Model Informed Drug Development and Regulatory Decisions Today and Tomorrow

An Industry Perspective

Sandy Allerheiligen, PhD

October 2015

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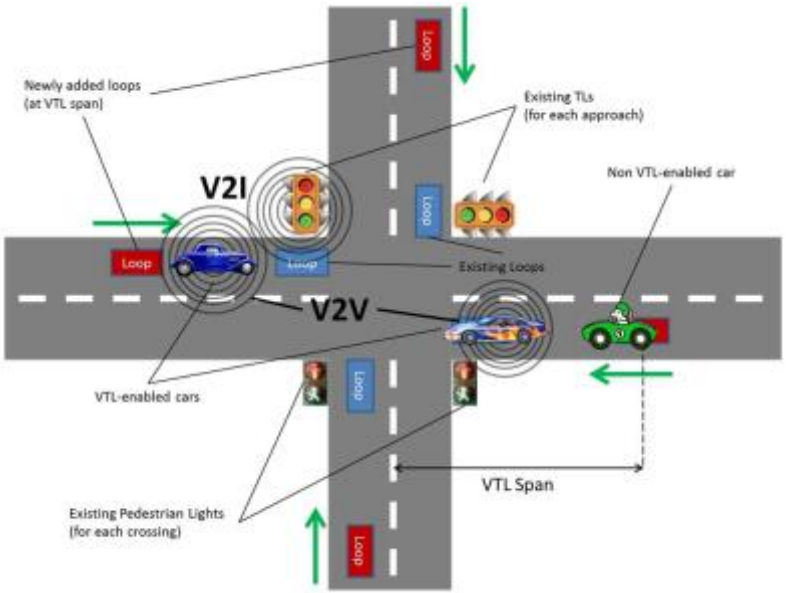
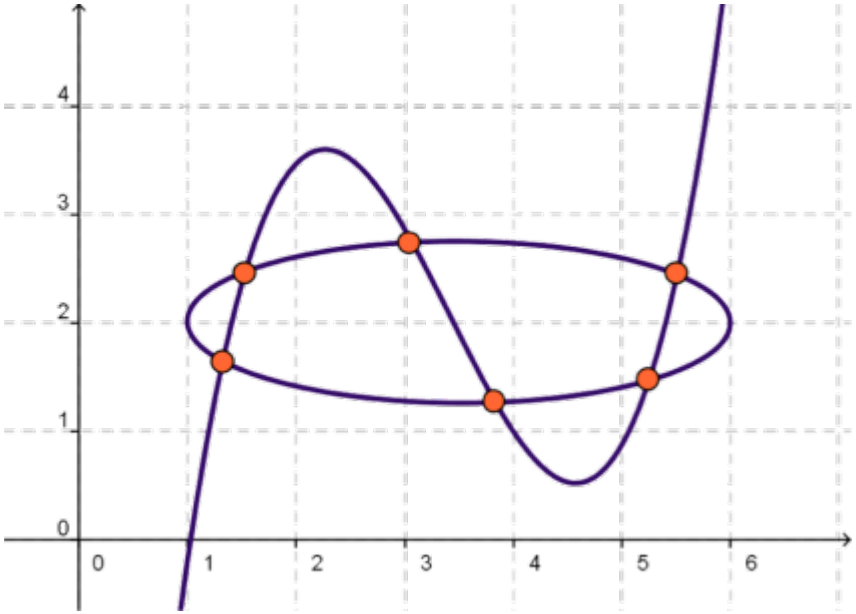
Model Informed Drug Development: Intersection between regulatory, industry, centers of expertise (CROs), and academia





•https://cdn.auckland.ac.nz/assets/engineering/about/our-research/images/iande/cl-vtl-intersection.jpg

•http://www.maa.org/sites/default/files/images/upload_library/46/stemkoski/cramer/Fig_1.png

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It is all about the question…

"He still believes that we get dose wrong most of the time." Bob Temple
Brookings July 2015

" We are not adequately understanding how patients conform to the dosing schedule and protocol. The lack of adherence overshadows traditional variability and likely keeps us from truly understanding both safety and efficacy."

Carl Peck
Brookings July 2015

•http://www.highjump.com/blog/supply-chain-management-technology/how -changing-demographics-will-affect-the-supply-chain

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The Challenge – An Answer

INPUTS

- Data
- Clearly Defined Assumptions
- Ideas & Scientific Knowledge

Integrated, mathematical representation of all inputs

OUTPUTS

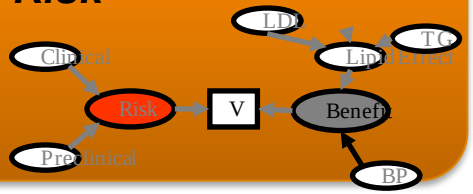
- Portable, integrated form of knowledge
- Exploration of Knowledge Gaps
- Enhanced Understanding

Enhanced Decision Making

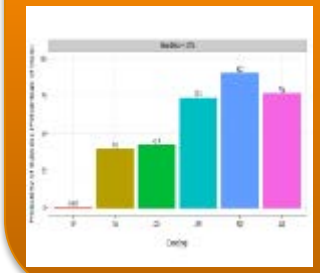
Internal, Regulators, Payors, Physicians, and Patients

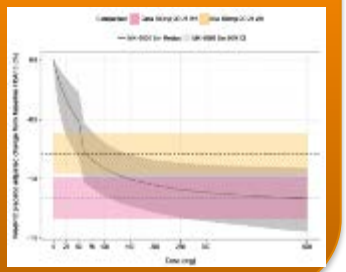
What is our goal: Enabling decisions from target to patient to quantitatively interpret pharmacology, disease, and exposure-response to optimize value for patients, providers, and payers…

Decision Models: Benefit -Risk

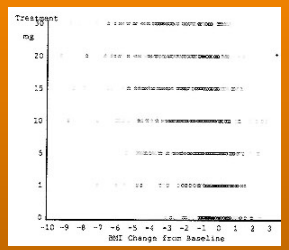


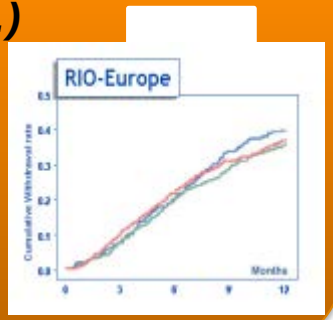
Comparator Models





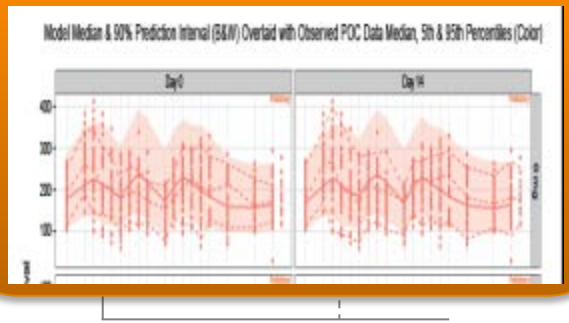
Understanding Variability (adherence,…)





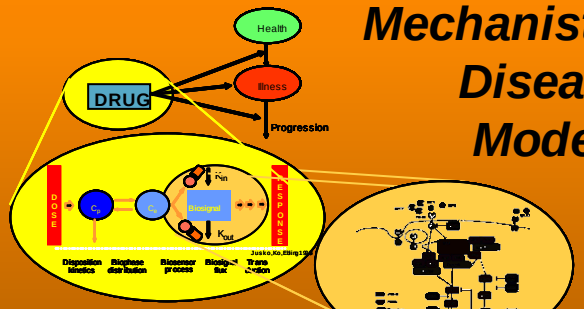
Integrated Models

PK/PD Models



Time

Mechanistic Disease Models

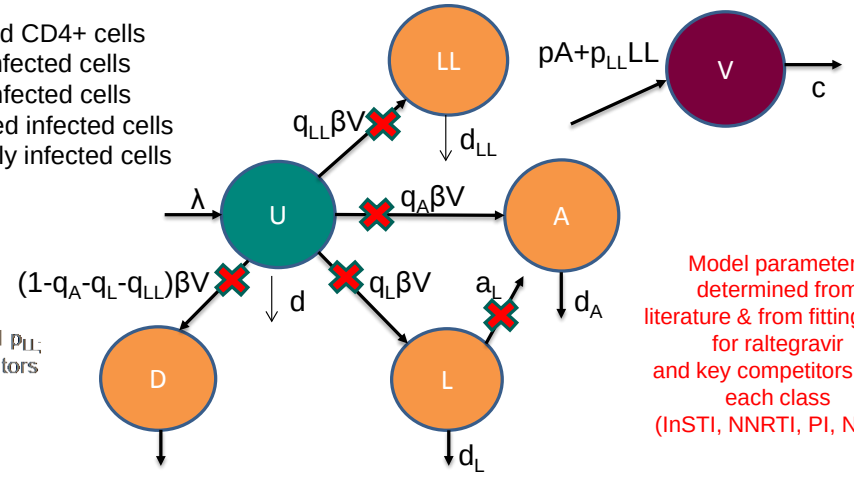


Right Target Right Drug Right Dose Right Patients

Integrating Knowledge, Enabling Decisions and Enhancing Submissions

Impacting Regulatory Approvals: HIV Mechanistic Modeling

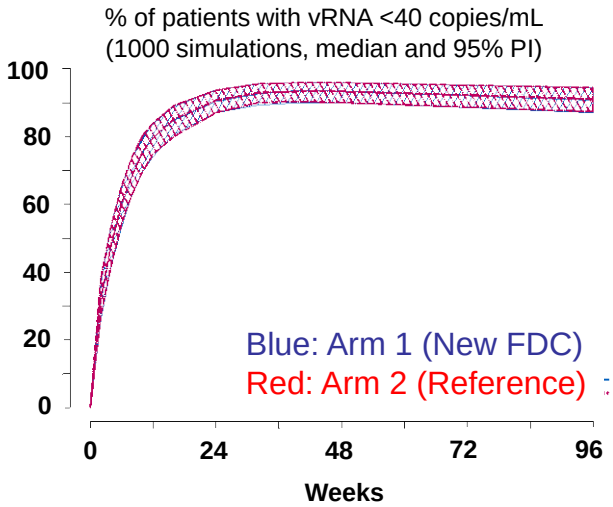
U = Uninfected CD4+ cells
A = Actively infected cells
L = Latently infected cells
LL = Long-lived infected cells
D = Defectively infected cells
V = Virus



PIs reduce p and p_{LL}; RTIs, entry inhibitors reduce β

Model parameters determined from literature & from fitting data for raltegravir and key competitors from each class (InSTI, NNRTI, PI, NRTI)

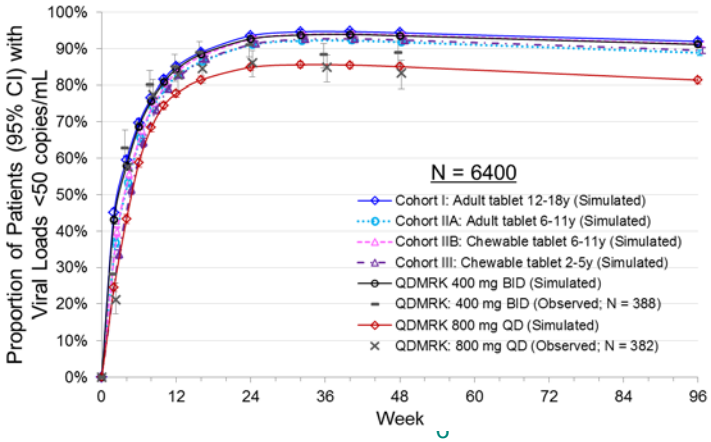
HIV Viral Dynamics Model



Questions from EMEA regarding appropriateness of pediatric doses

M&S used to demonstrate nearly identical efficacy as that seen in adults expected for children and adolescents given adult tablet or chewable formulation.

Result: Formulations approved for pediatrics, providing for a significant unmet medical need



99.6% POS of achieving non-inferiority to reference despite lack of bioequivalent PK

Result: No Phase 3 study needed for registration, save 2 years time and $37M

Wenning L, Risk M, et. al, 2015

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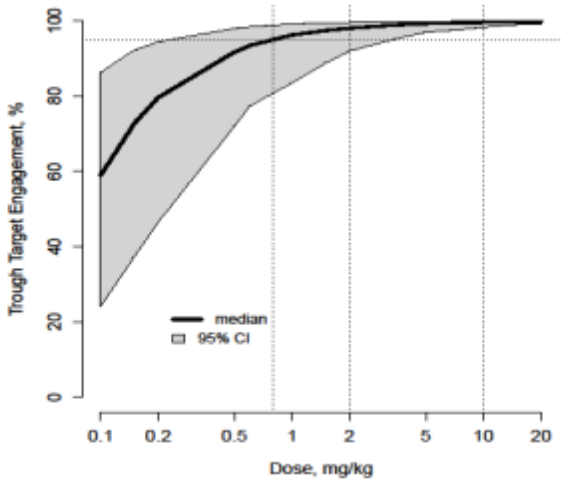
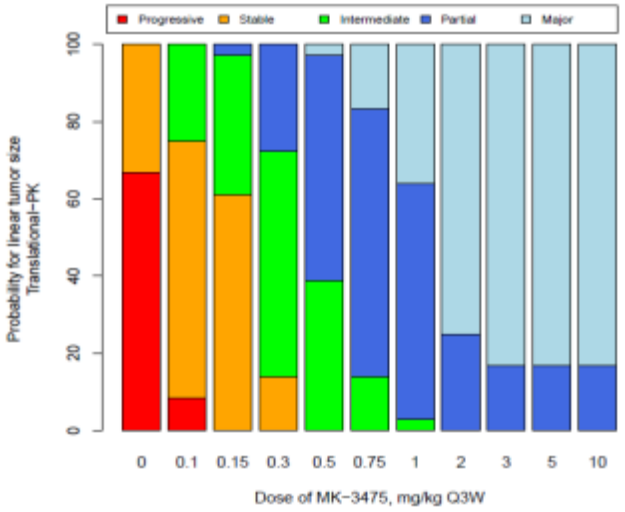
Keytruda: Selection of optimally efficacious dose

- At that time, very limited data on efficacy
- PK-PD: 95% target engagement at 2Q3W
- Translational PK-PD: maximal at 2Q3W
  - Hybrid modeling of mouse and human PK data
  - In vitro and in vivo (clinical) experiments
  - Prediction of optimal tumor exposure
- Two approaches fortify each other
  - IL2 and Tran PK/PD based on mouse data Converge on 1 or 2 mg/kg Q3W as lowest dose, supporting 2 mg/kg Q3W





→2 mg/kg Q3W successfully selected as lowest dose in clinical program

De Alwis *et al.,* AADV Workshop 2015

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•http://people.howstuffworks.com/population-six-billion.htm

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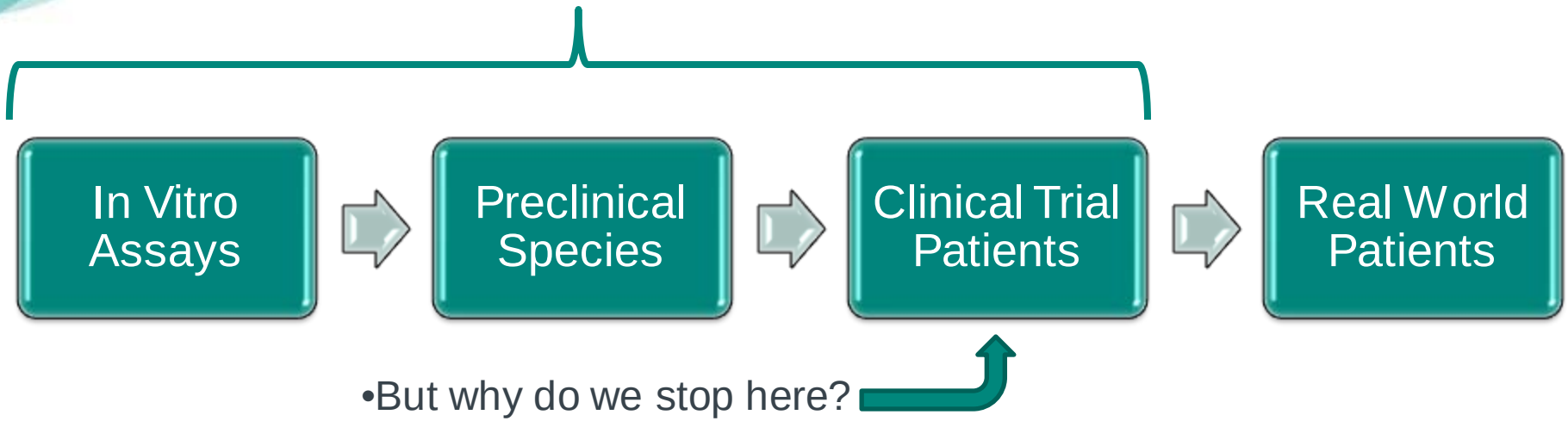
Translating clinical trial patient (CTP) to the real world patient (RWP)

- Current state: focus of "translational" sciences



- But why do we stop here?

- ***Our ultimate goal is to understand the real world effectiveness of our therapies, which is only partially informed by clinical trial efficacy***

- ***This requires robust translation between patient "species" from the randomized clinical trial to the real world patient***

- **CT to RW translation requires a quantitative framework around the 5 C's – characteristics of patients, costs, compliance, co-morbidities and concomitant treatments**

Digital health technologies improving information capture

"No covariate can have a bigger impact than not taking the drug." **Y. Wang (FDA)**

•Date and time stamp
•(Automatic capture)

•SMART
•DOSING

•PK Concentrations

•SMART
•SAMPLING

•Patient identity

•Biomarkers

•SMART
•ANALYTICS

•Informed consent

SMART PKPD

ePRO (eDiaries)

Smart Dosing

Finger-stick Dried Blood Spot

Point of Care Diagnostics

DNA profiling/Identity

Real-time analytics

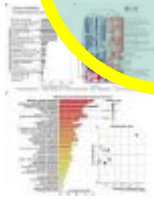
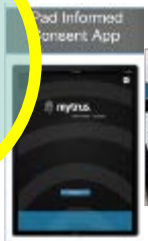
eConsent










•Reference for the images: Google images/vendor websites

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Clinical Trials: Site Model to Patient-Centric

•Hospital

H I G H

•Cost
•Skill
•Burden

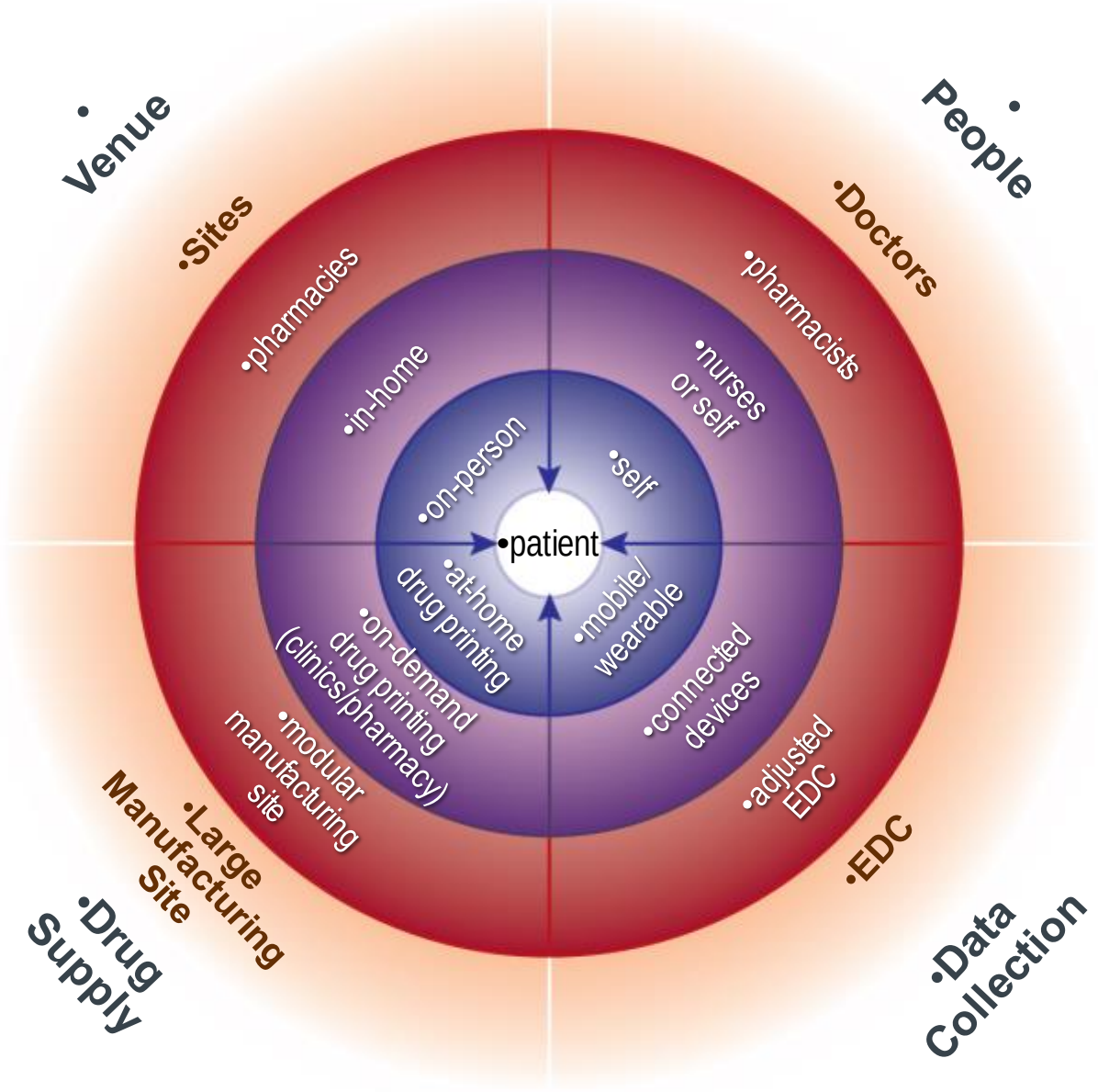
•*Bring the patient to the trial*

•*Bring the trial to the patient*

L O W

•Cost
•Skill
•Burden

•Patients



•Modification of: http://www.christenseninstitute.org/wp-content/uploads/2013/09/LocusofCare.jpg

From Models to Real-time Simulation to Bedside

Our current models are non-interactive, non-accessible for non-modeler


MODELING & SIMULATION REPORT

CONFIDENTIAL

Merck Research Labs
Merck & Co, Inc

Program: Authors: [Author (affiliation) – indicate contact details for primary author]*
[Author (affiliation)]
[update as necessary]...

•;Model [sing ADVAN3, TRANS4
ples
SCRIPTION

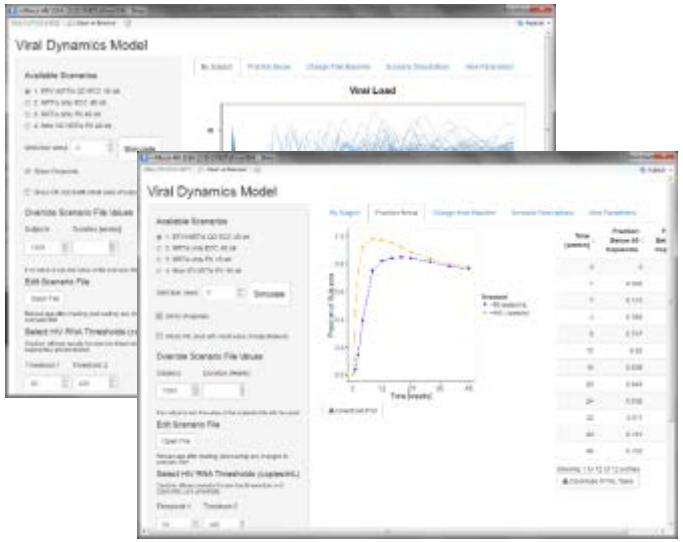
•$INPU) samp5l)
IC AMT=DOSE RATE
EVID MDV CMT CLX V1X QX V2X SDIX SDSX
•$DATA wexample1b.csv IGNORE=C

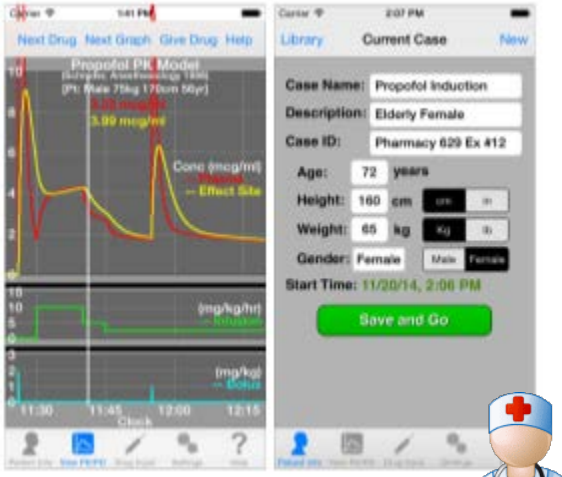
•; INSERT $PRIOR STATEMENT HERE

•$SUBROUTINES ADVAN3 TRANS4

•$PK
•MU_1=THETA(1)
•MU_2=THETA(2)
•MU_3=THETA(3)
•MU_4=THETA(4)
•CL=DEXP(MU_1+ETA(1))
•V1=DEXP(MU_2+ETA(2))
•Q=DEXP(MU_3+ETA(3))
•V2=DEXP(MU_4+ETA(4))
•S1=V1

Open our models through interactive tools (e.g. R-shiny)
Provide real-time simulation for the non-modeler
Real-time Q&A for teams: increase communication and impact of the model





And beyond
Launch drug with Label plus app for physician
Model-based treatment individualization at the bedside
High model qualification needs, high patient impact

Special thanks to Drs. T Kerbusch and W. Polland,

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Changing Environment….

What are the new intersections?

Model Qualification

Technologies to understand adherence

Real World Data

Models at the Bedside

Clinical Trial Advances

Others?

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