variability distribution

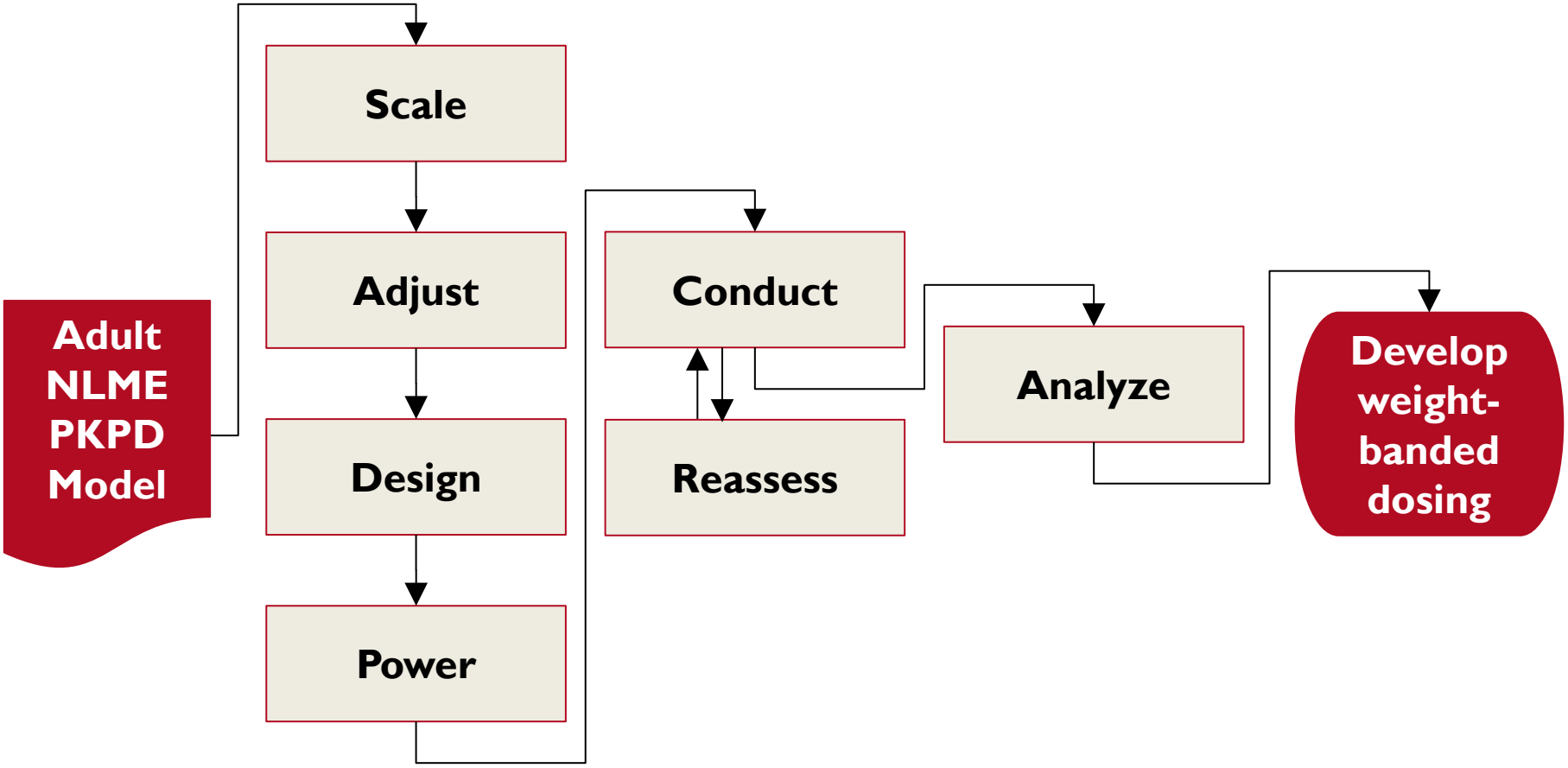
4. Maximum likelihood estimation of parameters – fit the model to the data

5. Evaluate



Secondary parmeters (AUC, Cmax, T½, …)

Workflow


Adult NLME PKPD Model
Scale
Adjust
Design
Power
Conduct
Reassess
Analyze
Develop weight-banded dosing

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Power

Sample size and sampling schedule needs to be chosen to:

- Give sufficient power for characterization of covariate effect(s) of interest

- Fulfill criteria for parameter precision

  ".. 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]

1. Y 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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Example IMPAACT 2005
Background

- Pharmacokinetics, Safety, and Tolerability of Delamanid in Combination with Optimized Multidrug Background Regimen for MDR-TB in HIV-Infected and HIV-Uninfected Children

- 4 age cohorts
- 6 HIV+ and 3 HIV- children per cohort → 36 ID
- Experience from ongoing pediatric trials by Otsuka

What is the minimal sampling schedule we can use while still fulfilling precision criteria for both HIV+ and HIV- children?

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Example IMPAACT 2005

Clinical trial simulations

- Age-weight distribution from adjusted growth-reference
- Population PK model from Otsuka
  - Developed primarily with data from adults
  - Readjusted with data from 12 children 6-18 years
- Final analysis jointly with data from study 232 and 233
- Precision separately for HIV+ and HIV- children
- Multiple sampling schedules evaluated

Design number	**Week**	**1**	**2**	**4**	**8**	**12**	**16**	**24**	**N samples**
	Day	**1**	**10**	**28±2**	**56±2**	**84±2**	**112±2**	**168±2**	
1	h postdose	0, 4, 10	0,2,4,10,12,14,24	0	0, 4, 10	0	0	0	17
7	h postdose	0, 4, 8	**0,2,4,8**	0	0, 4, 8	0	0	0	14

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Example IMPAACT 2005
Conclusions

- ✓ The suggested sampling schedule and 9 subjects per cohort is adequate to fulfill FDA's precision criteria for clearance
- ✓ The clinical trials simulation allowed us to remove 3 PK samples, including an overnight stay, and shorten the duration of the (semi-)intensive sampling from 10 to 8 h
- ✓ A model-based analysis will be used when data is collected
  - ✓ Characterizing delamanid PK in HIV+ children
  - ✓ Determining optimal doses

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Example P1108 and BDQ CRUSH

Background 1/2

- P1108: Pharmacokinetics, Safety and Tolerability of Bedaquiline (BDQ) in Combination with Optimized Individualized MDR-TB Therapy in HIV-Infected and HIV-Uninfected Infants, Children and Adolescents

- Age de-escalation in four steps down to infants
- Uncertain access to pediatric formulation

Can we use crushed/dissolved adult formulation of bedaquiline to dose the oldest children?

→ **BDQ CRUSH**

Example P1108 and BDQ CRUSH
Background 2/2

- Bioequivalence of Bedaquiline 400mg Administered in ~~Crushed~~ Dissolved Form Compared to Tablet Form in Healthy Adults under Fed Conditions

- Bedaquiline has extremely long terminal half-life
- Historic drug-drug-interaction studies > 6 weeks long
- Non-compartmental analysis problematic[1]

What is the shortest sampling time and washout period we can use and still be able to characterize a potential effect?

1. EM Svensson *et al.* "Pharmacokinetic interactions for drugs with a long half-life – evidence for the need of model-based analysis." AAPS J, 2016;18(1):171-9

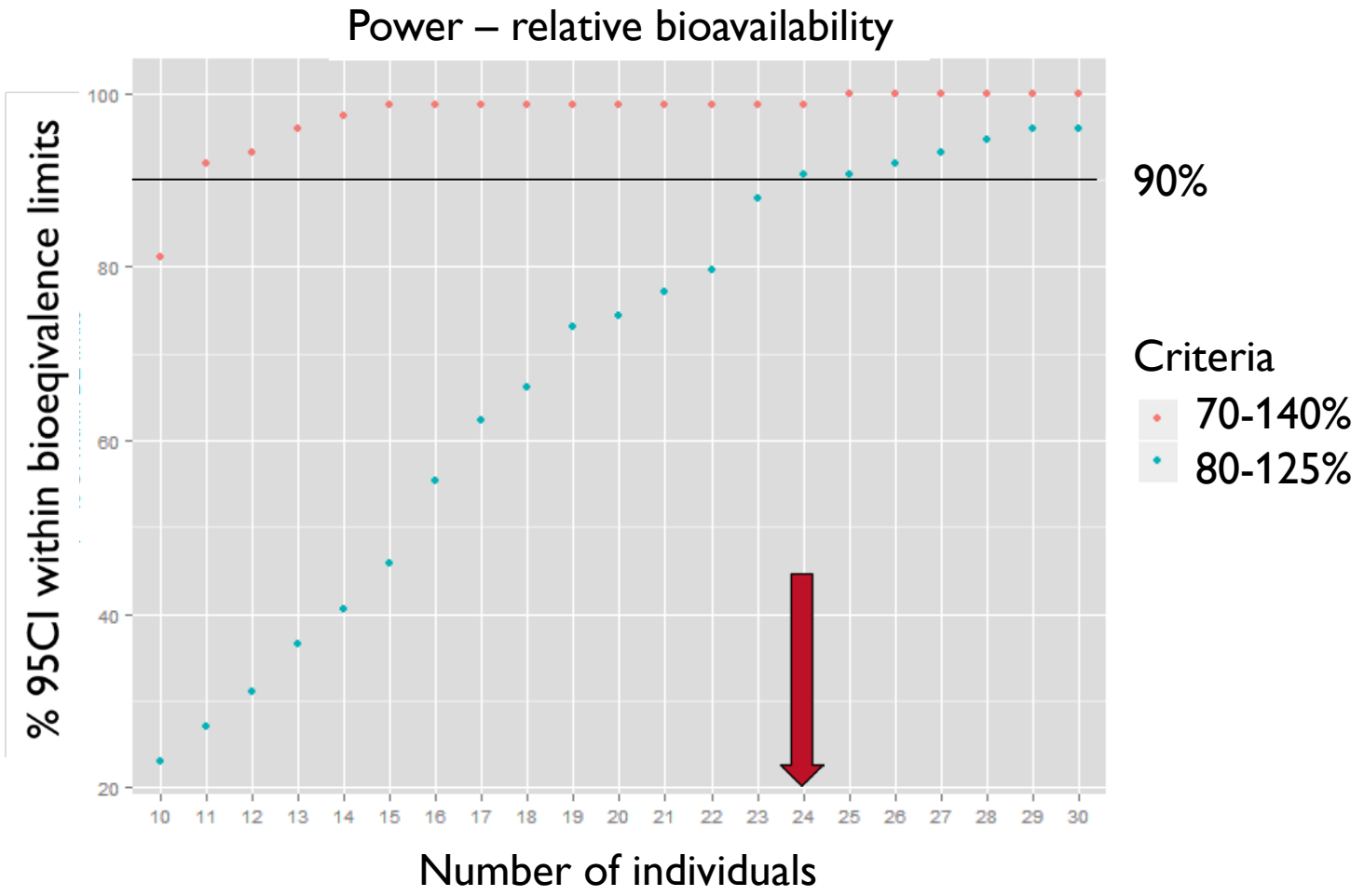
Example BDQ CRUSH
Clinical trials simulations

- Age-weight distribution from DDI studies
- Population PK model of bedaquiline and metabolite M2[1]
- Power to determine a 95% confidence interval for relative bioavailability within bioequivalence criteria (80-125% or 70-140%), assuming no effect of dissolving
- Multiple sampling schedules evaluated
  - Reduced from 17 samples at different 8 days to 11 samples at 4 different days per dosing occasion

1. EM Svensson *et al.* "Model-based estimates of the effects of efavirenz on bedaquiline pharmacokinetics and suggested dose adjustments for patients coinfected with HIV and tuberculosis" Antimicrob Agents Chemother, 2013;57(6):2780-7

Example BDQ CRUSH

Clinical trial simulations



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Example P1108 and BDQ CRUSH
Conclusions

- ✓ A substantially reduced design to test bioequivalence of dissolved bedaquiline could be implemented
- ✓ P1108 design itself also evaluated for precision criteria
- ✓ A model-based analysis will be used when data is collected
  - ✓ Re-evaluate doses in interim analyses
  - ✓ Characterizing bedaquiline PK in HIV+ children
  - ✓ Determining optimal doses

Summary

Pharmacokinetic Modelling to Evaluate Novel TB Drugs in Children

Advantages

- Characterization of complex non-linear relationships
- Incorporate existing knowledge
- Quantify variability
- Make use of information in metabolite data
- Sparse sampling possible
- Gain mechanistic understanding
- Handle long half-life
- High statistical power
- Enables clinical trial simulations and selection of optimal dose

Drawbacks

- Specific skills and knowledge
- Time-consuming
- Communication of results can be difficult

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Thank you!

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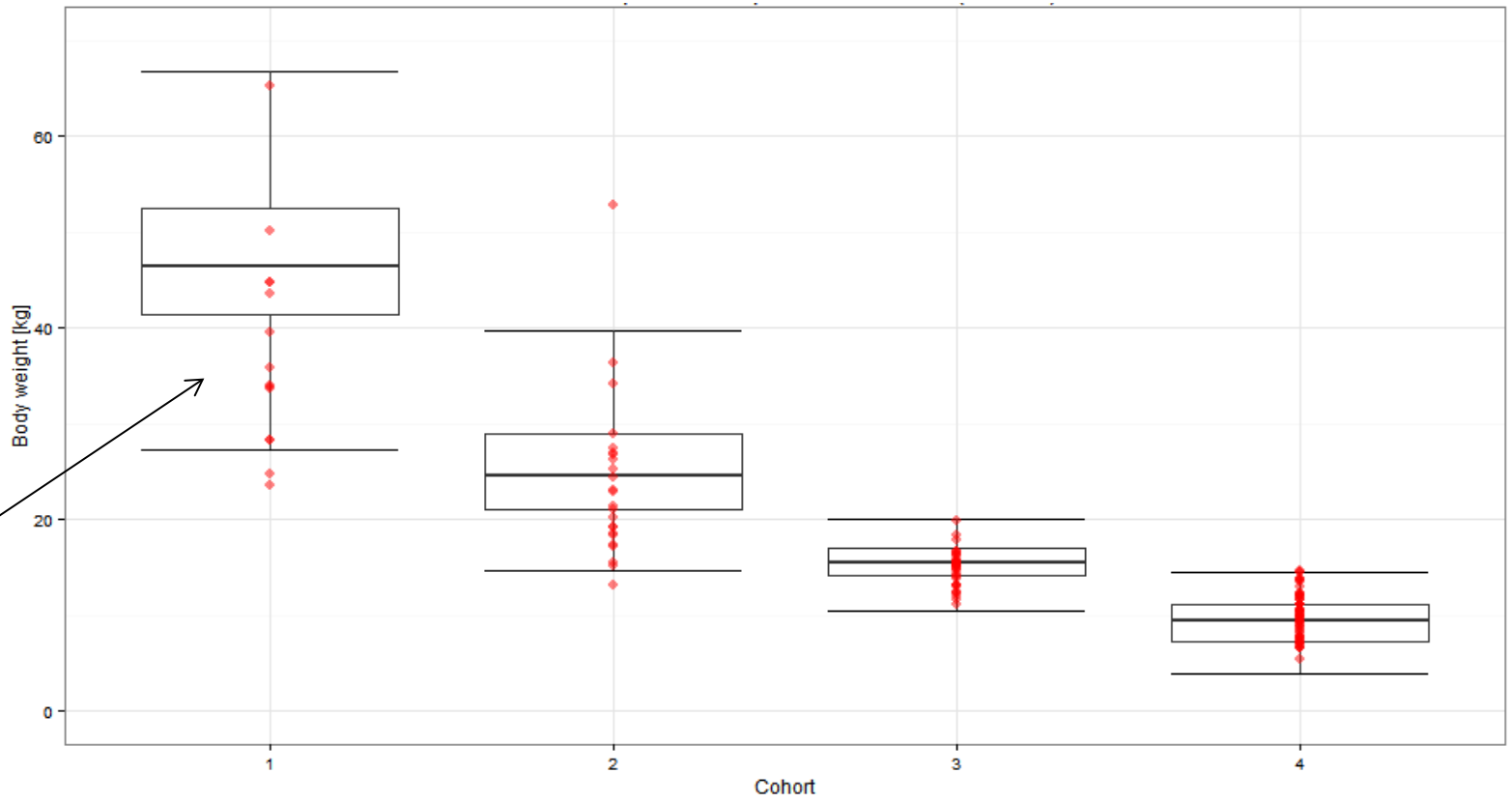
Backup slides

Example IMPAACT 2005
Population



Reference including children <15 years

Reference: 143 children from South African pediatric TB trials at Desmond Tutu TB Center