

Modeling, simulation and meta-analysis in drug development

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Overview of Lecture

Modeling, Simulation and meta-analysis

- Particulars and motivation

Meta-database creation

- Process, precautions and use

Example

- RA

Drug Model Explorer (DMX®) simulation exploration

- Utility example

Simulation

- RA

Models & Simulations

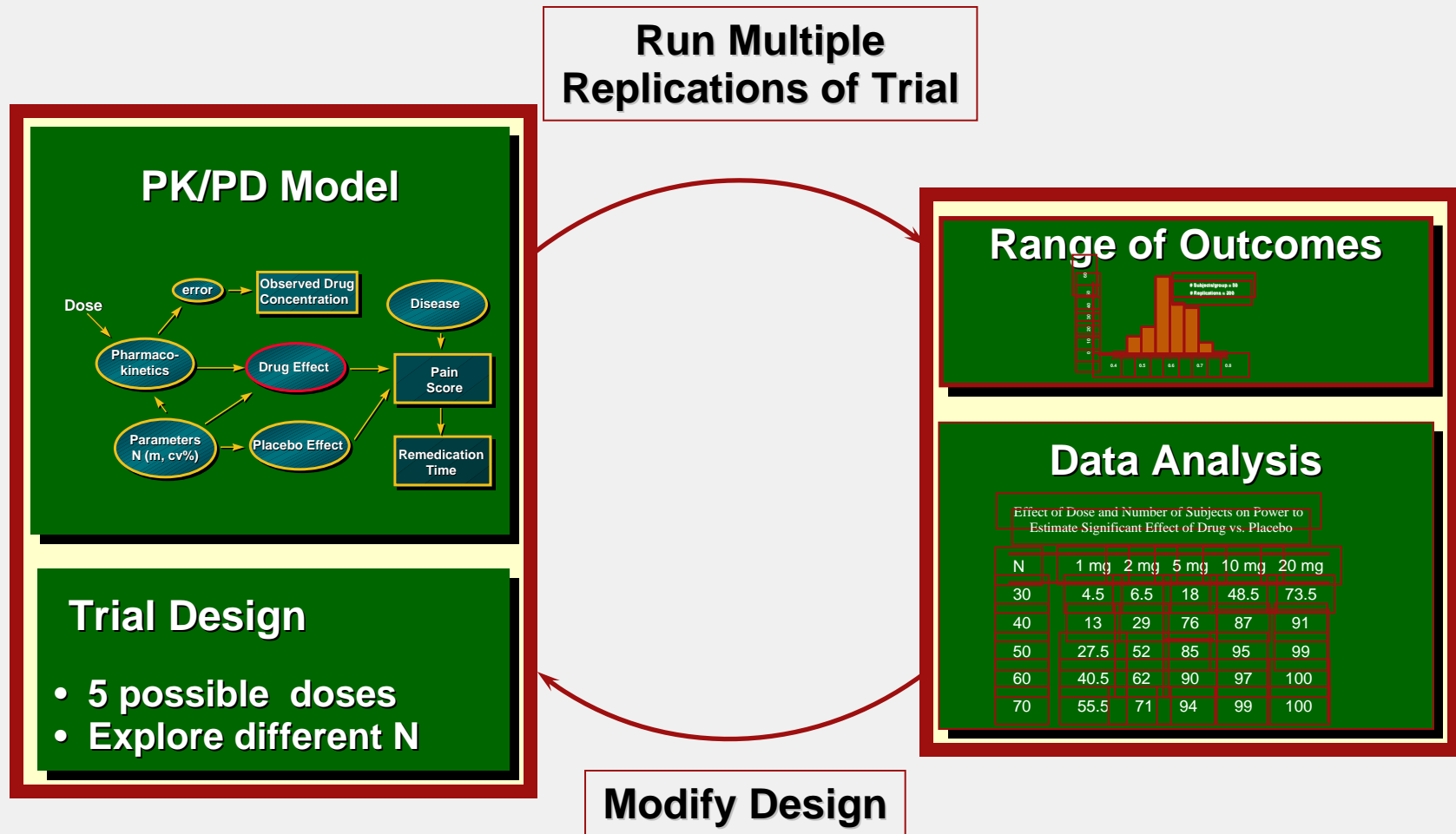
Models summarize our knowledge about the response(s) of a biological system to a drug

- Longitudinal models (concentration-time, dose-response) or statistical, point-estimate models
- Population models quantify both that relationship and the magnitude of variability, given the current state of our data
 - The quality of the models reflects (a) the quality of our measurements (b) and that is quantified in the standard errors (precision of parameter estimates)
- Highly complex, data intensive knowledge becomes leveraged in the relatively simple structure of the model

Simulations using these models explore alternative states of the same system under different scenaria

- Different dose regimens,
- Model validation (posterior predictive checks)
- Significance of the uncertainties given the current level of knowledge
- Costly trials can be reproduced or decided upon

Modeling & simulation allows iterative optimization of trial designs



Meta Analysis*

Much more common than thought! Summaries of multi center trials are meta analyses, 2x2 contingency tables of categorical responses are meta analyses

Two main types of meta-analyses:

- **A. Where all individual patient data is available from each trial/center**
 - E.g. multi-center analyses within a development program
- **B. Where only summary measures are available**
 - Usually retrospective not necessarily with proprietary data...

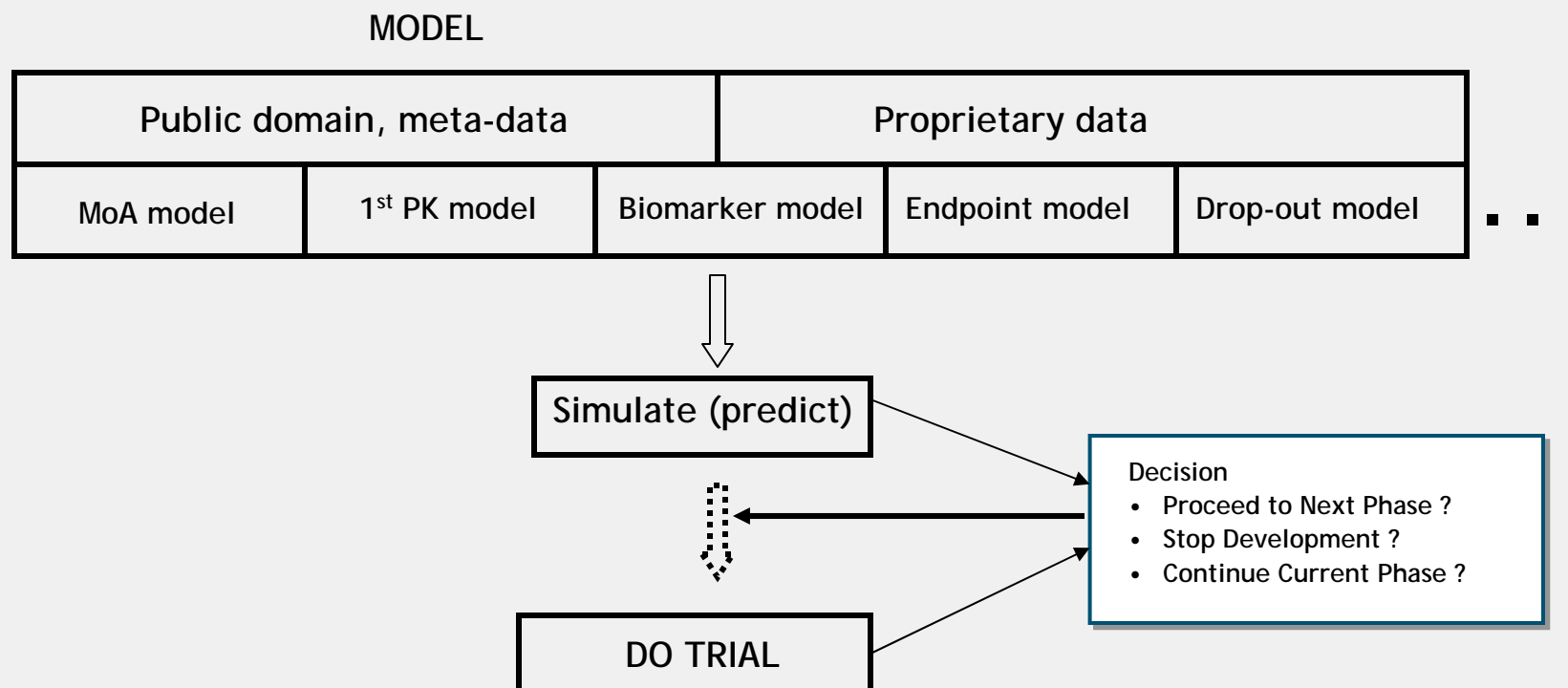
Public domain data can be used in meta analysis to aid in decision making

* Refers to quantitative summaries of entire trials (or centers) producing point estimates of e.g. difference between treatment - control and a reliability estimate of that difference (Glass GV. Primary, secondary and meta-analysis of research. Ed Res. 1976; 5: 3-8)

Model & Simulation (M&S) + meta-analysis

M&S and meta-analysis are each extremely important tools for internally summarizing results, aid in decision making, communication with regulators

- Combine M&S and meta-analysis to increase efficiency!
- Include public domain data to complete knowledge about the drug in development



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Why should we consider quantifying meta-data from published material?

- Placebo has been studied extensively in a very heterogeneous patient population.
 - You will never be able to study placebo to this extent as a function of this many patient and/or trial characteristics in this many patients.
- Go from imprecise sketches of how your drug compares to the competition to quantifying the differences
- The clinical program may not provide for study of a certain comparator, yet the comparison is urgently warranted by the team
 - The required information may be accessible by quantifying public domain data.
- Pool model predictions based on public domain with model predictions based on in-house data
- Broaden the horizon of drug development team
 - qualitative sense: more drugs & more factors of impact
 - quantitative sense: distributions rather than point estimates
- Last but not least: Everybody else (and especially the regulator) is doing some form of meta-analysis with your data !

Public Data Sources

Public data sources on competitors and analogues from the clinical and scientific literature, collectively called “meta data”, are diverse and include:

- Published journal articles
- Regulatory documents (e.g., FDA Summary Basis for Approval)
- Package inserts or promotional materials from the drug manufacturer
- Published abstracts or poster presentations
- Meeting proceedings
- Web documents (e.g., press releases about new clinical trial results)
- Online clinical trial registries

Digitization software is available to accurately capture data from graphs.

All data are formatted and entered in a meta database that undergoes multiple quality design and check stages

Building a useful meta-database is a human intensive interactive inter-disciplinary effort

Capturing data requires continued collaboration among

- Librarians
- Data base specialists
- Modeling scientists / Biostatisticians
- Clinical Experts (clinical pharmacologists, MDs)

Clinical expertise is crucial

- Clinicians from company team typically have read the key papers and understand the nature and features of the endpoints, populations
- What endpoints are hot and which are not?
- Clinician's involvement from the start creates buy-in and commitment
 - Clinician's are the modeling & simulation effort's recipients

Modeler opinion is crucial

- The modeler understands the limitations of the data regarding its use for the development exercise

The meta-data team working closely with clinicians and the modelers can ensure that the endpoint database and models built are useful in development

Some precautions with metadata capturing and processing

Be aware of sources of bias

- Publications tend to be overenthusiastic on drug effect
- Limited data availability may lower the criteria for database entry

Can we combine multiple endpoints that really mean the same thing?

- Increase data density by combining through “effect size” scaling or other assumptions
- At times the naming only differs...

Even the same endpoint can be reported differently

- Change from Baseline (CFB) not the same as mean baseline - mean outcome!

Baseline values may be missing or not clear

- Run-in, pre/co-medication

Observed case / LOCF

- Not always well reported
- non-random drop-out effect

What metrics are reported, of interest to modeler?

- Mean, median, proportions, counts, etc
 - But also, LS mean, adjusted mean, counts per patient, per year etc...

Classify by design

- Separate randomized vs non-randomized, parallel, cross over

The Caveats And Limitations of Meta-Databases

Like any powerful tool, it is wise to understand not only the benefits but the limitations of meta-databases.

Meta-databases provide a publicly available start point for modeling efforts to address specific drug development program questions

Each meta-database is developed to provide a directed view of the public source information landscape for a given disease state/indication

Meta-databases available from Pharsight have evolved and been updated over time to include additional endpoints and comparators

The meta-database will likely require additional development to meet TA-area investment and modeling strategy needs

- Choice of literature to be searched
- Criteria for data/information inclusion in the meta-database
- Content of information extracted from qualifying literature

A meta data base : what does it look like?

Spreadsheet program (e.g. Excel®) containing the data.

Endnote / Reference Manager files containing references that are linked via a unique number to the spreadsheet.

Screenshot of the data base for Diabetes:

	A	B	C	D	AG	AH	AI	AJ	AK	AL	AM	AN	AO	AP
	Reference	Protocol	Mod	Who	Time	T unit	Endpoint	Matrix	Fasted measurement	Variable	Value	Value unit	SD	SE
1														
2	91	core study		IDC	0	wks	HbA1C	blood	fasting	mean	7.81	percent		0.11
3	91	core study		IDC	4	wks	HbA1C	blood	fasting	mean	7.70	percent		0.12
4	91	core study		IDC	8	wks	HbA1C	blood	fasting	mean	7.79	percent		0.11
5	91	core study		IDC	12	wks	HbA1C	blood	fasting	mean	7.89	percent		0.14
6	91	core study		TAB	0	wks	HbA1C	blood	fasting	mean	7.62	percent		0.08
7	91	core study		TAB	4	wks	HbA1C	blood	fasting	mean	7.35	percent		0.08
8	91	core study		TAB	8	wks	HbA1C	blood	fasting	mean	7.23	percent		0.09
9	91	core study		TAB	12	wks	HbA1C	blood	fasting	mean	7.16	percent		0.11
10	91	extension study		IDC	0	wks	HbA1C	blood	fasting	mean	7.75	percent		
11	91	extension study		IDC	4	wks	HbA1C	blood	fasting	mean	7.58	percent		0.15
12	91	extension study		IDC	8	wks	HbA1C	blood	fasting	mean	7.61	percent		0.12
13	91	extension study		IDC	12	wks	HbA1C	blood	fasting	mean	7.77	percent		0.14
14	91	extension study		IDC	16	wks	HbA1C	blood	fasting	mean	7.83	percent		0.16
15	91	extension study		IDC	24	wks	HbA1C	blood	fasting	mean	7.90	percent		0.22
16	91	extension study		IDC	36	wks	HbA1C	blood	fasting	mean	7.96	percent		0.21
17	91	extension study		IDC	52	wks	HbA1C	blood	fasting	mean	8.36	percent		0.24

List of randomly selected metadata bases built at Pharsight. There are actually databases available on 18 Therapeutic Areas.

Project	Abstracts Reviewed	Studies Included	Drugs Included
Sleep	195	51	Diazepam, Flunitrazepam, Flurazepam, Lorazepam, Lormetazepam, Triazolam, Zaleplon, Zolpidem
Asthma	118	31	Beclomethasone dipropionate, Montelukast
Asthma/COPD	570	104	Beclomethasone dipropionate, Fluticasone, Montelukast, Albuterol, Theophylline, Cilomilast, Ipratropium, Tiotropium, Salmeterol
Depression	940	129	Citalopram, Duloxetine, Fluoxetine, Fluvoxamine, Nefazodone, Paroxetine, Reboxetine, Sertraline, Venlafaxine
Schizophrenia	620	90	Aripiprazole, Chlorpromazine, Clozaril, Haloperidol, Olanzapine, Risperidone, Ziprasidone, Quetiapine, Amisulpride
Diabetes	750	106	Glyburide, Glipizide, Metformin, Glimepiride, Tolazamide, Chlorpropamide, Exenatide, Liraglutide, Pioglitazone, Rosiglitazone, Troglitazone, Vildagliptin, Sitagliptin
Rheumatoid arthritis (RA)	170	38	Adalimumab, Anakinra, Etanercept, Methotrexate
Gastro-esophageal reflux disease (GERD)	250	70	Cisapride, Esomeprazole, Lansoprazole, Metoclopramide, Mosapride, Omeprazole, Pantoprazole, Rabeprazole, Tegaserod, Zaccopride

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Case study is focused on Rheumatoid Arthritis (RA)

RA = therapeutic area with multiple endpoints & new, promising drug molecules

Competition is fierce as standard of care anti-TNF- α antibodies show very good efficacy/AE profiles.

Various pharma companies are investing in NCEs for RA treatment aiming to at least equate the standard of care.

Abstracts Reviewed: 170

Studies Included: 38

Treatments Included

- Placebo, Adalimumab, Anakinra, Etanercept, Methotrexate

Scope of Therapies

- Drugs intended to mitigate the signs and symptoms of rheumatoid arthritis

RA database details (drugs, classes, endpoints)

Drugs	Class	Endpoints
Adalimumab	anti-TNF alpha	ESR, SJC, PGA, MDGA, SDAI, HAQ, ES, TSS, JSN, Serious Infection
Anakinra	interleukin antagonist	SJC, TJC, MDGA, PGA, HAQ, CRP, ESR, ACR20, ACR50, ACR70, SDAI, CRP, DAS28, TSS, SJC, Serious Infection
Etanercept	anti-TNF alpha	ESR, DAS28, PGA, MDGA, SJC, TJC, ACR20, ACR50, ACR70, DAS28, CRP, SDAI, TSS, ES, JSN, CRP, Infections, Serious Infection
Methotrexate	antimetabolite (dihydrofolic acid reductase inhibitor)	ACR20, ACR50, ACR70, TSS, JSN, ES, CRP, TJC, SJC, DAS28, MDGA, SDAI, PGA, ESR, Infections, Serious Infection

..and of course the entire package of endpoints is available for placebo treatment!

A client is at the start of a project - receptive to M&S and use of metadata analysis

The aim is to have a quantitative reference cadre of the competitive landscape in place when new Phase II data comes in.

Challenges:

No uncertainty range is defined around Critical Success Factors

- “ACR20 Enbrel = 80% at steady state effect” => this statement is far too precise
- Need to be non-inferior to Enbrel (what does that exactly mean/imply?)

Clinical team’s perception of competitor landscape is maybe qualitative to semi-quantitative, but not fully quantitative

- Example : client is convinced Enbrel beats MTX in terms of efficacy, but is not aware of the associated probabilities across all uncertainties.
- Know roughly the effect of marketed doses, but do not know the full dose-response curve of competitor drugs

Approach:

Develop fully integrated models for ACR20, ACR50, ACR70 for the most prominent competitors in the field.

We built a comprehensive ACR efficacy model using the metadata set

ACR - American College of Rheumatology

For example: ACR20 = Proportion of patients showing:

- 20% improvement in tender and swollen joint counts
- 20% improvement in ≥ 3 out of 5 other measures of RA activity

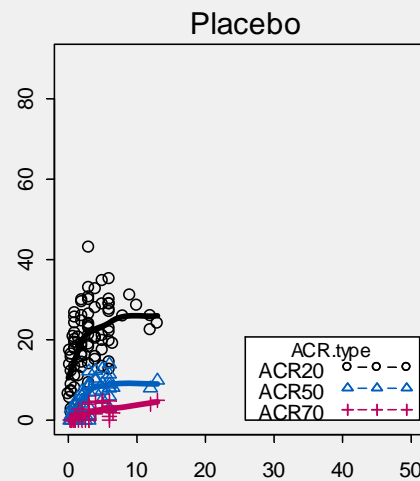
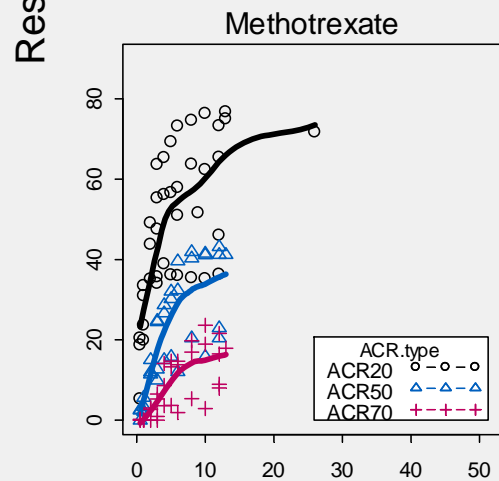
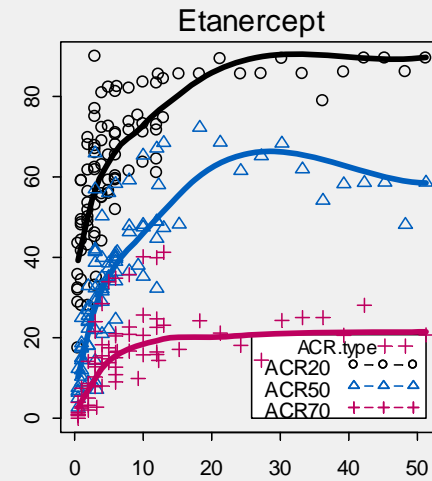
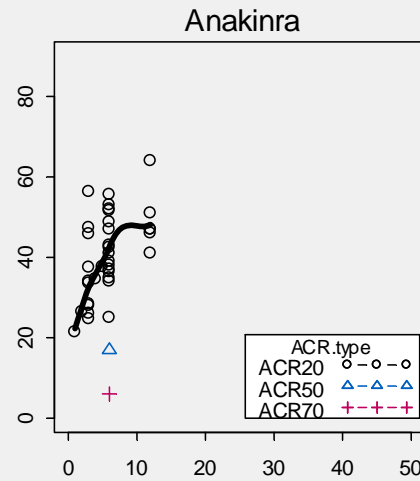
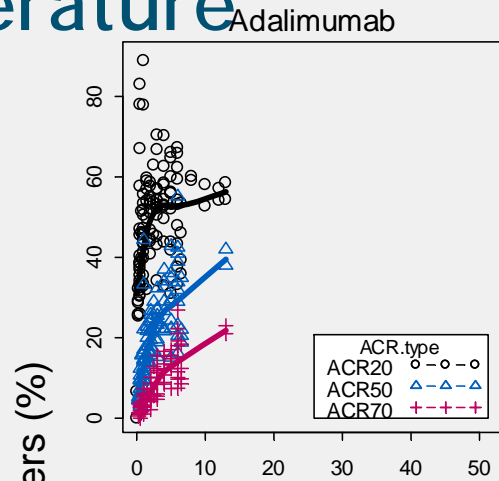
A joint ACR20, ACR50, ACR70 model

- Relatively rich data set
- Model as function of drug, time, dose and other covariates
- Acknowledge drug-specific differences in time course
- Dose response for nearly all competitors

Simulations from this model were uploaded to DMX[®]

- communication and visualization tool to interactively display multidimensional simulation results

Time course of ACRn scores of a selection of anti-RA drugs & Placebo on as collected from the literature



Dots are observed published data
 Lines are loess smooths

An ACRn Model was established.

Joint estimation of ACR20, 50 and 70 ($f(ACR)$)

Logit-transformed fraction of responder data was modeled assuming normal distribution.

Saturable time course model: $t/(t_{50}+t)$

$$\text{logit}(E(t, drug, dose)) = \frac{\textit{structural model} \quad \textit{trial error model} \quad \textit{residual}}{f(ACR) \cdot Emax_{drug} \cdot t}{t_{50} + t} + N(0, \omega^2) + N(0, \sigma^2 / N)$$

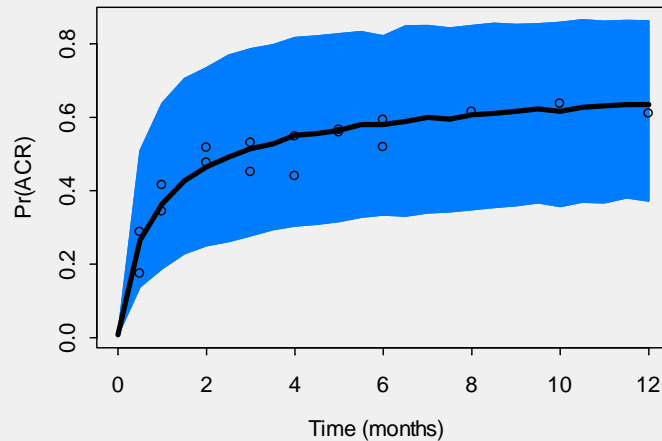
Different effect sizes for each treatment ($Emax_{drug}$)

Difference in results across trials was modeled by an additive random inter-trial error (ω^2).

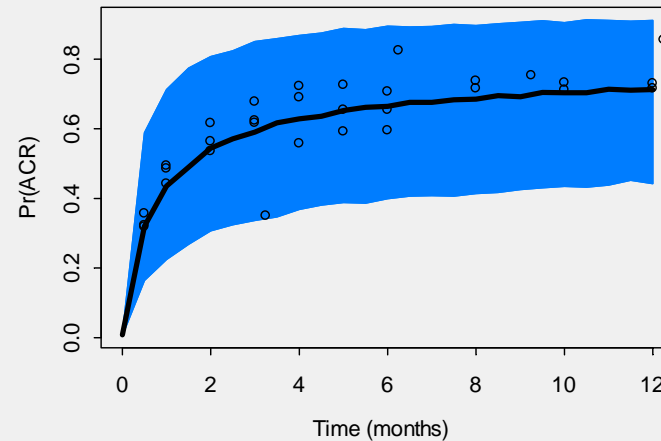
Simple additive residual error model (σ^2), weighted by sample size.

Visual Predictive Check for Etanercept confirmed the model was doing a good job in describing the data.

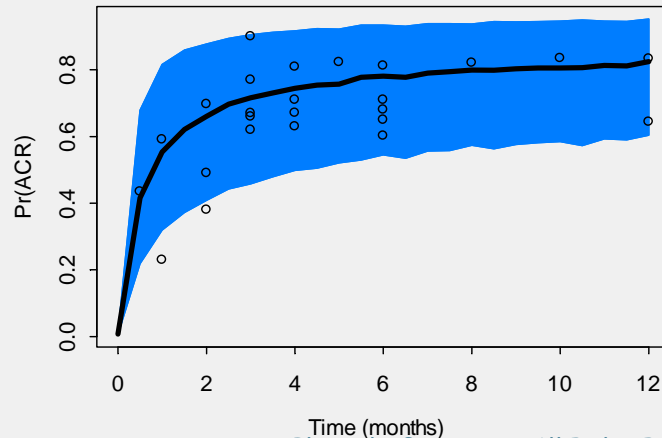
Etanercept TYPE=20 MTX=0 Dose=10



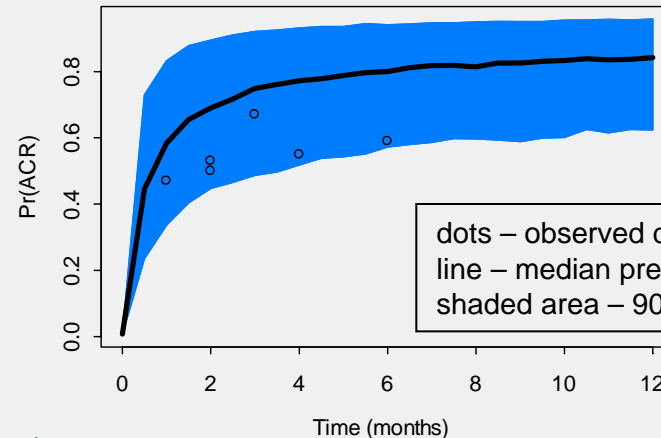
Etanercept TYPE=20 MTX=0 Dose=25



Etanercept TYPE=20 MTX=1 Dose=25



Etanercept TYPE=20 MTX=1 Dose=50



dots – observed data
line – median prediction
shaded area – 90% prediction interval

Simulations of expected mean $\Pr(\text{ACR})$ given certain covariate combinations can now be explored to address development team questions

Predictions of the model using the uncertain parameter estimates were obtained for given sets of covariates

- done by sampling from the multivariate parameter estimate distribution

To each prediction a single random draw from the inter-trial error distribution was added.

- This reflects our conservativeness towards these summary statistic models that typically originate from heterogeneous trial designs and populations.

These predictions reflect the state of knowledge of the mean response in the infinite patient population.

BUT: How to best present the typically voluminous products of simulation?

The resulting grid of response predictions was explored in DMX[®].

DMX[®] is a communication and visualization tool that facilitates point-and-click exploration of predictions of multivariate models.

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Effective communication is a key component of a successful M&S project

Communication is often a significant factor limiting the impact of M&S work to wider audiences. Challenges include...

The Models

- Lack of familiarity with models or modeling techniques leads to distrust of a perceived 'black box' methodology

The Questions

- M&S frequently stimulates dynamic team discussions, where the ability to quickly address "what if" questions is key

The Decisions

- Achievement of consensus on key decision points for the compound attributes can be difficult

Some key questions answered by simulation

What does the dose-response profile with its range of uncertainty in relation to the safety-efficacy margin tell us about dosing the next trial?

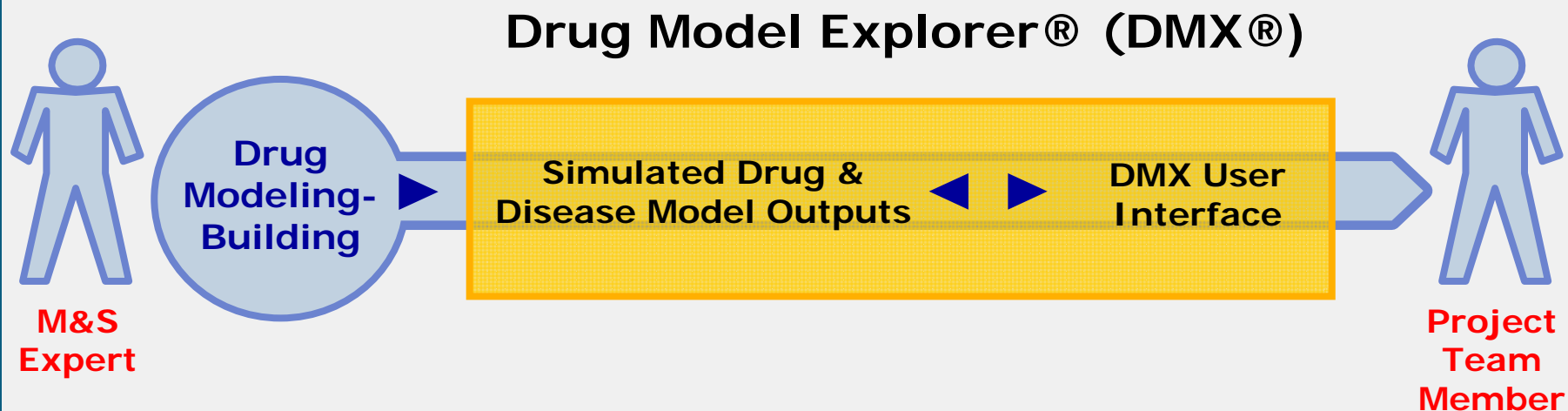
- What are the maximum efficacy, tolerance, safety doses?

What is the probability that a given dose will show a certain effect?

- Versus our placebo
- Versus the competitors

What trial design has the highest probability of showing how our drug performs better than the competitor(s)?

DMX: Exploring modeling results in real time



DMX is a visualization and communication tool to interactively explore M&S results

- Used by modeling **experts** to make M&S results available to teams and decision-makers
- Used by the project **team** to compare performance vs. competing treatments, evaluate product profiles, and understand trade-offs
- Used by **companies** to capture knowledge and update as new information becomes available



A Note on DMX Theory of Operations and Publishing

DMX takes simulation results, created outside DMX, as inputs and prepares (“publishes”) them for use by the development team via the viewing interface.

SIMULATION OUTPUT

- 3 files per simulated endpoint
- Structure file
 - Sample matrix
 - Expectation vector

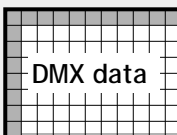
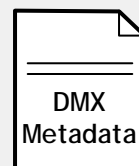
Create results in (or write to)
S-PLUS® or SAS® XPORT format

DMX DATA CONVERSION AND PUBLISHING TOOLS (for modelers)



Drug Model Explorer

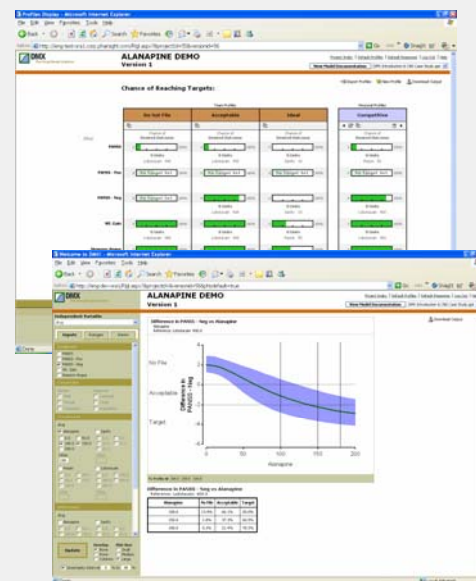
- Create metadata file (.xml) that describes relationships between all variables
- Convert simulation output into a binary format DMX can read
- Publish for viewing: upload results to central database or make output available locally



DMX VIEWING INTERFACE (for modelers, team)

Two modes of exploration, with interaction between them:

- Response mode (plots, tables)
- Profiles mode (summary, details)



Example of DMX output: Allows team to view and query model-based drug attributes

Response Selection

Uncontrollable Variables & Assumptions

Controllable Inputs (Treatments, Competing Therapies)

Output Controls

Plots Display Trends

Shaded area shows prediction interval for expected dose-response

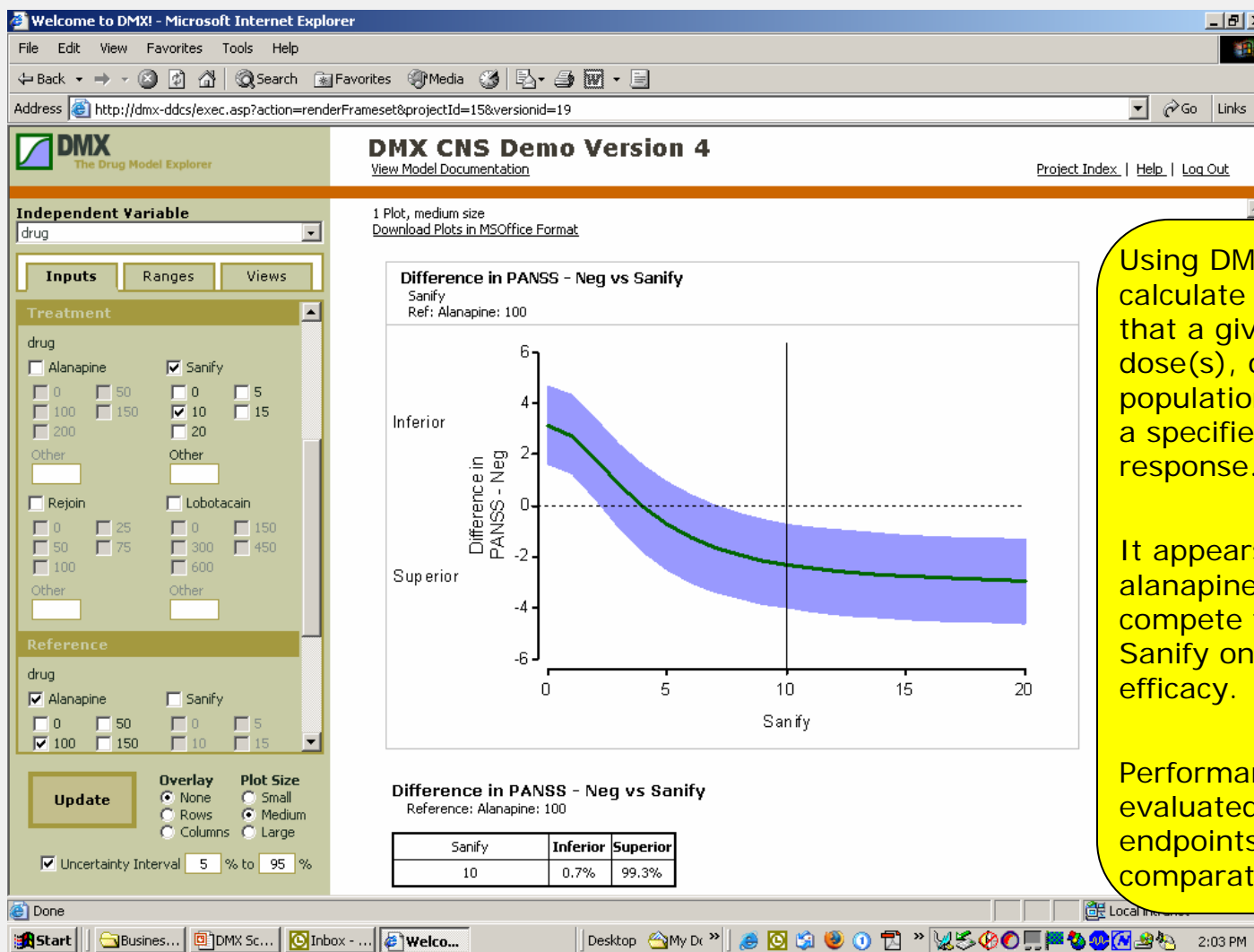
Vertical lines show doses of interest

Tables Display Details

Tables display quantitative estimates of prediction intervals or other information

Drug B Dose (mg)	5.0%	mean	95.0%
150	-45	-44	-43
300	-48	-47	-45

Example of DMX output: Compare response vs. competing treatment(s)



Using DMX, teams can calculate the probability that a given treatment(s), dose(s), or patient population(s) will achieve a specified target response.

It appears unlikely that alanapine will be able to compete favorably with Sanify on the basis of efficacy.

Performance can also be evaluated on safety endpoints and vs. other comparators ...

Benefits of DMX

Modeling results are more effectively communicated to the project team.

- Answer 'what if' questions on-the-spot.
- Rapid generation of statistics on relevant reference and critical success factor "cut-points"
- Facilitates greater acceptance of the model by the entire project team

DMX as a software platform facilitates the incorporation of M&S into the decision making process of an organization

- Supports the methodology and makes it accessible to a broader audience
- Optimizes the workflow and decision making process
- Provides a standardized visual presentation structure for representing complex information

DMX captures current and future knowledge about a compound and its competitors

- Applicable within and across development programs, can be easily updated when new information becomes available

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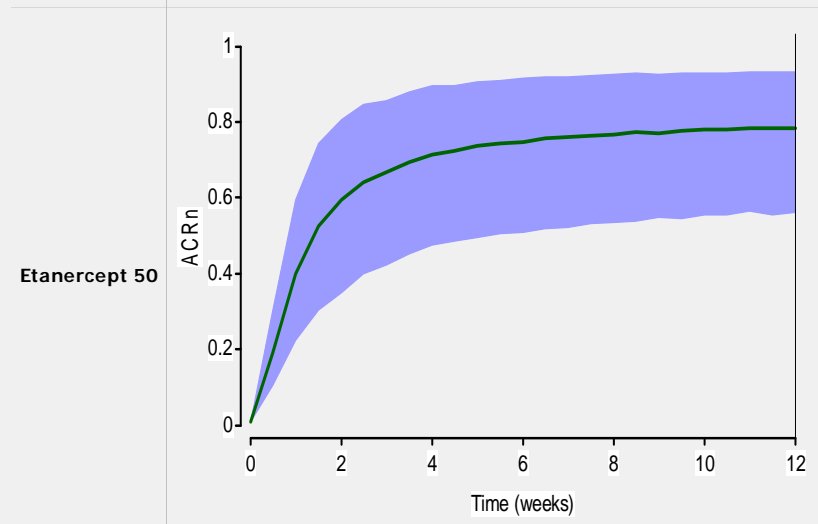
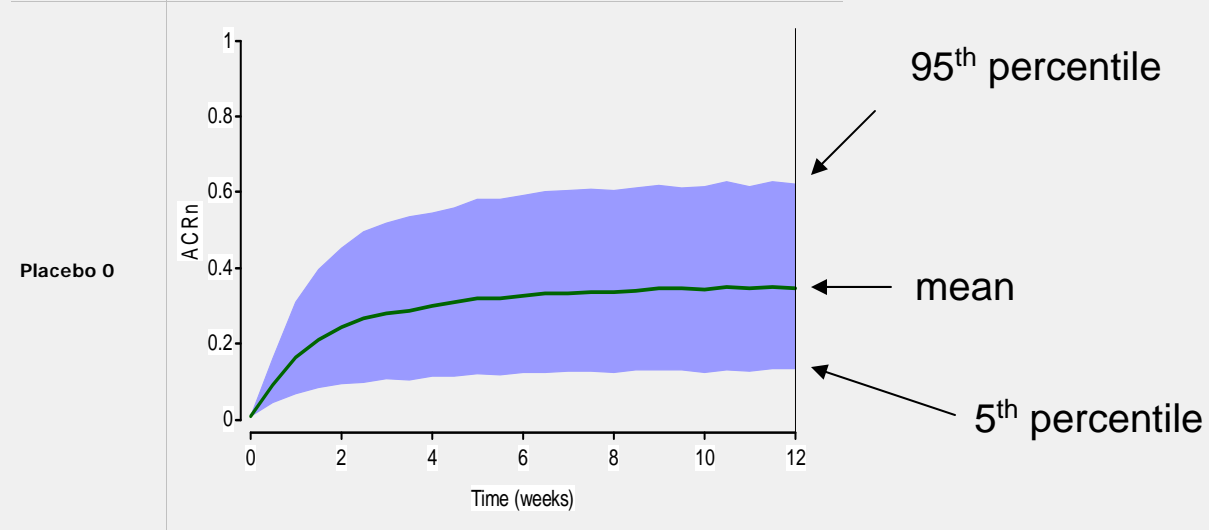
- Utility example

Simulation

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Screen shot 1 of the DMX[®] viewer containing these simulations. Plots and table highlighting mean drug response & uncertainty

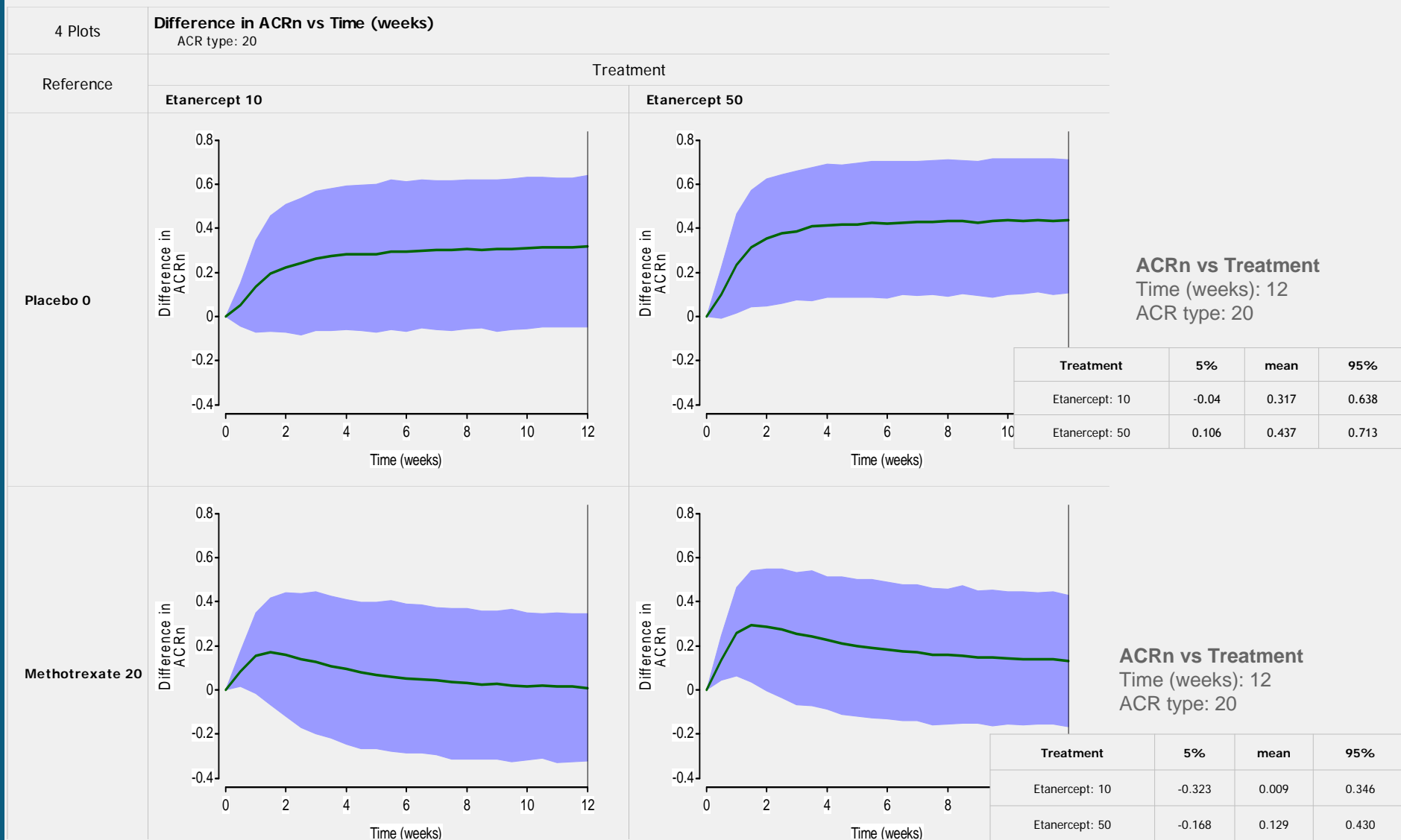
2 Plots	ACRn vs Time (weeks)
Treatment	ACR type: 20



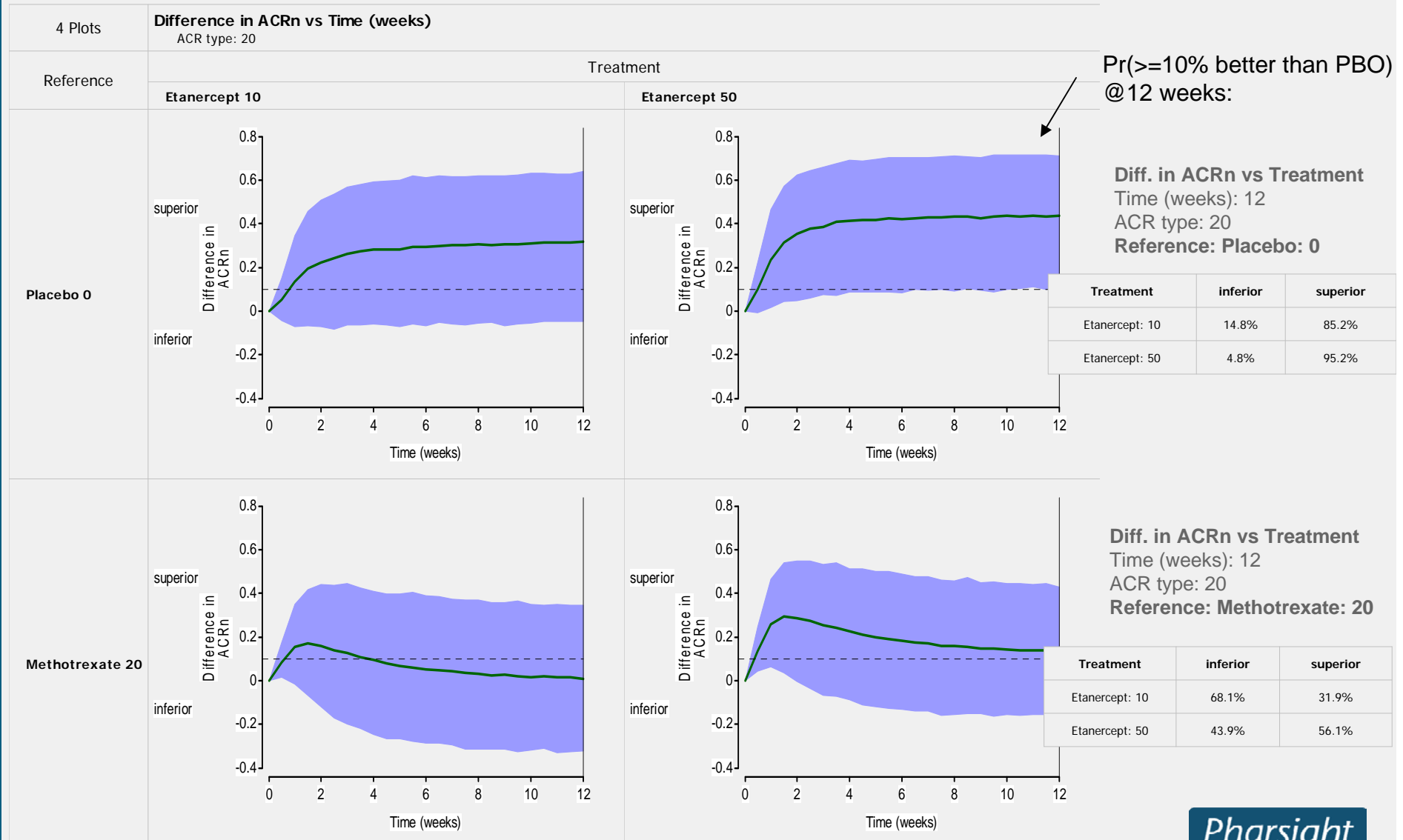
ACRn vs Treatment
Time (weeks): 12
ACR type: 20

Treatment	5.0%	mean	95.0%
Placebo: 0	0.132478	0.347253	0.619311
Etanercept: 50	0.559614	0.784595	0.931161

Screen shot 2 of the DMX[®] viewer containing these simulations. Plots highlighting mean drug response vs. reference treatment & uncertainty



Screen shot 3 of the DMX® viewer containing these simulations. Plots of drug response vs. reference treatment with uncertainty and tables with probabilities of hitting a defined target.



The quantitative imprint of the competitive landscape has been established using published data!

Simulations in DMX are currently used by clinicians to reference drug performance vs. competitors.

They have a quantitative understanding of the RA therapeutic area based on real (published) data.

They have predictions of efficacy across many covariates incorporating all uncertainties captured during modeling of the available literature data

Note that this all was done using published data only!

This framework for this RA problem is dynamic and growing:

- Can continuously be updated with new trial data being published.
- Can continuously be updated when new internal (patient) data comes in.
- Creating an ever growing quantitative picture of the client's pipeline in relation to the competition.
- DMX[®] software has been specifically designed for these type of analyses.

Was the gain in knowledge from this effort unique to performing this type of metadata analysis?

Yes, no pharma company will execute trials investigating efficacy/safety of all compounds in all patient settings.

Creates a state of knowledge far beyond what any pharma company could learn from their development program.

More precise estimate of placebo/drug effect

- across multiple covariates
- in a wider/more heterogeneous patient population

Pharma does not have to *invent the wheel again*; the information is out there and ready to be picked up from the street.

All it needs is data management, appropriate modeling technology & clinical expertise to quantify the information with its uncertainties.

Summary

- Modeling & Simulation is a key tool in efficient and cost - effective drug development
- Meta-analysis of summary public domain data can be built into the M&S process
 - This requires quantifying public domain data in metadata models.
- Metadata capture is an extensive process requiring involvement of multiple disciplines of pharma industry
- The M&S exercise can start/continue with meta-data providing help in development decisions
 - Metadata model predictions can be pooled with model predictions from patient data models.
- DMX[®]-like communication of metadata model predictions facilitates drug development discussions and, among other benefits, takes the regression analysis out of the black box for clinicians