Models for Computer-Aided Trial & Program Design

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“MODELS”

What is a model and Why do we use them?
MODELS: what are they?

A mathematical representation of the relationship between an input and an output

- Is expressed in terms of equations
- Is quantitative
- May also contain representations of variability
MODELS: why do we use them?

- For analysis of data
  - Condense data and provide summary views
  - Explore relationships using various models
    - Understand factors (covariates) which affect output/outcome

- For interpolation & extrapolation from data
  - Predict the range of possible outcomes of various untested inputs into a model derived from data from other inputs
    - Models may be empirical, mechanistic or a combination of both
    - Interpolate from empirical models, extrapolate from mechanistic models

- As a tool for communication
Models used in improving the efficiency of drug development

- Drug and Disease Models
- Trial Models
- Predictive Market Models
- Dynamic Financial Models
Models are the foundation to optimize the drug development process.

Models integrate all available information on the drug, analogues and markets to predict outcomes, quantify uncertainty, and understand trade-offs.
Different views of models in drug development

- Models are used to predict the outcome of the next trial
- Models aid in planning of the next trial by predicting the probability distribution of trial outcomes conditional on current knowledge, assumption and trial execution uncertainties. The use of those predictions is to evaluate the ability of the trial to support a certain decision
  - Two aspects of prediction:
    - Probability distribution.
    - Context. The model is a mixture of abstractions from data (what we already know) and assumptions (what we don’t already know, but have some ideas about based on scientific judgments or experience)
Drug-Disease Models

- Usually composed of 3 submodels
  - A Pharmacokinetic model
    - Relates dose to concentration at site(s) of action
  - A Pharmacodynamic Model
    - Relates concentration at site of action to effect
  - A Disease progress model
    - Describes natural history of the disease in the absence of treatment, or, preferably, in the presence of a placebo
Drug-Disease Models

A drug-disease model predictively characterizes the distribution of treatment outcomes (safety, efficacy, surrogate outcomes) for the NCE and related compounds as a function of dosing strategy, disease, patient, and trial characteristics.
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Integrates all available information on NCE and analogues to predict outcomes and quantify uncertainty.
Trial Models

A trial model predicts outcomes and reductions in uncertainty around the trial as a function of dosing strategy, number of treatment arms, type of control, sample population characteristics, sample size, and treatment duration.
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A trial model predicts outcomes and reductions in uncertainty around the trial as a function of dosing strategy, number of treatment arms, type of control, sample population characteristics, sample size, and treatment duration.

- Integrates all available information on a possible trial market in dynamic form to quantify uncertainties and sensitivities
- Quantifies impact of trial design choices on outcome and uncertainty
- Creates the basis for simulations to optimize trial design within clinical, regulatory, commercial, and financial constraints
A market model characterizes the demand for products under different feature sets and different competitive and innovation scenarios.
Predictive Market Models

A market model characterizes the demand for products under different feature sets and different competitive and innovation scenarios.

- Integrates all available information on a market in dynamic form to quantify uncertainty and make trade-offs
- Quantifies impact of product features on market share (individual and groups)
- Identifies key uncertainties in the market that could have major consequences for product success
Dynamic Financial Models

A dynamic financial model incorporates scientific, clinical, and commercial insights to create a dynamic understanding of the value of a program. This is the foundation for assessing the cost and value of assets, specific program strategy elements, and trial designs.

Integrated Valuation Models

Expected Net Present Value (ENPV)

Cumulative Investment
Dynamic Financial Models

A dynamic financial model incorporates scientific, clinical, and commercial insights to create a dynamic understanding of the value of a program. This is the foundation for assessing the cost and value of assets, specific program strategy elements, and trial designs.

Integrated Valuation Models

*Translates all scientific, clinical and commercial information into common language of uncertainty, cost, and value*
Models are the foundation to optimize the drug development process.

**Drug & Disease Models**
- Product Profile:
  - Dose
  - Efficacy
  - Side-effects

**Predictive Market Models**
- Market share impact of various product profiles

**Trial Models**
- Quantify how a certain trial or sequence can reduce uncertainty around safety, efficacy

**Dynamic Financial Models**
- ENPV at various market shares

*Models integrate all available information on the drug, analogues and markets to predict outcomes, quantify uncertainty, and understand trade-offs*
Model-Based Integrated View of NCE

The Models together create an integrated, uncertainty-based view of an NCE that can support all key decisions in drug development.

Sample Questions Requiring Dynamic, Integrated View

- What is the expected value of each product feature or group of features in the Target Product Profile (TPP)?
- By how much does value decline vs. TPP if feature X is 25% lower than TPP?
- What is the probability that NCE will achieve target safety? Efficacy?
- What is the value of a trial that reduces that uncertainty by 20%? 40%? 60%? What is the cost?
- How confident do we need to be before:
  - In-Licensing a compound?
  - Killing a program?
  - Moving into Full Development
How does it work in practice?

- **Step 1:** Build Models, Quantify Information
  - Drug/Disease Models
  - Trial Models
  - Predictive Market Models
  - Integrated Valuation Models

- **Step 2:** Design Asset Strategy
  - Target Product Profile
  - Alternative Development Plans
  - Downstream Options, Scenarios
  - Value-Maximizing Asset Strategy

- **Step 3:** Design Program Strategy and Trials
  - Optimize Trial Sequence
  - Optimize Trial Design
  - Define decision points

- **Step 4:** Re-Assess/Modify Program Strategy
  - New data
  - Market changes
  - Post-Approval Strategy

- **Late Discovery**
- **Late Discovery**
- **Late Discovery**
- **Phase I**
- **Phase II**
- **Phase III**
- **Phase IV**

These models can be used in two basic ways to optimize value – Asset Strategy and Program Strategy/Trial Optimization. The combination, begun in Late Discovery, can guide value maximizing decisions throughout development.
EXAMPLE #1: Application of Clinical Trial Simulation to Dose Selection

- A key challenge in drug development is to identify what dose or dose range, if any, provides a marketable risk/benefit profile in a certain patient population.
- The Strategic Development Program Question: what is an effective phase I-II strategy that will provide a clear, quantitative rationale for picking the dose (including go/no-go) for evaluation in Phase III?
- There are substantial opportunities to improve this process:
  - Make effective use of the wealth of information, ranging from pre-clinical, phase I safety, biomarker, to clinical response data, that are available on competitor products and analogues
  - Adjust the scope of the trials to yield only the required information
  - Use creative trial strategies (for example adaptive trials) to get to a certain decision points more quickly (such as stop development, start gearing up for phase III, or early initiation of phase III)
  - Evaluate the strategy from a business perspective as well as a scientific perspective.
The specific problem: Determine the Phase II dose ranging strategy for n\textsuperscript{th} in class NCE for treatment of migraine pain

- Development status of the NCE
  - 5-HT 1D agonist
  - NCE more selective for 5-HT 1D receptor
  - NCE more selective for cerebral blood vessel constriction
  - NCE better bio-availability, faster absorption
  - Phase I completed and about to start phase II

- The development question: what is an effective trial strategy to identify the dose, if any, that has equivalent efficacy to competitors (standard of care) and the potential for a reduction in CV AEs

- Specific trial design questions to be answered are:
  - What Is the Best Dose Ranging Strategy: How Many, What Range and Spacing?
  - How many patients?
  - How do we analyze the data?
  - What is the best dose selection strategy?
  - What are appropriate targets?
  - Robust design across model assumptions and uncertainties
Step 1: Building the Drug and Disease Model

• The model is the tool allowing effective use of prior information and highlighting assumptions as well as uncertainties in those assumptions.
• The model should quantify and integrate the available information that pertains to the particular question or decision. This could span NCE, analogues and competitors, pre-clinical to biomarker to multiple clinical endpoints.
• The model should specifically list the assumptions that were made, or a likely range of alternatives. The model could be a family of models.
• Since the purpose of the methodology is to understand a stochastic process, the model should quantify the uncertainty in future trial outcomes due to:
  – The (un)certainty in the model parameters (assumptions).
  – The sampling variability (because only a sample of the patients is being studied in each trial) at each appropriate level such as measurement, patient, center, and/or trial.
Drug-Disease Model

We build drug-disease models incorporating all available relevant information on Drug X, Competitor, and related compounds.
DRUG DISEASE MODEL FOR MIGRAINE

- Primary efficacy measure is fraction of patients with pain relief at 2 hours

\[ P(\text{PainRelief}) = g\{E_0 + \frac{E_{\text{max}} \cdot D_T^n}{D_T^n + ED_{50,T}^n} + \eta \} \]

- \( E_0 \): placebo effect derived from > 1500 patients exposed to placebo across a number of trials*
- \( E_{\text{max}} \) and \( n \): Efficacy and shape of dose response relationship derived from > 5000 patients exposed to sumatriptan, rizatriptan, naratriptan, and zolmitriptan*
- \( G(x) \): inverse logit transformation
- \( ED_{50} \): Potency of NCE derived from pre-clinical potency evaluations relative to sumatriptan, phase PK data, and \( ED_{50} \) of sumatriptan*
- \( \eta \): trial-to-trial random variability derived from > 10 trials*

*Pieces of information contributing to the understanding of the dose response relationship of the NCE
Process: Fit a dose-response model to the clinical trial data for four marketed 5-HT\textsubscript{1D} agonists

The symbols reflect the data derived estimates of the fraction of patients with pain relief at two (sumatriptan, zolmitriptan, and rizatriptan) or four hours after treatment (naratriptan) at each evaluated dose in each trial. The vertical line around each of the symbols reflects a 95% confidence interval on the data derived estimates of the fraction of patients with pain relief.
What information was gained by using prior data to develop the model for the NCE?

• Several model assumptions were supported by the prior data:
  – Assumption 1: There is a consistent dose-response relationship (same $E_{\text{max}}$ and shape) across $5\text{-HT}_1\text{D}$ agonists
  – Assumption 2: There is little or no trial-to-trial variability in $E_{\text{max}}$
  – Assumption 3: The relative potency derived from pre-clinical efficacy models is predictive of the clinical relative potency

• Other key lessons:
  – Relative potency: $2.5$ mg Zolmitriptan $\approx 10$ mg Rizatriptan $\approx 75$ mg Sumatriptan. At suggested doses $60\%$ of patients have adequate pain relief, whereas maximum response is $70\%$ at expected placebo response of $28\%$. This defines target product profile for efficacy. It confirms the validity of the equal efficacy better safety strategy.
  – Baseline pain (moderate or severe) is an important determinant of outcome; therefore, need to stratify by baseline pain
The next step—simulation: What does the model tell us about the likely response to the NCE as a function of dose?

To characterize the uncertainty in the dose response relationship of the NCE, a sample of 1000 sets of model parameters is drawn from a multivariate normal distribution with mean and variance-covariance matrix obtained from the model building step. The dose response relationship for the NCE is calculated for each set of parameters, yielding a distribution of likely response rates as a function of dose. Shown are the 5th, 10th, 20th, 50th, 80th, 90th, and 95th percentiles of the distribution.
Results: The NCE dose expected to achieve the targeted level of pain relief (60% of patients) is 19.3 mg (80% Predictive Interval: 11-43 mg)

Given the MTD from phase I safety and tox studies, 40, 20, and 10 mg seem adequate initial choices to evaluate in the phase II dose ranging trial.
How many patients are needed to show efficacy?

Study power is a distribution due to model uncertainty

The figure shows the distribution across model uncertainty of the power of obtaining a significant difference between placebo and 20 mg at a sample size of 50 patients per treatment arm and alpha of 0.05.
Explore power of dose-ranging trial for comparisons to placebo as a function of dose and sample size

Mean power across model uncertainty to detect a difference from placebo as a function of dose and sample size

Relationships between NCE dose, number of patients per treatment arm, and study power. Shown is the average power to determine a significant difference between placebo and active treatment (at alpha of 0.05) as a function of NCE dose and sample size.
Additional Question: What is the power of the trial to detect a dose-response relationship and ability to select doses for further development

- Sample a large set (>1000) of model parameters from the prior distribution of the model parameters
- Simulate Alternative Trial Strategies by varying
  - dose strength
  - sample size
  - number of treatment arms
- Simulate one trial for each set of model parameters and trial strategy
- Analyze each trial replicate using logistic regression
  - use $E_{\text{max}}$ model to test for dose response relationship
  - evaluate dose selection strategies
Impact of Trial Strategy on the Power to Detect Dose-Response relationship:

<table>
<thead>
<tr>
<th>Design</th>
<th>Dose groups</th>
<th>sample size</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0, 10, 20, 40 mg</td>
<td>50,50,50,50,50</td>
<td>0.34</td>
</tr>
<tr>
<td>2</td>
<td>0, 10, 25, 50 mg</td>
<td>50,50,50,50,50</td>
<td>0.37</td>
</tr>
<tr>
<td>3</td>
<td>0, 5, 25, 50 mg</td>
<td>50,50,50,50,50</td>
<td>0.79</td>
</tr>
<tr>
<td>4</td>
<td>0, 5, 10, 25, 50 mg</td>
<td>40,40,40,40,40</td>
<td>0.71</td>
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<tr>
<td>5</td>
<td>0, 5, 10, 25, 50 mg</td>
<td>50,33,33,33,50</td>
<td>0.68</td>
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</tbody>
</table>

- Power is mean power across model uncertainty
- Significance of dose response is determined by likelihood ratio test of $E_{\text{max}}$ model vs model assuming all active doses are similar
- Minor change in design has large impact on information yield, without changing cost or duration.
Value derived from the modeling and trial simulation effort

- One low dose (5 mg) and two at the upper end of the dose range (25 and 50 mg) has 80% power to establish dose-response.
- Modeling and simulation do not support selection of single dose for further development on basis of phase II data alone. Results make it possible to select 2-3 doses to achieve success in phase III.
- This example takes a very traditional, empirical approach to decision making on basis of phase II data, but completely ignores the prior information to augment that decision
  - If we accept the $E_{max}$ and shape assumption we could support the dose selection on basis of a joint analysis of prior clinical data on 5-HT$_{1D}$ agonists with NCE specific data
  - If we accept the $ED_{50}$ assumption we could support dose selection on basis of a Bayesian analysis of prior model and phase II data, accounting for the trial-to-trial variability
  - Given this extensive prior knowledge, we could have decided to skip the phase II dose finding study and do a phase III trial at 2-3 doses to confirm model expectations and build up safety data base
Example #2: Adaptive Trial Strategy

Compound: • CNS

Status: • Phase I

Competitor: • On market for 5 years

Target Product Profile:

• Similar or better efficacy than Competitor with reduced side-effects

Issues: • What is the best (highest NPV) Program Strategy for determining:
  – If Drug X is a “dud” and should be killed?
  – If “Effective”, how and when to move to Phase III?
The Models Supported a Dynamic Program Strategy

The Pharsight Phase II Design:

- Collect data in small groups
- Populate / update models
- Re-run models

Build Models

Collect another group

• Negative NPV
• Side effects unacceptable
• Efficacy much worse than Competitor
• Efficacy much better than Competitor
• Expected learning increases NPV

Phase III

GO

STOP

Build Models
Models Allowed Design of a Development Program That Was Up To Two Years Faster
Phase II Strategy for novel CNS compound with High Uncertainty

- Patients: 100, 200, 300, 400
- Original stopping point
- Model-based stopping point
- Model-based go point

**Pharsight**
The adaptive design demonstrated significant value for any outcome:

If the Drug Candidate was…

- “Effective” → +$500M in earlier revenue
- “Dud” → +$55M in cost avoided from earlier “kill”
Any modeling strategy depends on the amount/type of prior information!

<table>
<thead>
<tr>
<th>Amount of information</th>
<th>Example</th>
<th>Number of assumptions</th>
<th>Uncertainty in predictions</th>
<th>Goals of modeling &amp; simulation</th>
<th>Trial designs</th>
<th>Role of preclinical and biomarker data</th>
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</thead>
<tbody>
<tr>
<td>High</td>
<td>Pre-clinical models</td>
<td>Few</td>
<td>Low</td>
<td>Shorten and focus development</td>
<td>Fixed-dose dose finding</td>
<td>Quantitative prediction</td>
</tr>
<tr>
<td></td>
<td>Known MoA</td>
<td></td>
<td></td>
<td></td>
<td>Skip PoC &amp; dose finding</td>
<td>Rescales existing clinical models</td>
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<tr>
<td></td>
<td>n&lt;sup&gt;th&lt;/sup&gt; in indication</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>n&lt;sup&gt;th&lt;/sup&gt; in class</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>Mixture</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Robust strategy</td>
<td>Fixed-dose PoC &amp; dose finding</td>
<td>Semi-quantitative Mechanistic rationale</td>
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<tr>
<td>Low</td>
<td>No pre-clinical models</td>
<td>Many</td>
<td>High</td>
<td>Manage risk</td>
<td>Adaptive stopping</td>
<td>Limited Qualitative</td>
</tr>
<tr>
<td></td>
<td>Unknown MoA</td>
<td></td>
<td></td>
<td></td>
<td>Adaptive dose assignment?</td>
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<tr>
<td></td>
<td>1st in indication</td>
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<td>1st in class</td>
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Value Proposition for M&S:
Faster, Cheaper, Better Development

• Shorter phase I-II (including early attrition)
  – Using prior information more effectively
  – Deleting unnecessary trials from critical path
  – Adjust scope of trial to required information yield
  – Use adaptive trial strategies

• Reduce failure in phase III
  – Increase information yield of phase I-II program
  – Robust phase I-II program

• Increase market performance
  – Better candidate selection
  – Improve treatment (dosing/patients) strategy
  – Improve competitive positioning