Modelling and simulation as a tool for translation, prediction and extrapolation of pharmacokinetics, pharmacodynamics, safety and efficacy in children

Oscar Della Pasqua
Chair Clinical Pharmacology & Therapeutics

ePTRI
European Paediatric Translational Research Infrastructure

Outline

1. Evidence generation: from data to models to paediatric patients
2. Drug-disease modelling, trial models, population models
3. Modelling and simulation services
4. Examples: experimental protocol optimisation, translation and extrapolation
5. Clinical trial designs: RCT, RWE, digital twins, virtual cohorts
6. Q&A

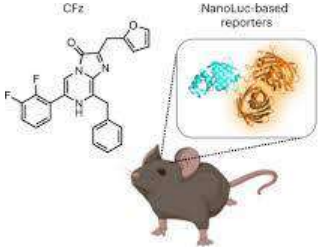
Evolution is happening all the time

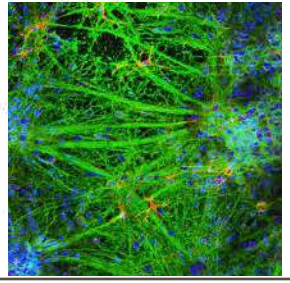
Different functionality has been enabled during the evolutionary process

https://gulfnews.com/world/a-brief-history-of-the-telephone-1.1603713110135

Evolution is happening all the time

Different research techniques and methodologies have evolved over the last 3 decades





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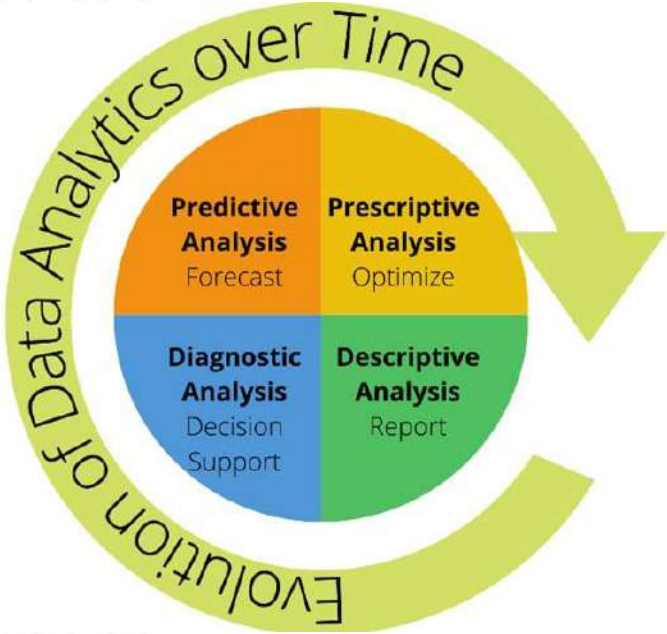
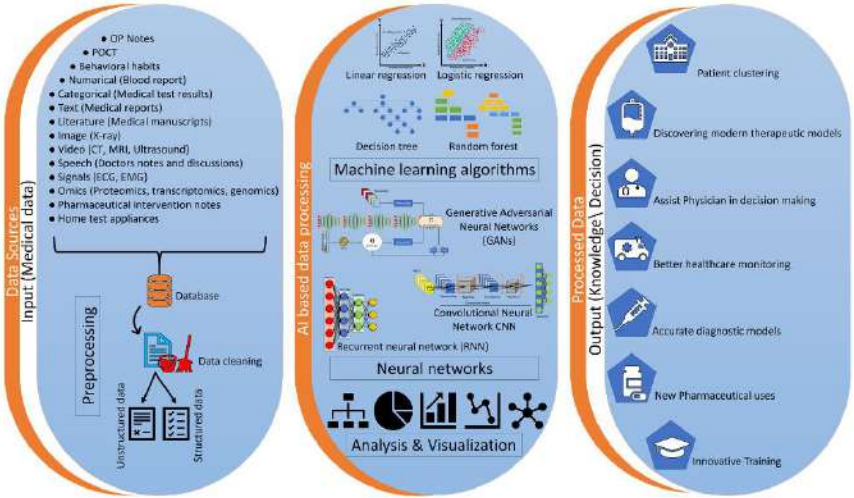


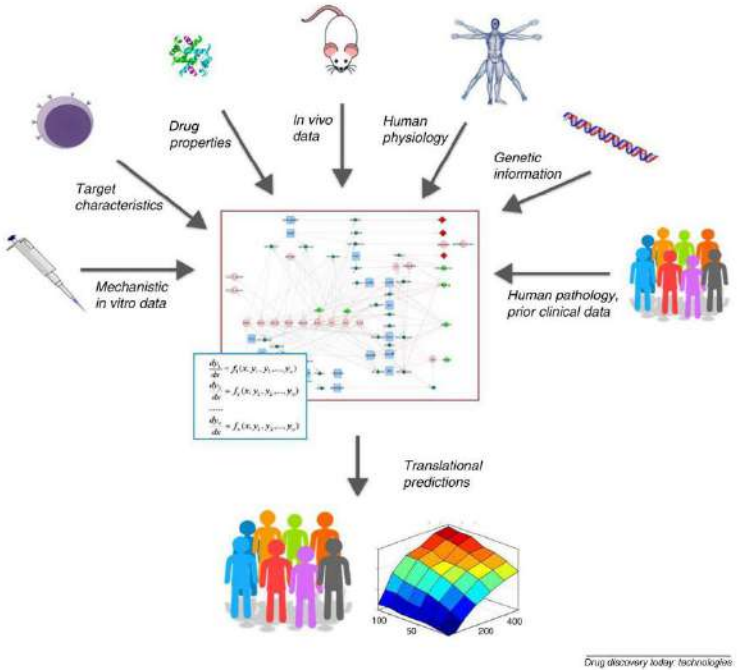
Has our data analytics skills also evolved?

Experimental protocols vs. data analytics

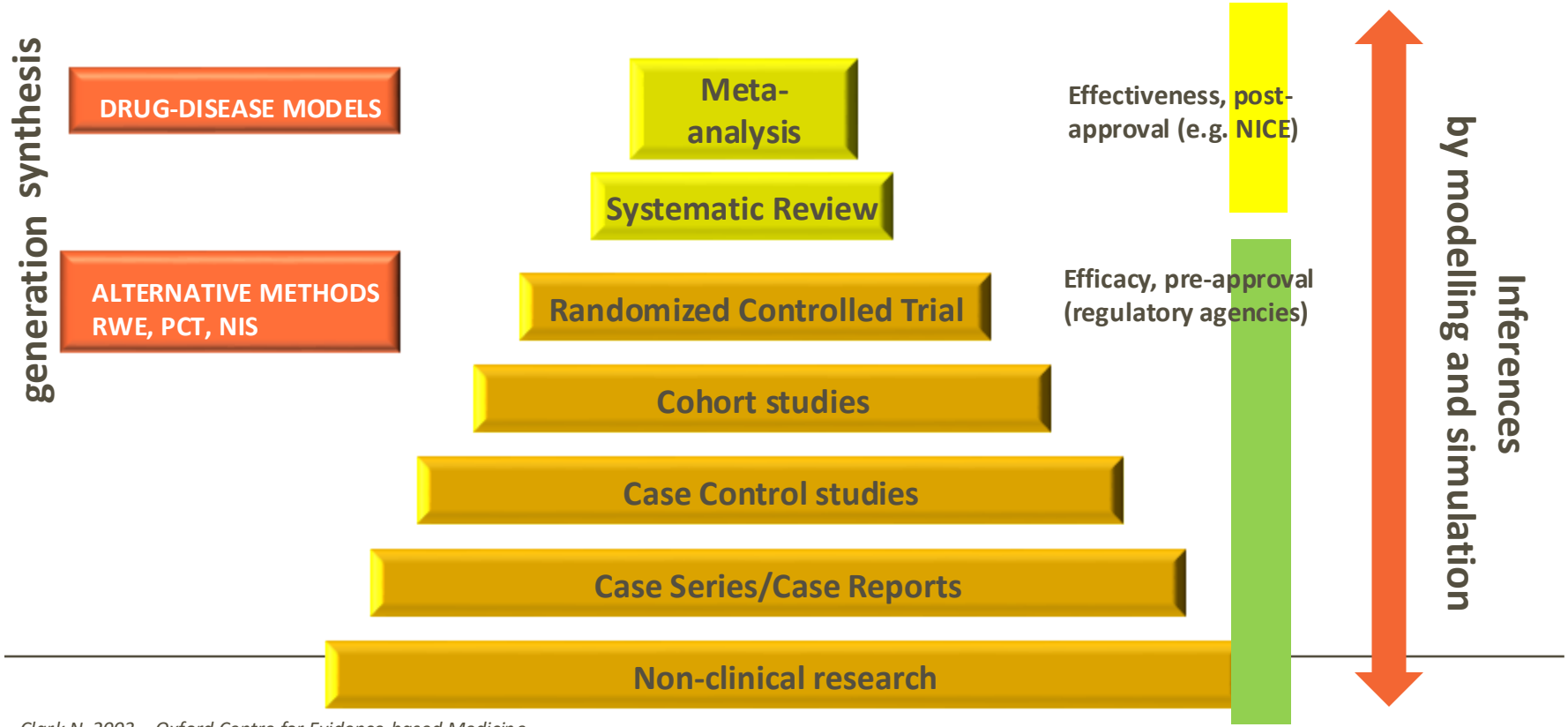


Data-driven approaches

Model-based approaches

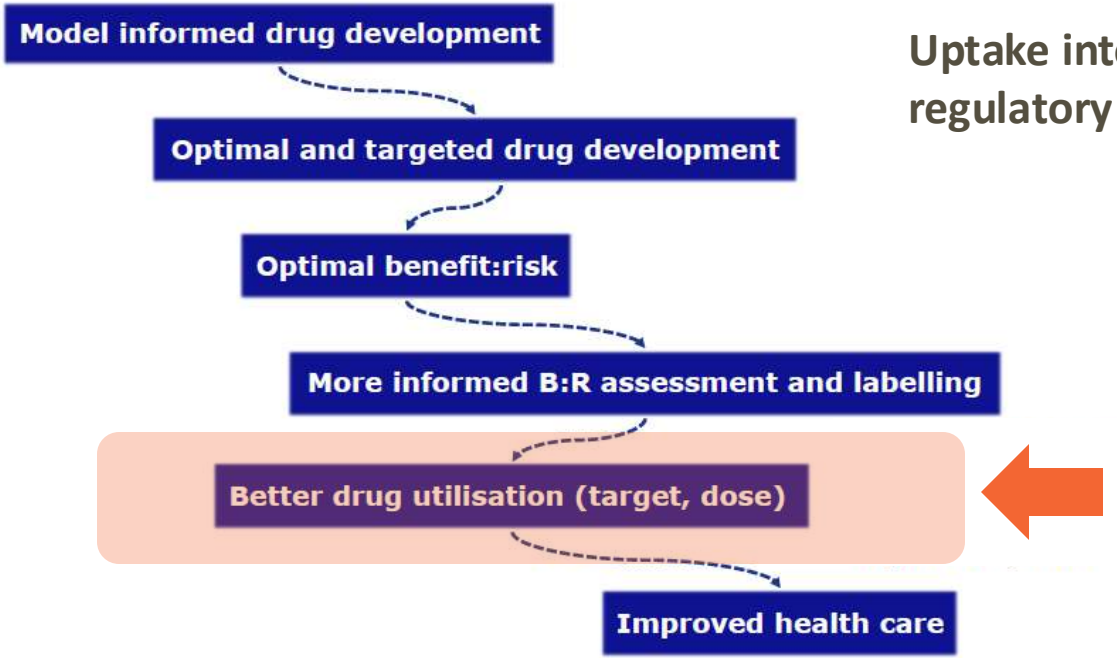


Evidence pyramid



Clark N, 2003 - Oxford Centre for Evidence-based Medicine

Long term scientific vision



Uptake into (paediatric) drug development, regulatory processes and clinical practice

Shepard T, PAGE meeting (Alicante), 2014

Drug-disease modelling and simulation framework

Disease model

Biology
- Biomarker(s)/outcome relationship
- Natural progression

Placebo effect

Drug model

Pharmacology
- Effectiveness
- Safety

Preclinical/Healthy/Patient

Product features

Not-in-trial model

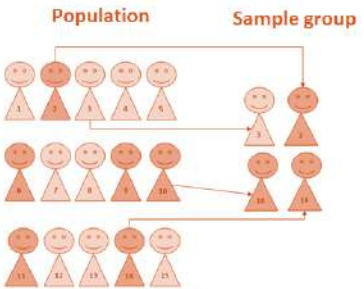
Co-morbidities

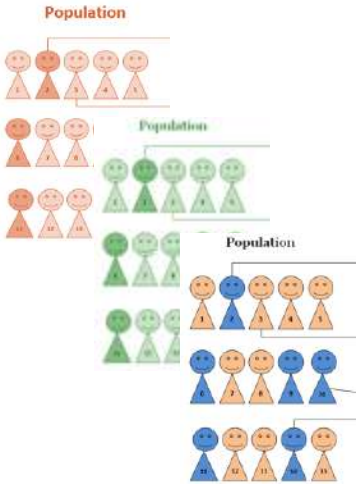
Drop-out

Adherence

Medical practice

Patient pop. model





Gobburu & Lesko, Annu Rev Pharmacol Toxicol. 2009;49:291-301.

M&S SERVICES

Protocol optimisation – Informative protocol designs

Translation and extrapolation

Diagnostics – Simulations, dosing algorithms and decision support

→ *Dose selection, sampling scheme, sample size, study design*

→ *Predict exposure (PK), response (pharmacodynamics, safety, efficacy)*

→ *Predict disease progression, patient inclusion/exclusion criteria, select formulation, dosing regimen,*

→ *Support assessment of treatment response relative to control groups using virtual patient cohorts and/or digital twins*

Protocol optimisation

- Multidrug-resistant tuberculosis (MDR-TB) is a leading cause of death globally, manifesting severely in children.
- Preclinical animal models are required to explore new treatments for tuberculosis (TB)
- Experimental models should mimic or reflect the underlying pathology in humans. To that purpose, standard of care (SoC) drugs can be used to calibrate the model assess its potential relevance as translational tool
- Marmosets offer such a possibility – i.e., comparable pathology.
- However, the pharmacokinetics (PK) of SoC drugs and relevant biomarkers have not been fully characterised in marmosets

This investigation aimed to:

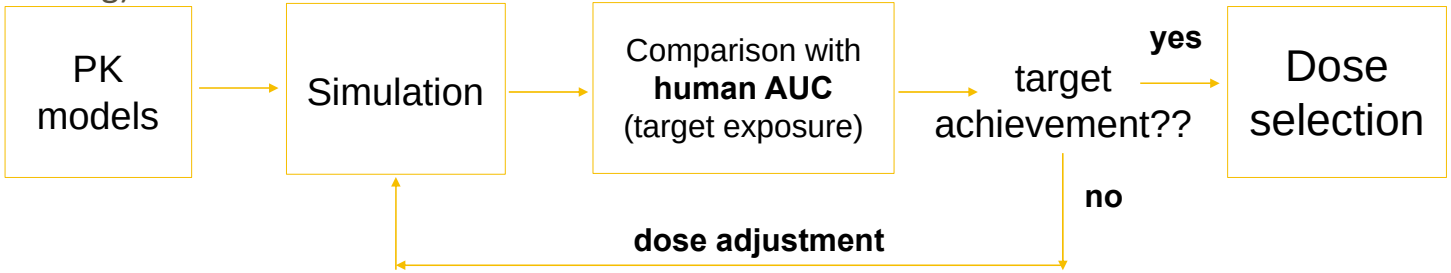
1. establish the dose of SoC drugs that yields systemic exposure in marmosets comparable to that observed in humans
2. assess the feasibility of an optimized sampling schedule to minimise the number of samples required per animal and reduce number of animals required in a prospective efficacy study

PAGE 31 (2023) Abstr 10684 [www.page-meeting.org/?abstract=10684]
Yang HJ et. al. One size fits all? Not in *in vivo* modeling of tuberculosis chemotherapeutics. Front Cell Infect Microbiol. 2021
Via LE al. Differential virulence and disease progression following mycobacterium tuberculosis complex infection of the common marmoset (Callithrix Jacchus). Infect Immun. 2013
't Hart BA et. al. The marmoset monkey: A multi-purpose preclinical and translational model of human biology and disease. Drug Discov Today 2012

Protocol optimisation

Dose Selection

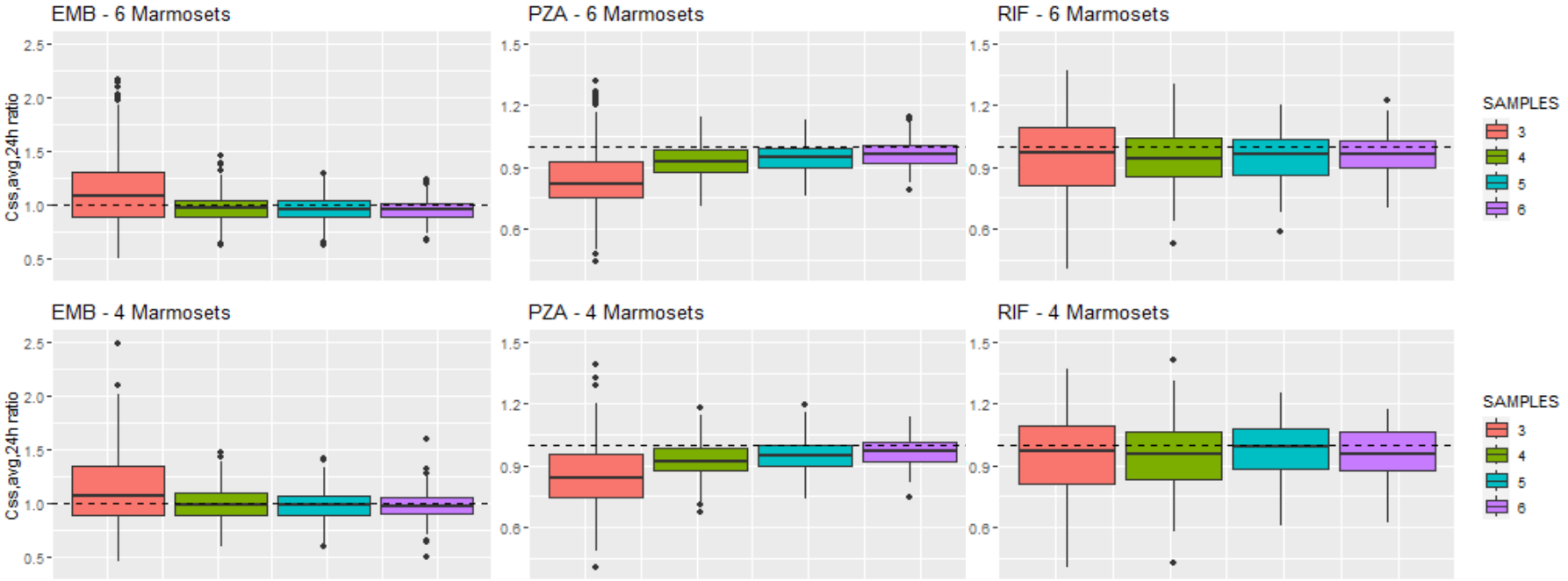
- Simulations were implemented to generate concentration vs. time profiles at steady-state (SS) according to a q.d. dosing regimen.
- Predicted exposure at SS, expressed as AUCss, was compared with that in TB patients (RIF 600 mg, EMB 750 mg, PZA 1500 mg).



Drug	AUCss [mg/L*h] median (5th-95th percentile)	AUC [mg/L*h] published for humans (range)	Previously used dose [mg/kg]	Dose recommended [mg/kg]
ETHAMBUTOL	15.3 (10.5 – 48.9)	14-25	50	50
RIFAMPICIN	29.8 (12.1-56.9)	20-60	15	15
PYRAZINAMIDE	414 (255-686)	381-561	125	75

Protocol optimisation

Impact of different sampling times and animal number on Css, driver of efficacy in the PKPD model



Protocol optimisation

Drug Discovery Today • Volume 22, Number 3 • March 2017 PERSPECTIVE

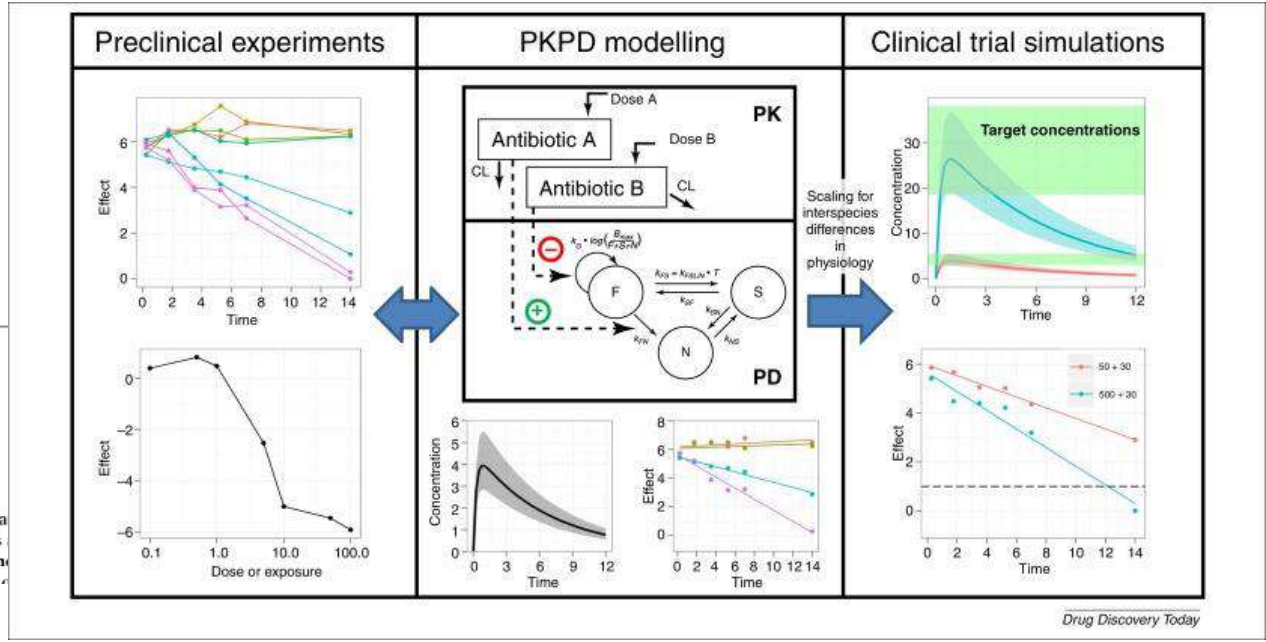
ELSEVIER

feature

The implications of model-informed drug discovery and development for tuberculosis

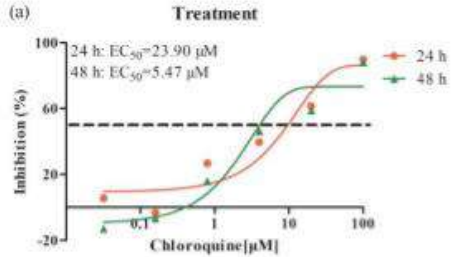
Morris Muliaditan[1], Geraint R. Davies[2], Ulrika S.H. Simonsson[3], Stephen H. Gillespie[4] and Oscar Della Pasqua[1,3], o.dellapasqua@ucl.ac.uk

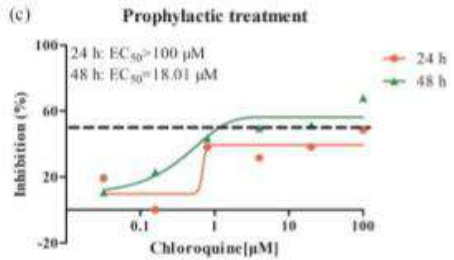
Despite promising advances in the field and highly efficacious first-line trea
million people are still infected with tuberculosis (TB). Innovative methods
transition the growing number of compounds into novel combination regim
of compounds into patients occurs despite the lack of clear understanding



Translation and extrapolation

Chloroquine – *In vitro* antiviral activity





Which levels of antiviral activity is required to translate viral suppression into a clinically relevant response?

Treatment
23.90uM x 319.872 μg = 7.6 mg/L
5.47uM x 319.872 μg = 1.75 mg/L

Treatment
IC90 = 68 mg/L
IC90 = 15.75 mg/L

Prophylactic dose
100uM x 319.872 μg = 31.99 mg/L
18.01uM x 319.872 μg = 5.76 mg/L

Prophylaxis
IC90 = 51.84 mg/L

Chloroquine and hydroxychloroquine were found to decrease the viral replication in a concentration-dependent manner.

Yao et al. Clin Infect Dis 2020;71(15):732-739.

Translation and extrapolation

pharmaceutics

MDPI

Article

Model-Informed Repurposing of Medicines for SARS-CoV-2: Extrapolation of Antiviral Activity and Dose Rationale for Paediatric Patients

Federico Romano [1,†], Salvatore D'Agate [1,†] and Oscar Della Pasqua [1,2,3,*]

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2 Clinical Pharmacology Modelling and Simulation, Glaxo
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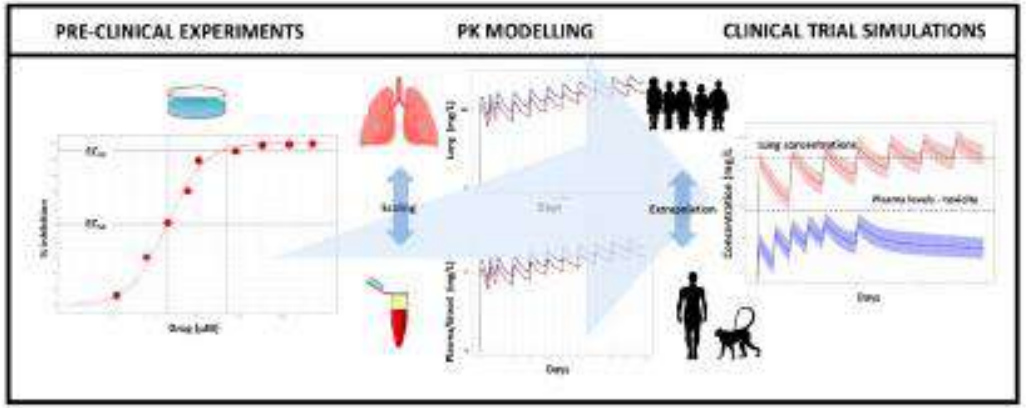
* Correspondence: o.dellapasqua@ucl.ac.uk; Tel: +44-20-7
† These authors contributed equally to this work.

Abstract: Repurposing of remdesivir and other drugs
basis of numerous clinical trials aimed at SARS-CoV-
designed trials without careful consideration of dos
failure and toxicity in the target patient population, wh
Here we show how paediatric regimens can be identifi



Treatment optimisation / personalised interventions

Pharm Res (2016) 33:498–509
DOI 10.1007/s11095-015-1805-0

RESEARCH PAPER

Model-Based Optimisation of Deferoxamine Chelation Therapy

Francesco Bellanti[1] • Giovanni C. Del Vecchio[4] • Maria C. Putti[5] • C
Oscar Della Pasqua[1,2,3]

Received: 6 July 2015 / Accepted: 2 October 2015 / Published online: 10

ABSTRACT

Purpose Here we show how a model-based approach may be used to provide further insight into the role of clinical and demographic covariates on the progression of iron overload. The therapeutic effect of deferoxamine is used to illustrate the

THIS SUBJECT
• Lamivudine is currently administered as a once daily

Journal of Thrombosis and Haemostasis, 17: 88–98 DOI: 10.1111/jth.14345

ORIGINAL ARTICLE

Pharmacokinetics of plasma infusion in congenital thrombotic thrombocytopenic purpura

A. TAYLOR,* C. VENDRAMIN,* S. OOSTERHOLT,† O. DI
*Haemostasis Research Unit, University College London; †Clinical Pharmacology an
‡Department of Haematology, UCLH and Cardiometabolic Programme-NIHR UCLH

To cite this article: Taylor A, Vendramin C, Oosterholt S, Della Pasqua O, Scully M
botic thrombocytopenic purpura. *J Thromb Haemost* 2019; 17: 88–98.

Essentials

- Congenital thrombotic thrombocytopenic purpura (**TTP**) is primarily treated with plasma infusion.
- We present a pharmacokinetic analysis of ADAMTS-13 in six patients following plasma infusion.
- A median half-life of 130 h was demonstrated, ranging between 82.6 and 189.5 h.
- Investigation of interindividual clearance of ADAMTS-13 is necessary to optimize treatment.

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Received: 4 July 2023 | Accepted: 14 July 2023
DOI: 10.1002/prp2.1138

ORIGINAL ARTICLE

Dose rationale for gabapentin and tramadol in pediatric patients with chronic pain

Paul Healy[1] | Luka Verrest[1] | Mariagrazia Felisi[2] | Adriana Ceci[3] | Oscar Della Pasqua[1] | GAPP Consortium

[1]Clinical Pharmacology & Therapeutics Group, School of Pharmacy, University College London, London, UK
[2]CVBF–Consorzio per le Valutazioni Biologiche e Farmacologiche, Pavia, Italy
[3]Fondazione per la Ricerca Farmacologica Gianni Benzi onlus, Valenzano, Italy

Abstract

Despite off-label use, the efficacy and safety of gabapentin and tramadol in pediatric patients (3 months to <18 years old) diagnosed with chronic pain has not been characterized. However, generating evidence based on randomized clinical trials in this population has been extremely challenging. The current investigation illustrates the use of clinical trial simulations (CTSs) as a tool for optimizing doses and protocol design for

Prediction of treatment response

ARTICLE OPEN

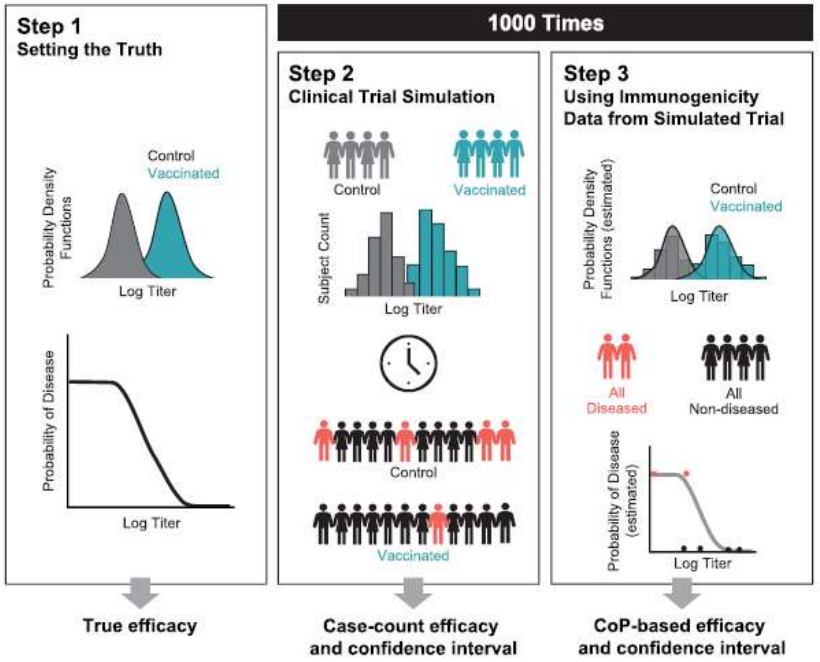
Check for updates

A method to estimate probability of disease and vaccine efficacy from clinical trial immunogenicity data

Julie Dudášová[1,2], Regina Laube[3], Chandni Valiathan[4,8], Matthew C. Wiener[4,9], Ferdous Gheyas[5], Pavel Fišer[6], Justina Ivanauskaite[6], Frank Liu[7] and Jeffrey R. Sachs[5]✉

Vaccine efficacy is often assessed by counting disease cases in a clinical trial. A new quantitative framework propo ("PoDBAY," Probability of Disease Bayesian Analysis), estimates vaccine efficacy (and confidence interval) using imm biomarker data collected shortly after vaccination. Given a biomarker associated with protection, PoDBAY describes t between biomarker and probability of disease as a sigmoid probability of disease ("PoD") curve. The PoDBAY fram illustrated using clinical trial simulations and with data for influenza, zoster, and dengue virus vaccines. The simula demonstrate that PoDBAY efficacy estimation (which integrates the PoD and biomarker data), can be accurate and than the standard (case-count) estimation, contributing to more sensitive and specific decisions than threshold-bas protection or case-count-based methods. For all three vaccine examples, the PoD fit indicates a substantial associatio biomarkers and protection, and efficacy estimated by PoDBAY from relatively little immunogenicity data is predicti standard estimate of efficacy, demonstrating how PoDBAY can provide early assessments of vaccine efficacy. Metho can help accelerate and economize vaccine development using an immunological predictor of protection. For exa current effort against the COVID-19 pandemic it might provide information to help prioritize (rank) candidates both and earlier in development.

npj Vaccines (2021)6:133; https://doi.org/10.1038/s41541-021-00377-6



Prediction of treatment performance – from RCT to RWE

BJCP British Journal of Clinical Pharmacology

DOI:10.1111/bcp.12151

Not-in-trial simulation I: Bridging cardiovascular risk from clinical trials to real-life conditions

Anne S. Y. Chain,[1,2] Jeanne P. Dieleman,[2] Charlotte van Noord,[3] Albert Hofman,[3] Bruno H. Ch. Stricker,[3] Meindert Danhof,[1] Miriam C. J. M. Sturkenboom[2,3] & Oscar Della Pasqua[1,4]

[1]Leiden/Amsterdam Center for Drug Research, Division of Pharmacology, Leiden University, 2300 RA, Leiden, The Netherlands, [2]Department of Medical Informatics, [3]Department of Epidemiology, Erasmus Medical Centre, 3015 GE, Rotterdam, The Netherlands and [4]Clinical Pharmacology Modelling & Simulation, GlaxoSmithKline, Uxbridge UB11 1BT, UK

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Keywords
model-based drug development, risk management, observational cohorts, pharmacokinetic–pharmacodynamic modelling, QTc interval prolongation, sotalol

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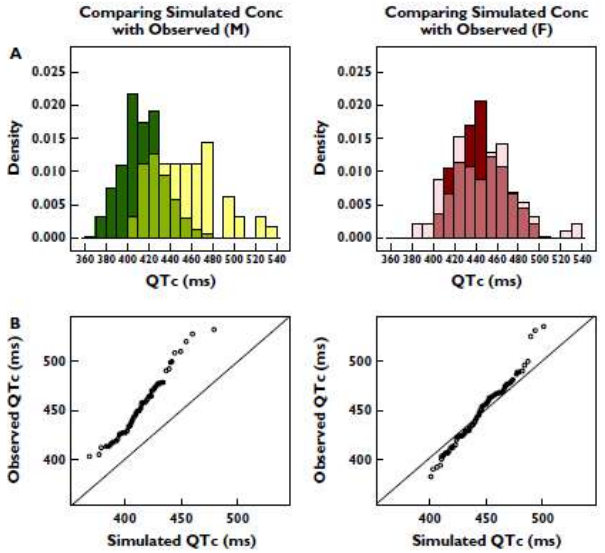
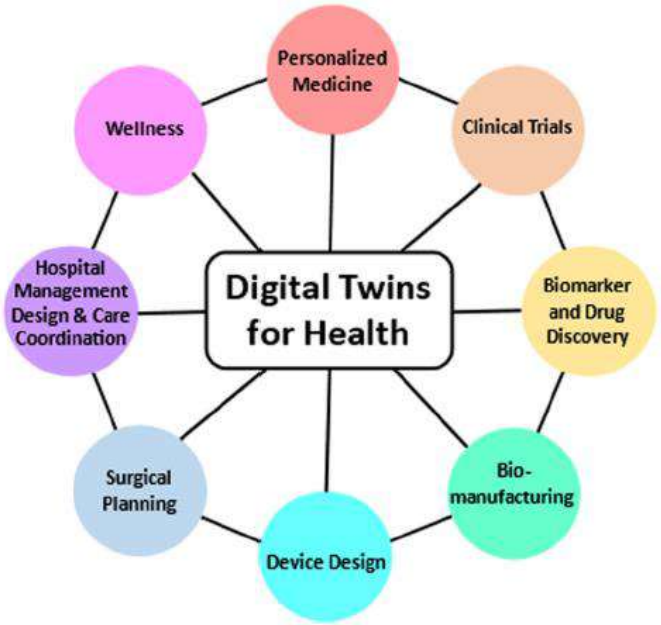
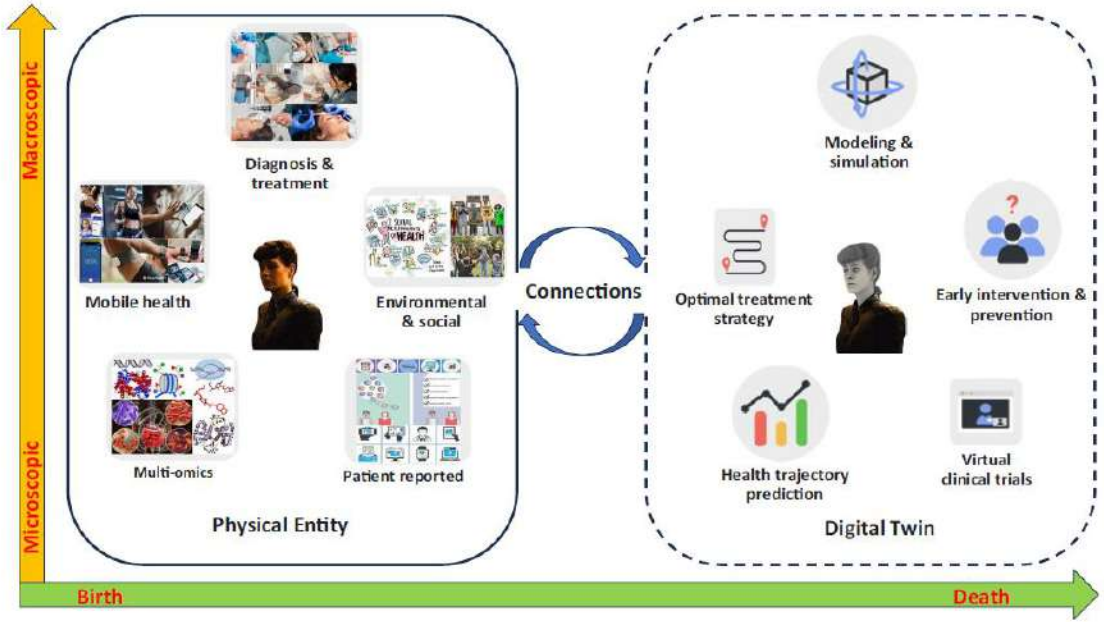
Accepted Article Published Online
25 April 2013

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

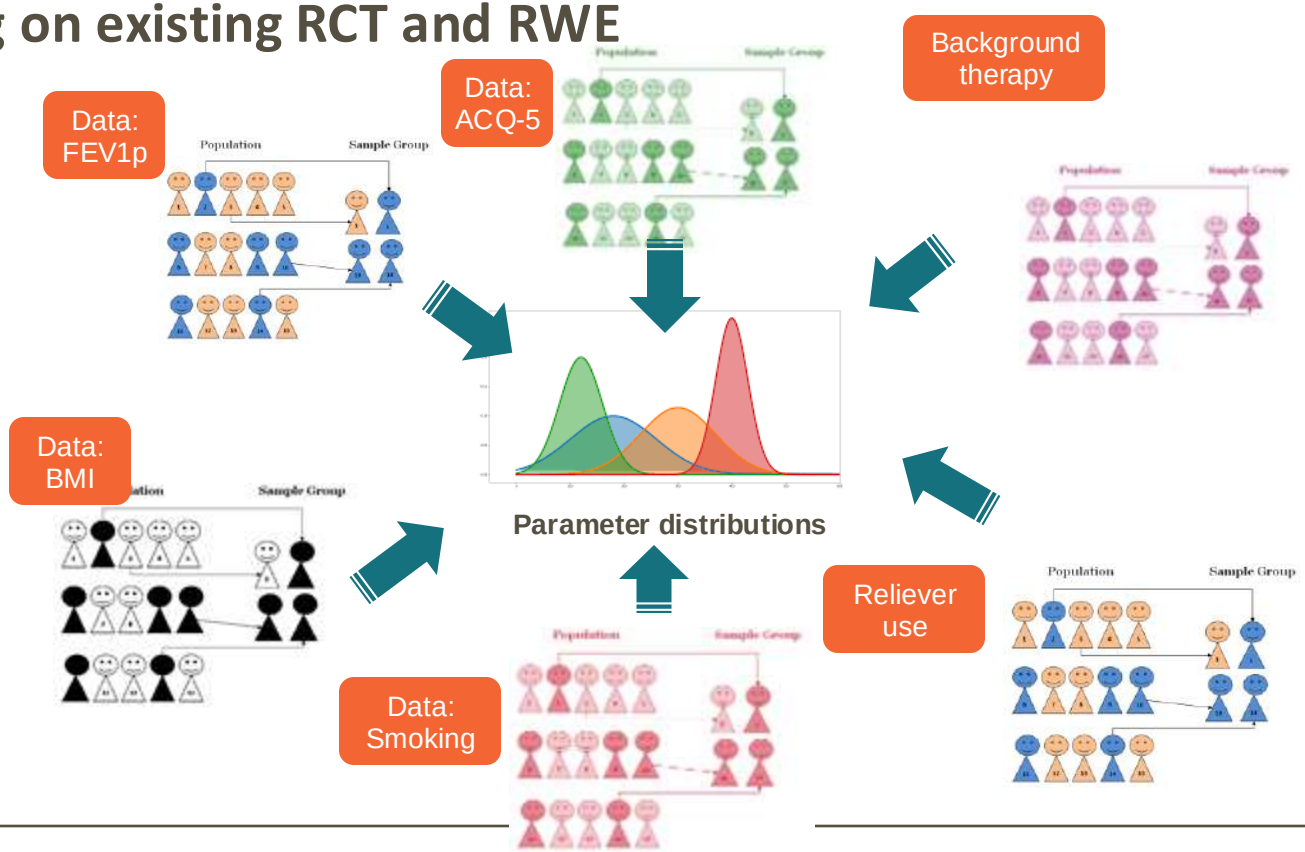


Generating Virtual Patients & Digital twins





Capitalising on existing RCT and RWE



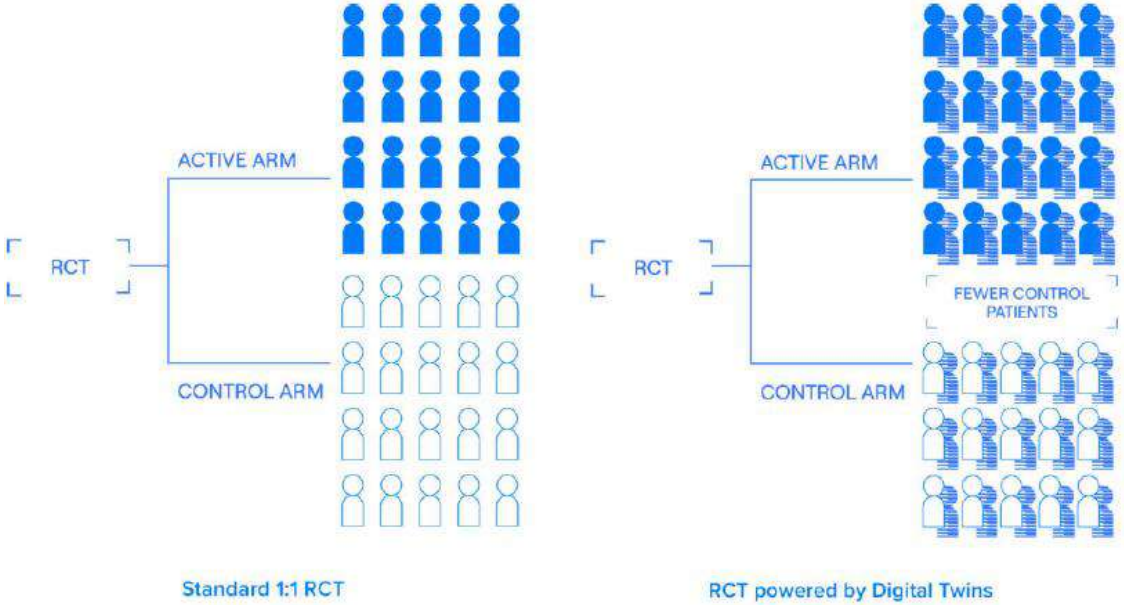
What is the difference?

Resampling, multivariate distribution, historical control, patient matching, digital twins

So, a participant's digital twin is **not** data from a matched patient in the historical dataset. In fact, it is **not** like a new patient at all; rather it is a model based forecast for the future clinical outcomes of a specific trial participant.

- To date most models are primarily based on ***deep neural networks, machine learning and AI,*** and describe empirical associations.
- There has been limited effort to identify mechanism-based models that ensure a biological plausibility

Tackling practical limitations: Digital twins



Generating Digital Twins

Increasing the efficiency of randomized trial estimates via linear adjustment for a prognostic score

"Super-covariates": Using predicted control group outcome as a covariate in randomized clinical trials

Björn Holzhauer[1] | Emmanuel Taiwo Adewuyi[2]

Holtzhauer et al., Pharm Stat. 2023;22:1062–1075
Schuler et al. Int J Biostat 2022; 18(2):329-356

Summary

1. Evidence generation: from data to models to paediatric patients
2. Drug-disease modelling, trial models, population models
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4. Examples: experimental protocol optimisation, translation and extrapolation
5. Clinical trial designs: RCT, RWE, digital twins, virtual cohorts
6. Q&A

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Research Collaborators and Postdoctoral Fellows are Welcome!

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gsk

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ERAMET

Bambino Gesù Ospedale Pediatrico

conect 4children
Collaborative Network for European Clinical Trials for Children

ERA 4TB
European Regimen Accelerator for Tuberculosis
IMI AMR Accelerator

UCL TRO
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