

Mechanism-based Risk Assessment

In Drug Development

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Problems with a target-based R&D:

- The gap between target site and bedside is currently bridged by “word models”.
- The bridge needs pillars (= biomarkers).
- The bridge needs connectors between pillars (= mathematical-statistical models).
- The reductionist approach (1 disease \Leftrightarrow 1 target \Leftrightarrow 1 drug) together with high throughput screening has accelerated the rate of discovery and the rate of failure of clinical projects.
- Discovery runs with up-to-date technology and overwhelms development with an avalanche of poorly understood projects.
- Development itself is stuck with the PCT (placebo controlled trial) technology of 60 years ago ($p < 0.05$).
- Nobody calculated the increased risk of R&D investment resulting from this technology clash.
- The answer of Big Pharma investors: “Let’s get out...”
- That results in opportunities for innovative ideas!

How do we assess risk?

- “gut feeling”
- Trust the expert
- Experience: “history repeats itself”
- Empiricism: draw inferences from similar situations

If I could do it all over again I would decide...

You can do it all over again and again... and then you can decide!

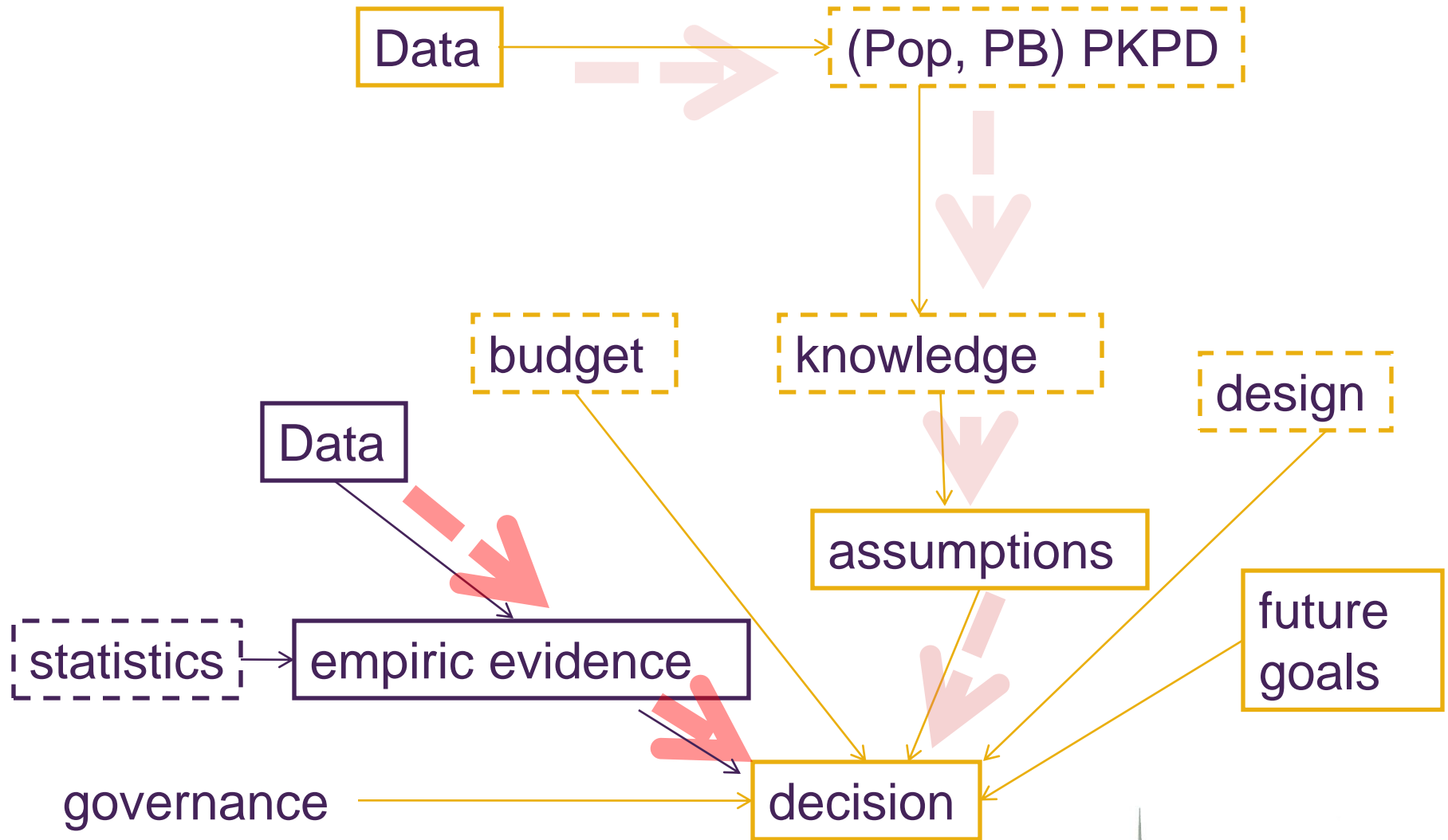
...with modelling and simulation!

EMA Workshop on M&S (30 Nov – 01 Dec 2011, London)

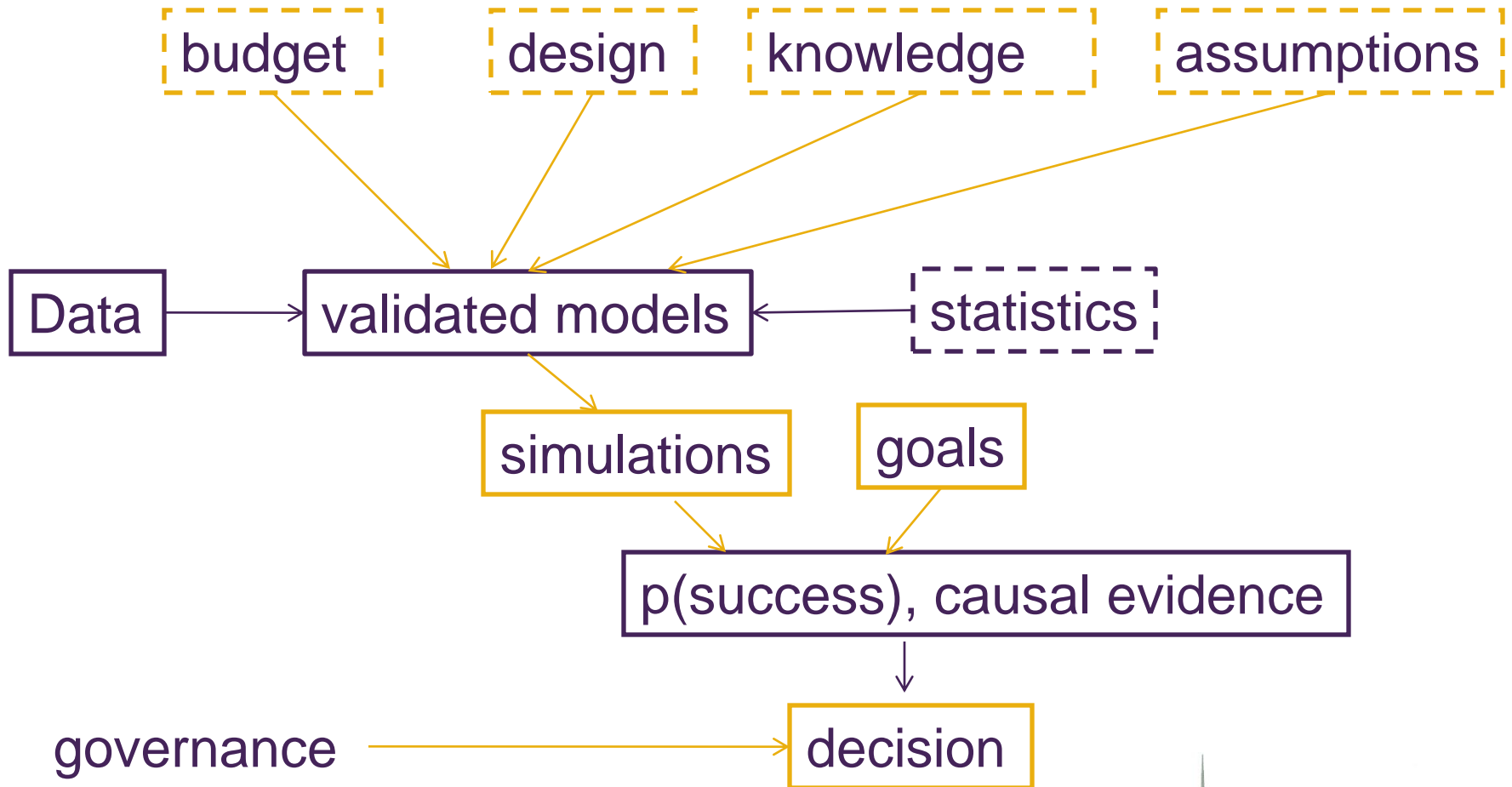
The changing paradigm of decisions:

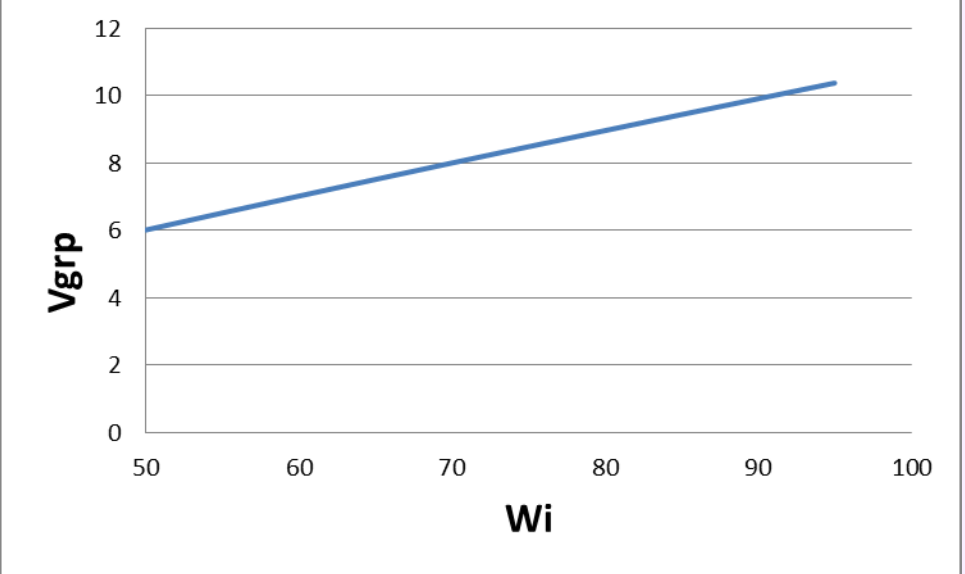
1. Decisions will not impact the present but the future.
2. An empiric understanding of the present (Type 1 error (α) rate of false positive and Type 2 error (β) rate of false negative) **does not guarantee control over the future.**
3. Why are most of our decisions based on $p < 0.05$?
4. The significance level p tells us nothing about the future success rate or the risk of failure in the future.
5. Irrational decision making has infected pharmaceutical research and development from the top down: starting from market approval based on $p < 0.05$
6. The healthcare providers (payers) have already awoken. The regulators may soon wake up!

How do we support our current decisions?



What are model-based decisions?



Language	Ontology														
Word Models	“volume depends on bodyweight”														
Picture models	 <table border="1" data-bbox="726 297 1696 865"> <caption>Data points for the Vgrp vs Wi graph</caption> <thead> <tr> <th>Wi</th> <th>Vgrp</th> </tr> </thead> <tbody> <tr> <td>50</td> <td>6.0</td> </tr> <tr> <td>60</td> <td>7.0</td> </tr> <tr> <td>70</td> <td>8.0</td> </tr> <tr> <td>80</td> <td>9.0</td> </tr> <tr> <td>90</td> <td>10.0</td> </tr> <tr> <td>95</td> <td>10.5</td> </tr> </tbody> </table>	Wi	Vgrp	50	6.0	60	7.0	70	8.0	80	9.0	90	10.0	95	10.5
Wi	Vgrp														
50	6.0														
60	7.0														
70	8.0														
80	9.0														
90	10.0														
95	10.5														
Mathematical models	$V_{\text{grp}} = V_{\text{pop}} \left(\frac{W_i}{70} \right)^\beta$														
Stochastic models	$\log(V_i) \sim N(\log(V_{\text{pop}}) + \beta \log(W_i/70), \omega_V^2)$														

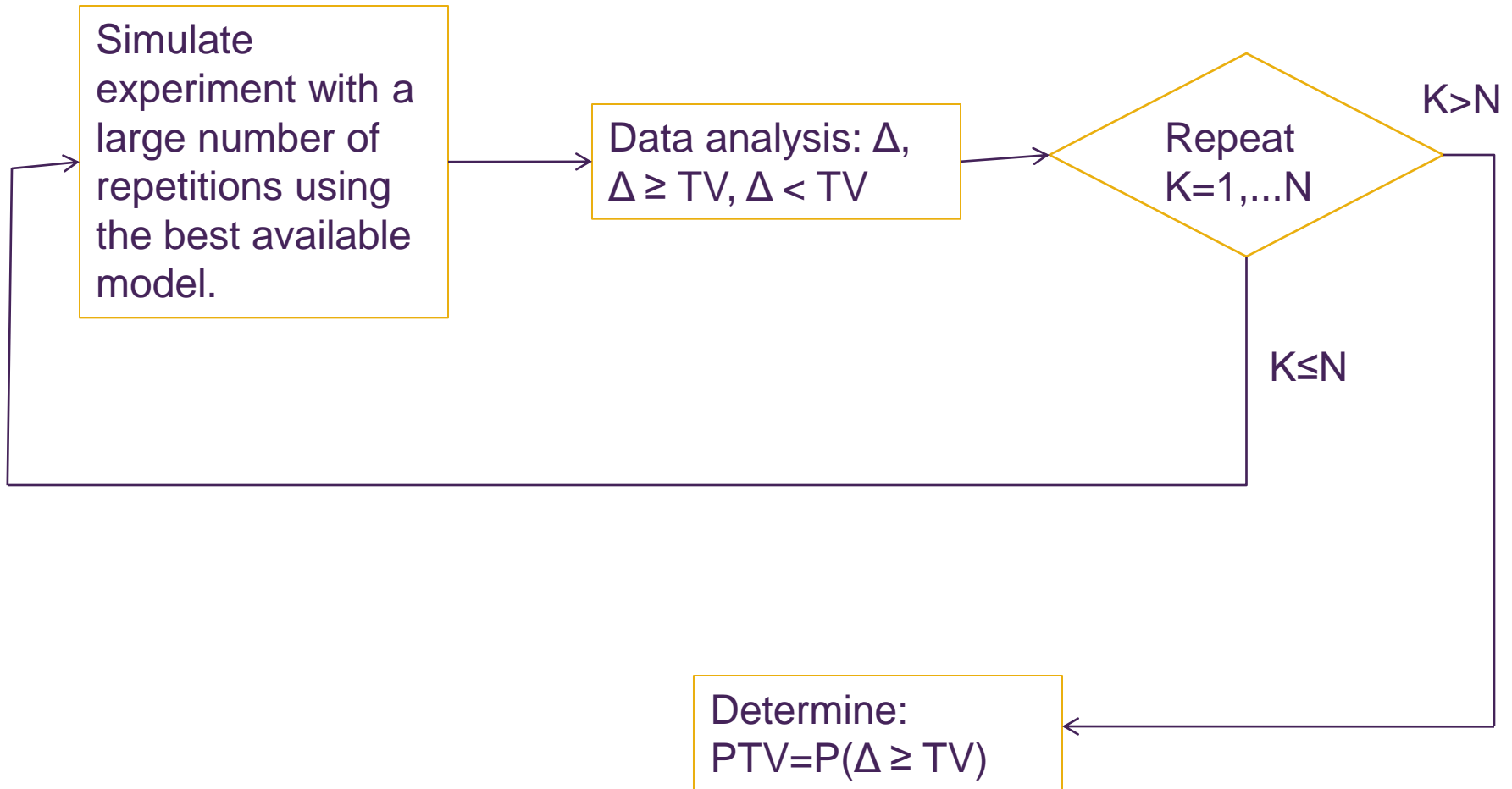
For risk analysis we need the probability distributions defined in stochastic models.

The Process of Risk Analysis: Notation

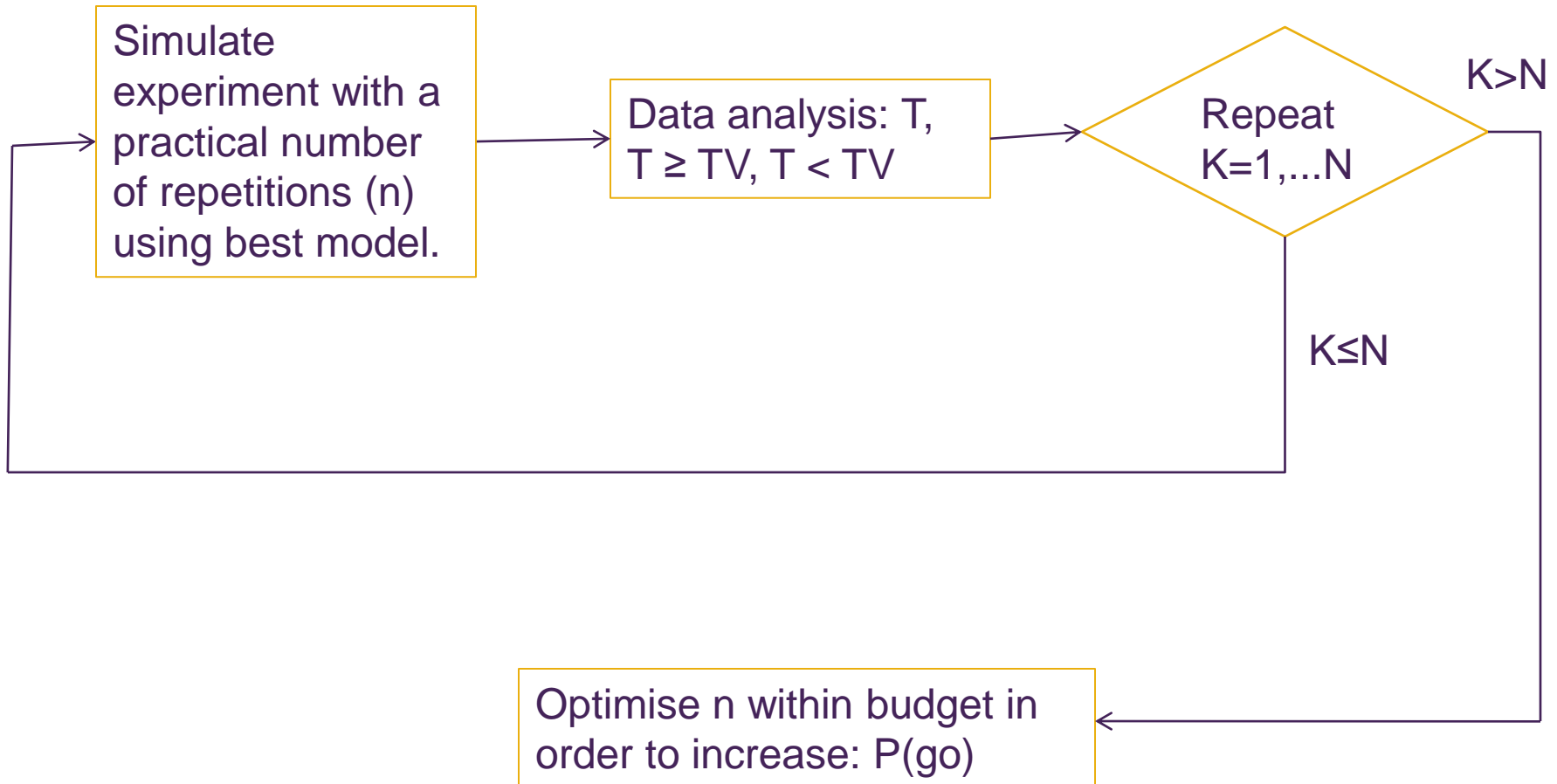
Symbol	Description
Δ	Denotes the "true" experimental outcome. It is assumed that Δ can be simulated with a very large number of repetitions (wells, animals, subjects, etc.).
T	Denotes the estimated experimental outcome. T can be obtained by simulating with a practical number of repetitions.
TV	The target value (TV) denotes the minimal desired outcome.
$P(\text{go}) = P(T \geq TV)$	Probability of success
$PTV = P(\Delta \geq TV)$	The probability of achieving the target value (PTV) is a measure of the confidence in the success of the experiment. PTV is a property of the project that is independent of the design of the latest experiment.

Simulation loop with large number of repetitions to obtain:

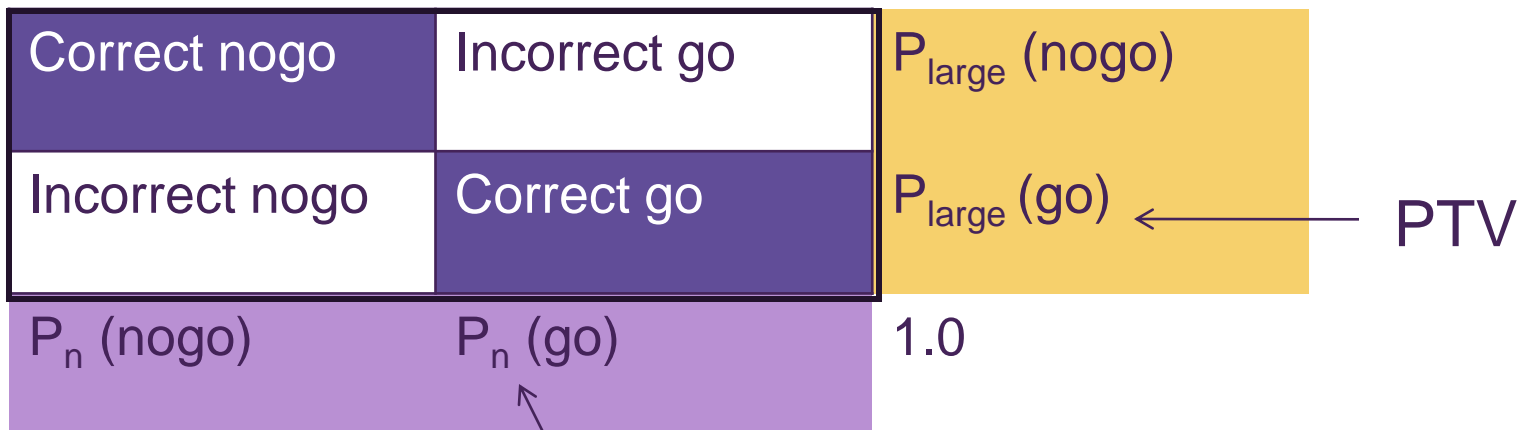
$$P_{\text{large}}(\text{go}) = \text{PTV}; P_{\text{large}}(\text{nogo})$$



Simulation loop with a practical number of repetitions to obtain: $P_n(\text{go})$; $P_n(\text{nogo})$



Performance Assessment

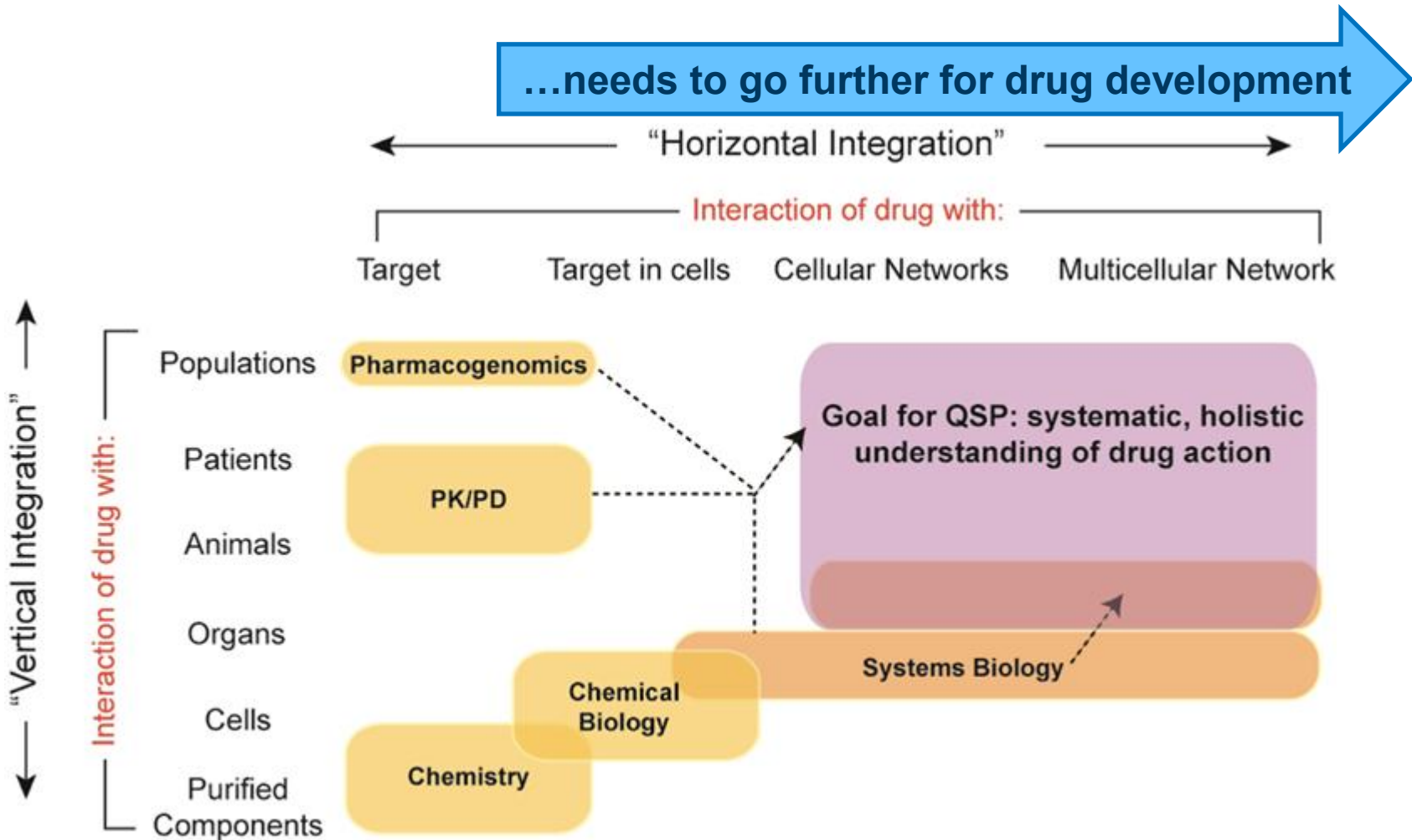


$P(\text{go}) = \text{probability of success}$

$$P(\text{correct}) = \text{Correct nogo} + \text{Correct go}$$

0.6	0.25	0.85
0.0	0.15	0.15 (PTV)
0.6	0.4 p(go)	1.0

Building the model continuum

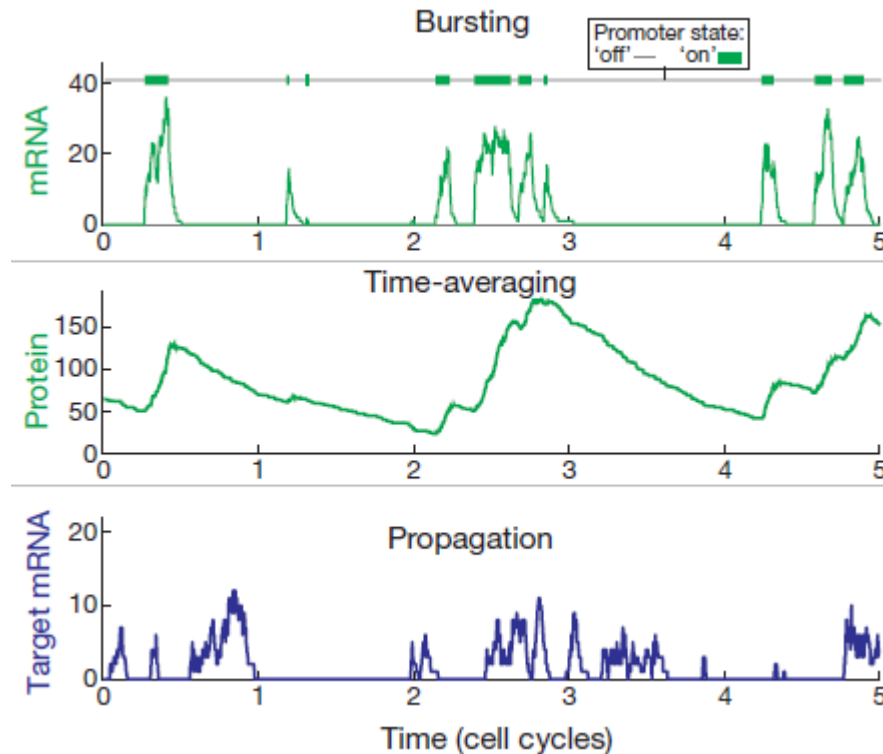


...taken from the NIH Whitepaper on QSP

REVIEWS

Functional roles for noise in genetic circuits

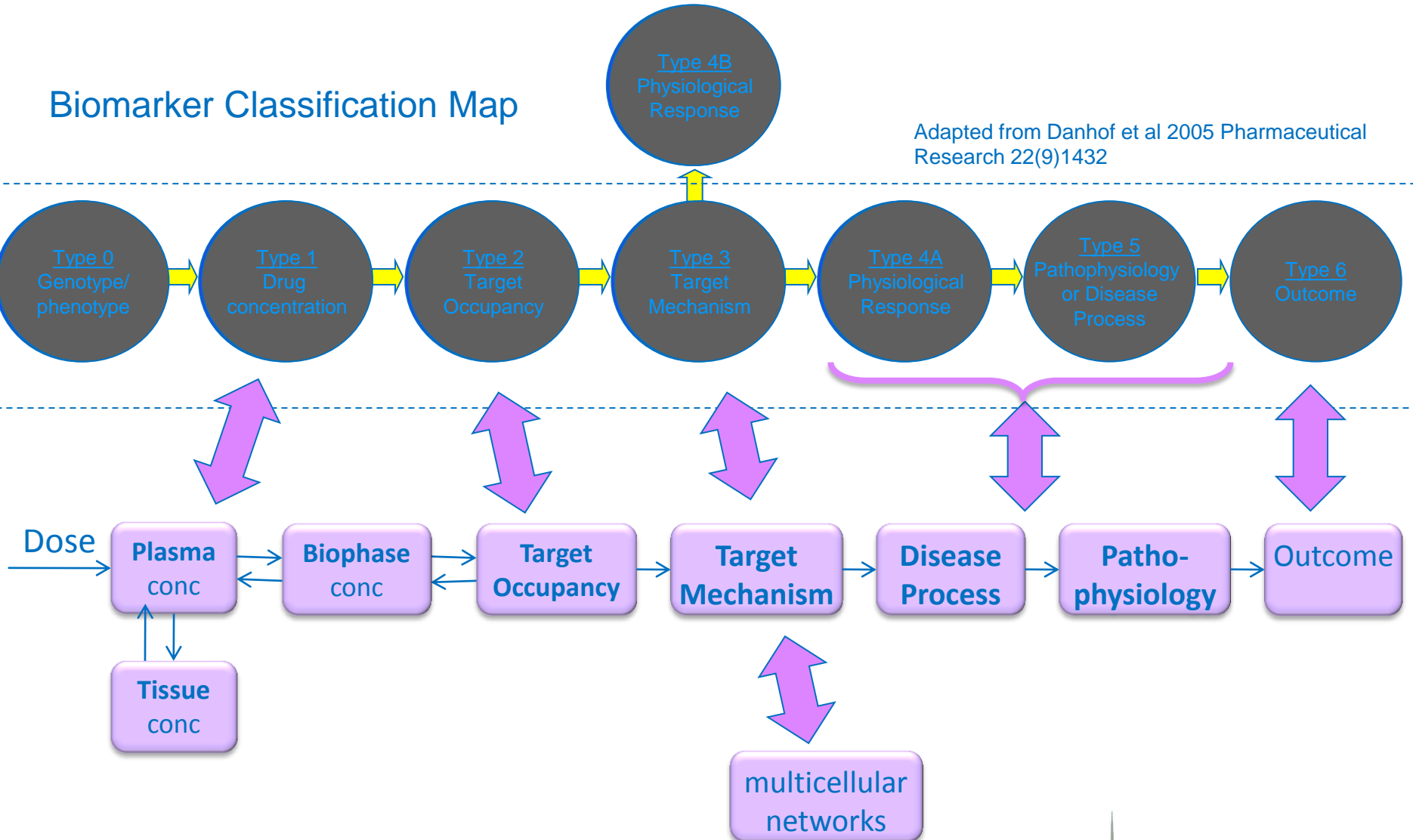
Avigdor Eldar¹† & Michael B. Elowitz¹



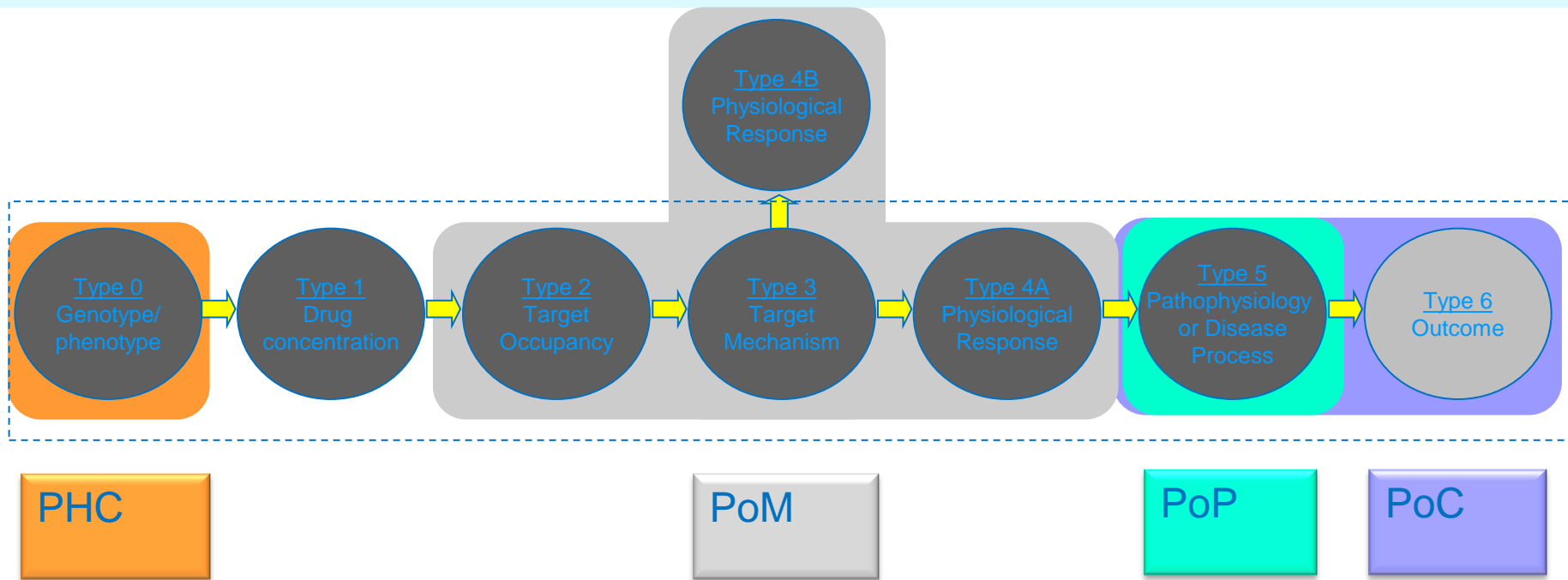
Horizontal Integration: Pharmacology Model to Project Model

Biomarker Classification Map

Adapted from Danhof et al 2005 Pharmaceutical Research 22(9)1432



Pharmacology model: mapped to discovery and development...



PoM: Is degree, duration of target engagement sufficient?

PoP: Is there a beneficial effect on targeted disease process or pathophysiology?

PoC: Does the effect on clinical outcome reach expectations?

PHC: Can subgroups of patients who benefit be identified?

Roles that build and maintain the model continuum

Phase	Biologist	Information Scientist	Pharmacologist	DMPK specialist	Pharmacometrician	Statistical modeller	Health Economics Modeller	Expertise, Activity (Methods)
Target identification	■	■	■					Computational Biology (Simbiology, MoBi,..)
Hit & Lead Generation	■	■	■					Mechanistic PD modelling, build model continuum (Simbiology, MoBi,..)
Preclinical Development		■	■	■	■			Physiology-based PK, update model continuum with animal PKPD, simulate FTIM (PKSim, MoBi, Simcyp, Matlab,...)
Toxicology			■	■	■			Add safety to model continuum (PKSim, MoBi, Simcyp, ..)
Phase I			■	■	■	■		Use relevant parts of model continuum for stochastic estimation, then use it for optimal (adaptive) design of clinical studies, validate biomarkers, maintain model continuum, use for quantitative risk assessment, simulate payer interests, update health economic estimations (NONMEM, Monolix, TS2, Matlab, R, SAS, ..)
Phase II a,b					■	■	■	
Phase III						■	■	

A case study: simulate – analyse – decide!

Work through the checklist:

- Define your decision.
- Build your model.
- Identify data that capture variability, realistically.
- Define the threshold between success and failure.
- Agree with your partners on how much risk (uncertainty) you are willing to accept.
- Contact an independent consultant capable to perform the risk assessment within the available time.

The Mechanics of Risk Assessment

How is a project represented in a “simulator”?

- The simulator is a computer program that uses the *in silico* twin of a situation to produce many repetitions.
- The *in silico* twin is a mathematical/statistical model that predicts outputs from inputs.
- To be realistic the model needs to be “stochastic”; i.e. it has to represent the variability in the situation.
- The model also needs to capture the temporal development of a situation: a kinetic model.



The
difference to
engineering

A case study of risk assessment in drug development

The checklist:

Task	Response
Define the decision	<ul style="list-style-type: none">• Project X, a novel anticoagulant, safer than warfarin.• Phase 1 in healthy volunteers is finished.• A mechanism-based PKPD model exists.• Project X should only progress to phase 2 if certain criteria are likely to be met or exceeded.
Define the threshold between success and failure	<ul style="list-style-type: none">• <u>Rapid onset of a clinically relevant effect</u>: PCA should fall within 24 hours after start of therapy, or earlier, to 20% or lower.• Safety has to exceed that of warfarin: the hazard of a haemorrhage should never exceed $2 \cdot 10^{-3}$.
Acceptable risk	<ul style="list-style-type: none">• For the therapeutic effect: less than 40%.• For safety: less than 5%.
Will payer expectations be met?	<ul style="list-style-type: none">• Yes.

Here a command file to simulate a Phase 2 study.

```
%% design
SizeArm={20 20 40 40};
DoseTime={0:24:192 0:48:192 0:24:192 0:48:192}; TimeUnit='h';
DoseSize={0.25 0.5 0.5 1}; DosePerKg='yes'; DoseUnit='mg/kg';
ObservationTime{1}=[0.5, 4:4:48, 52:24:192, 192:4:250];
ObservationTime {2}=0:24:288;
NumberReplicate=200;

%% covariates
ExtCovariatePath='F:\I\WP61\CTS\data';
ExtCovariateFile='warrain_data.txt';
ExtCovariateName={'wt','sex'};
ExtCovariateType={'continuous','categorical'};
ExtIdName='id';
ExtWeightName='wt';

%% Individual parameters model
ListParameter={'ka','V','Cl','Imax','C50','Rin','kout'};
DefaultDistribution='log-normal';
Distribution_Imax='logit-normal';
Covariate={'log(wt/70)','sex'};
CovariateType={'continuous','categorical'};

pop_ka      = 1;      omega_ka   = 0.6;
pop_V       = 8;      omega_V    = 0.2;
pop_Cl      = 0.13;   omega_Cl   = 0.2;
pop_Imax    = 0.9;    omega_Imax = 2;
pop_C50     = 0.4;    omega_C50  = 0.4;
pop_Rin     = 5;      omega_Rin  = 0.05;
pop_kout    = 0.05;   omega_kout = 0.05;

betal_V     = 1;
betal_Cl    = 0.75;

rho_V_Cl    = 0.7;

%% Observations model
ModelFile='mlxt:pkpd';
ModelPath='F:\I\WP61\CTS\library';

ObservationName={'Concentration','PCA'};
ObservationUnit={'mg/L','%'};
ModelType={'continuous','continuous'};
Prediction={'Cc','E'};

ResidualErrorModel{1}='combined'; residual_a{1}=0.5; residual_b{1}=0.1;
ResidualErrorModel{2}='constant'; residual_a{2}=4;

LOQ{1}=0.1;

%% tasks
PredictionList={'Cc','E','Ad'};
RunCTS1

WriteCTS('simuldata.txt')
StatsCTS('Cc','Concentration');
StatsCTS('mean(E)','mean(PCA)');
StatsCTS('Cc>10','E<20');
PublishCTS('doc/CTSReport.tex')
```

There will be four treatment arms:

- Arm A : 0.25 mg/kg every 24 hours during 9 days
- Arm B : 0.5 mg/kg every 48 hours during 9 days
- Arm C : 0.5 mg/kg every 24 hours during 9 days
- Arm D : 1 mg/kg every 48 hours during 9 days

Size of each treatment arm:

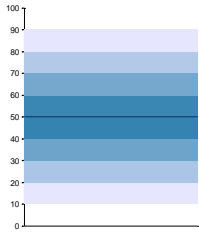
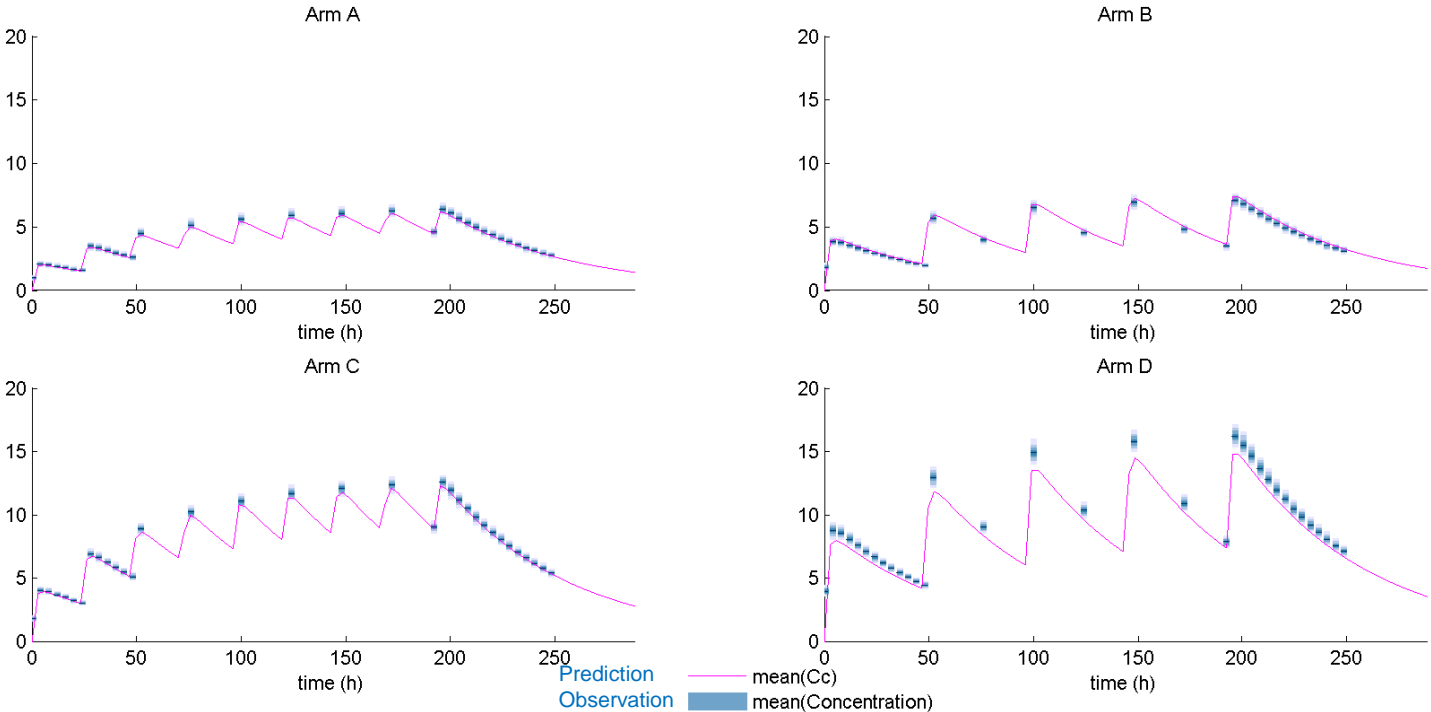
A: 20 patients

B: 20 patients

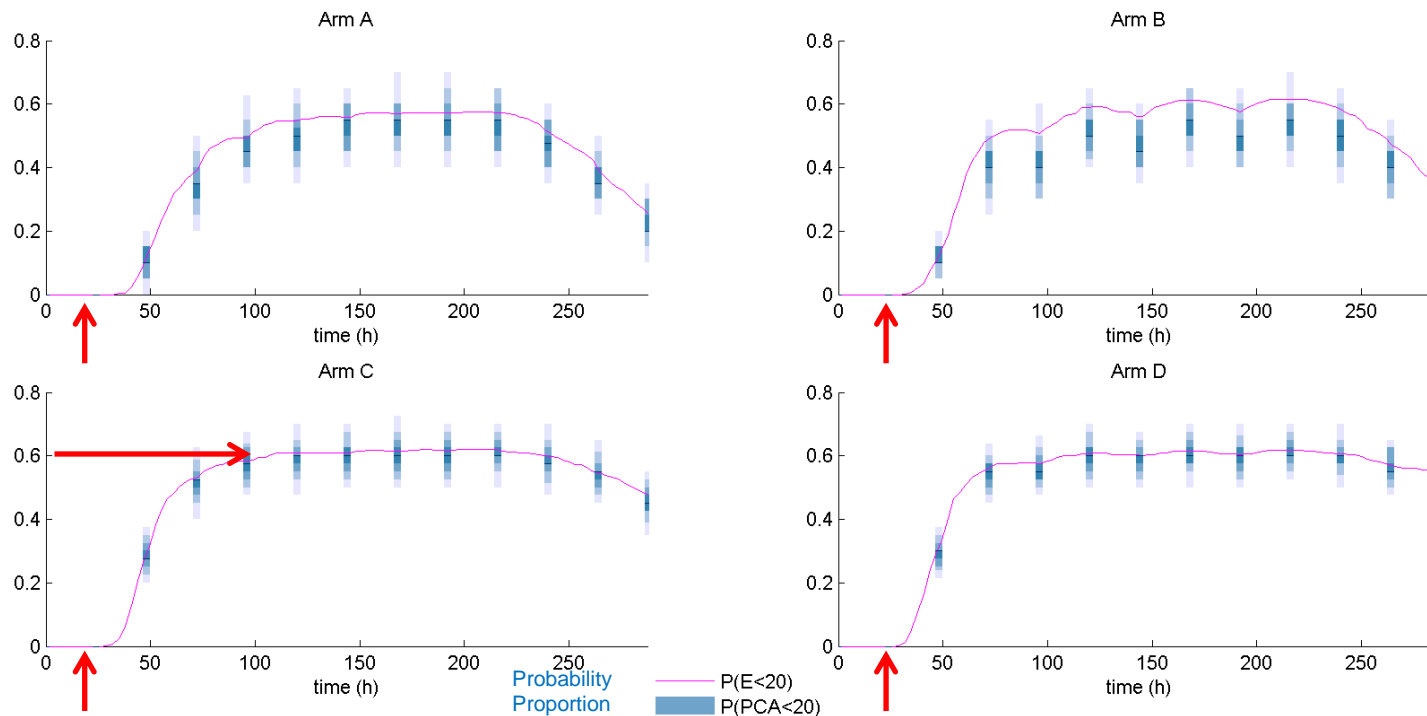
C: 40 patients

D: 40 patients

Distribution of PK profiles of 200 simulated trials.



Probability that $PCA < 20$ and observed proportion of 200 simulated trials.

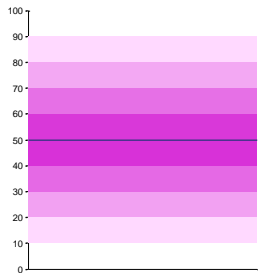
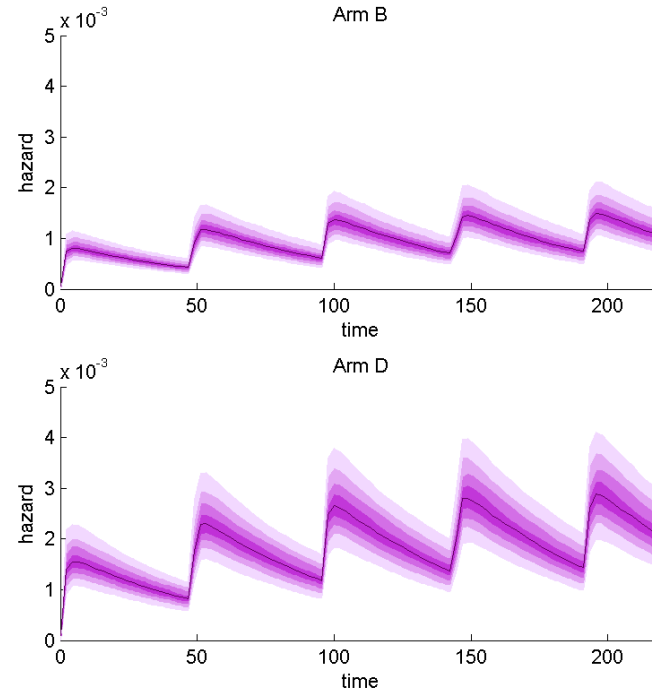
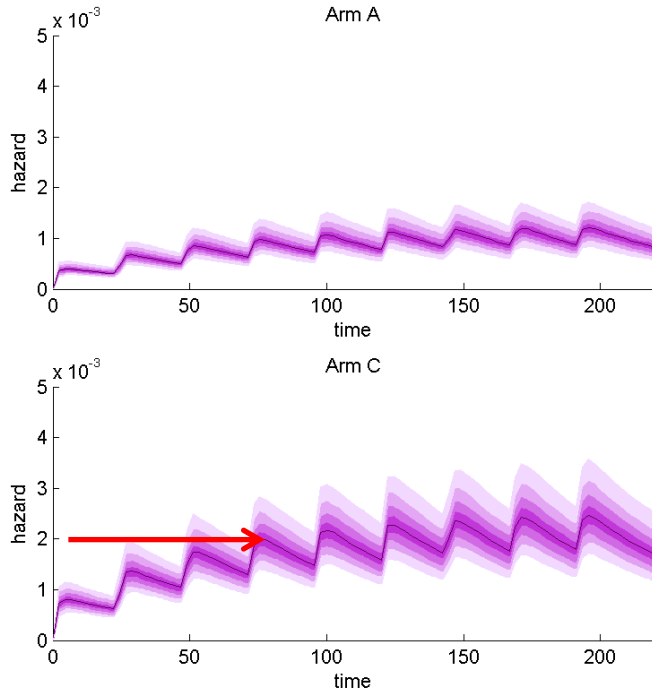


Define the threshold between success and failure

- Rapid onset of a clinically relevant effect: PCA should fall within 24 hours after start of therapy, or earlier, to 20% or lower.

Success is borderline, C.I. $30\% < \text{risk} < 50\%$

Population distribution of the “true” hazard predicted by the model. Simulating one trial with a very large number of patients (n=500) in each arm.



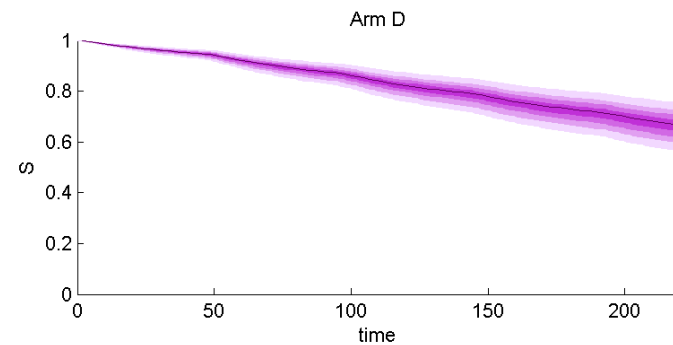
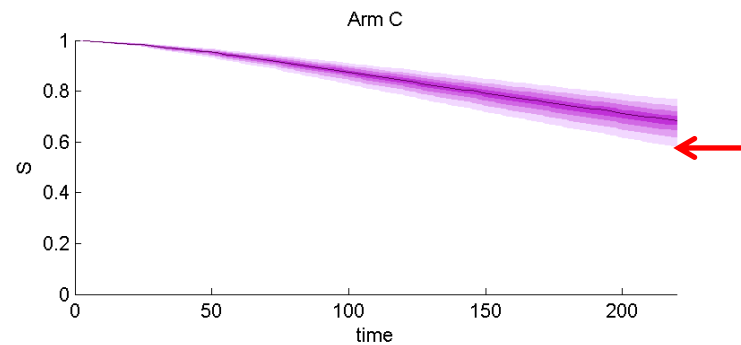
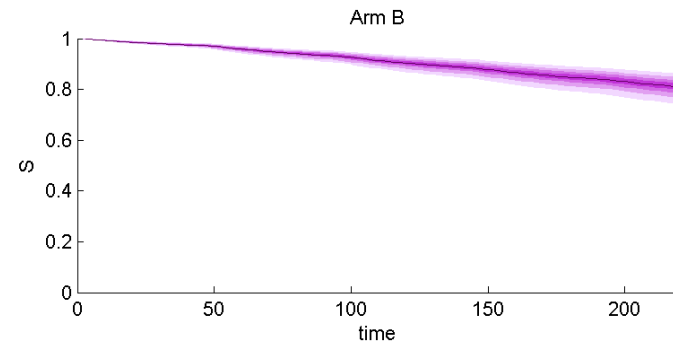
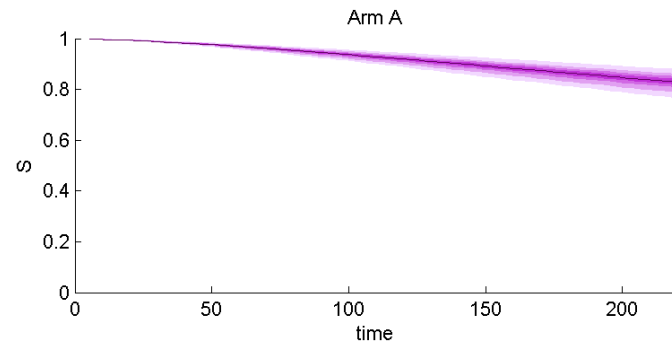
Define the threshold between success and failure

- Safety has to exceed that of warfarin: the hazard of a haemorrhage should never exceed $2 \cdot 10^{-3}$.

Criterion not met. The risk is $\gg 5\%$.

The “survival” is calculated from the cumulative hazard.

“Survival” stands for “absence of any haemorrhage”.



At the end of the trial, only about 65% of patients recruited into Arm C have a negligible risk of having had a haemorrhage.

Conclusion:

Despite efficacy and “acceptable” safety in Phase 1 this project should not advance to Phase 2!

This is the conclusion of the mechanism-based approach to risk assessment.

Another approach may come to another conclusion.

A case study: risk of failure of a phase 2b study

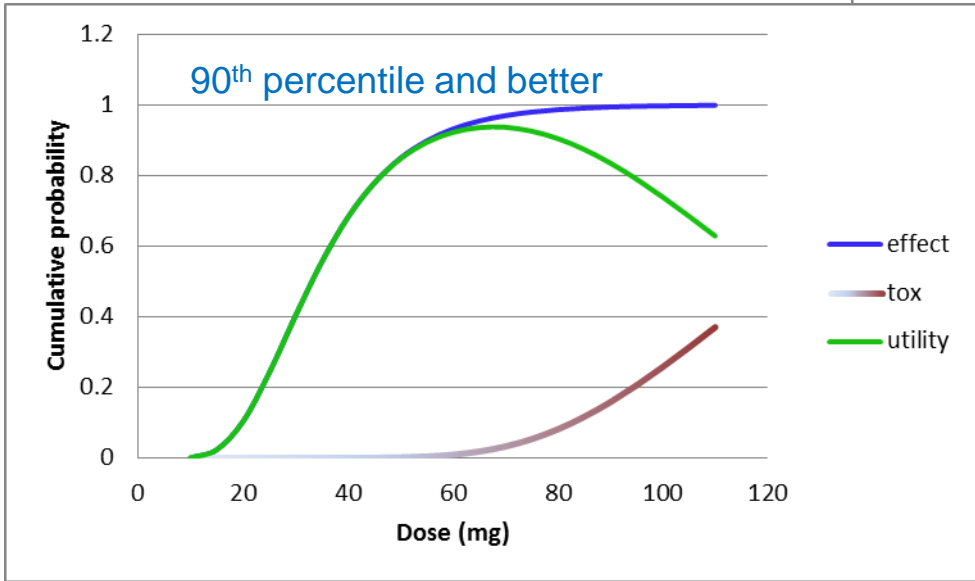
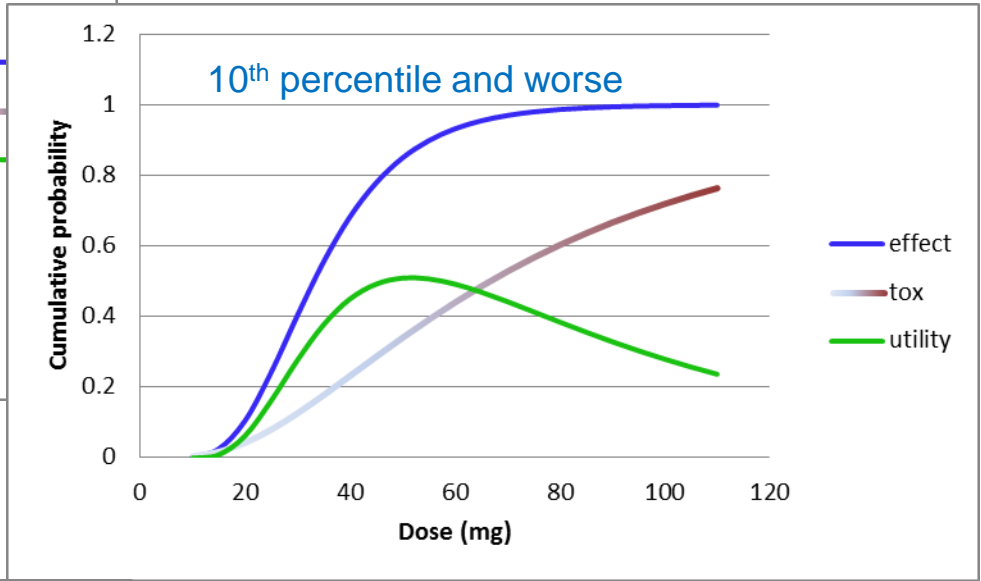
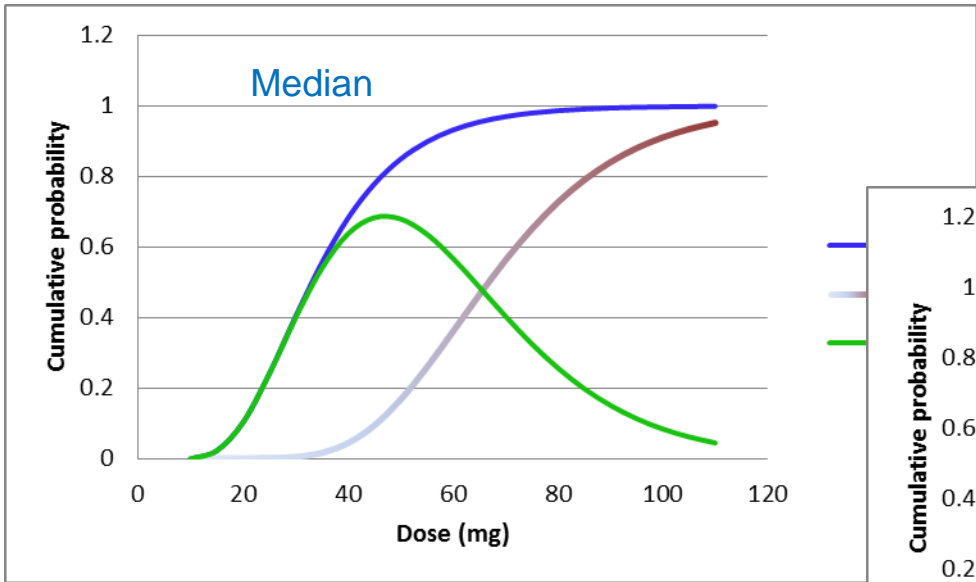
The checklist:

Task	Response
Define the decision	<ul style="list-style-type: none">• A new anti-depressant drug.• A phase 2a study showed that 100 mg was significantly ($p=0.03$) better than placebo at end of three weeks.• But 150 mg was not ($p=0.1$).• What are the chances that 50 or 100 mg are better than placebo in a longer phase 2b trial?
Define the threshold between success and failure	<ul style="list-style-type: none">• Lower MADRS than placebo at 3 and 6 weeks.• Safety is not an issue of concern.
Acceptable risk	<ul style="list-style-type: none">• For the therapeutic effect: less than 30%.
Will payer expectations be met?	<ul style="list-style-type: none">• Yes.

A case study: Dose selection at end of phase 2

The checklist:

Task	Response
Define the decision	<ul style="list-style-type: none">• A phase 2 program in infectious disease was simulated.• In contrast to traditional designs, the design did not facilitate pairwise comparisons, but probabilistic dose-response models .• Effect is well established, but uncertainty remains around toxicity.
Define the threshold between success and failure	<ul style="list-style-type: none">• Choose the dose level with the highest probability of utility.• $p(\text{utility}) = p(\text{effect}) - p(\text{toxicity})$.
Acceptable risk	<ul style="list-style-type: none">• $p(\text{toxicity}) < 10\%$.
Will customer expectations be met?	<ul style="list-style-type: none">• Yes.



Applicability of risk assessment in DMPK research?

The checklist:

Task	Response
Define the decision	<ul style="list-style-type: none">• Initiate preclinical program.• Stating dose for FTIM.• Dose escalation steps during FTIM.
Define the threshold between success and failure	<ul style="list-style-type: none">• <5% induction of CyP enzymes.• <10% inhibition of CyP.• Oral availability > 70%
Acceptable risk	<ul style="list-style-type: none">• Where lies the margin of unacceptable risk?
Will expectations of customer (clinical development) be met?	<ul style="list-style-type: none">• ??

The Nanocross proposal for IMI 4th Call

Biologics

- proteins
- peptides
- oligonucleotides)

...whose transport to “non-druggable” targets is impeded by

- metabolic instability
- immunogenicity
- limited solubility and diffusion

...are transported across barriers

- IB
- ABB
- BBB

...by tailored nanocarriers

- lipid-based
- polymeric
- biopolymeric
- magnetic
- hybrid

Our proposed role in the Nanocross consortium:

- Mechanistic models for in vitro experiments
 - model membranes
 - cell culture
 - tissue slices
- Mechanistic models for in vivo experiments
 - in situ permeability
 - immunologic response
 - absorption (pulmonic, intestinal)
- Optimal design of in vivo experiments
 - simulation immunologic response in humans
- Simulation of FTIM studies

Thanks to:

Coworkers at BAST

- Rupert Austin, PhD
- Sheila Mburu, MSc

Organisers of NEDMDG



More questions?

