The rheumatoid arthritis drug development model: a case study in Bayesian clinical trial simulation

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Problem statement

*What decisions should be made about a Phase IIb and Phase III study for a new Rheumatoid Arthritis treatment?*

- **Rheumatoid Arthritis**
  - A chronic, progressive, inflammatory disease which affects about 0.5% -1% of adults
  - Traditional Disease-Modifying Anti-Rheumatic Drugs - lots of them
    - Methotrexate (MTX) most effective
  - Biologic - more effective and more costly
    - Etanercept, infliximab, adalimumab (TNF-α), anakinra (IL-1 inhibitor)
  - A new drug we wish to test

- **We need to make decisions about the devolvement program**
  - Decisions about each study design
    - Sample sizes?
    - Exposure duration?
    - …
  - Stopping rules for the program
    - Efficacy thresholds? Safety thresholds?
Overview of the Decision Analysis method

What is needed for a Decision Analysis model

Collections of decisions that must be made about study design whose effects are simulated

- Sample size, comparator, endpoint, exposure, patient population, stopping rules

Consequences and effects of the decisions, plus other relevant variables, which the model will incorporate

- Treatment efficacy and safety
- Recruitment rates, drop out rates, costs

The final measures of the design, which the model will calculate, and by which we will evaluate candidate strategies

- Probability of success (registration), time LPLV, cost
A decision hierarchy identifies issues to be decided and issues already decided or that can be deferred.

- Policy
- Environment
- Decisions already made
- Near- and long-term strategic direction
- Near-term significant resource commitments
- Issues that must be resolved today
- Later significant resource commitments
- Decisions for specialists
- Operational or tactical decisions
## Decisions

*Rows have no meaning - options from different columns may be combined*

### Decisions already made

<table>
<thead>
<tr>
<th>Average disease duration</th>
<th>Both studies</th>
<th>Phase IIb</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stopping rule: safety criteria</td>
<td>Comparator</td>
<td>Doses</td>
</tr>
</tbody>
</table>
| 8 years                  | 1) SC1 withdrawal > 10%  
2) SC2 withdrawal >25%  
3) SC3 significantly different from MTX | MTX | L, M1, M2, H | 1) Fail superiority to MTX  
2) Fail non-inferiority to active comparator (indirect comparison) | MTX + Etanercept | Lowest successful dose in Phase IIb | Fail non-inferiority to active comparator | 6 months |

### Decisions to make now

<table>
<thead>
<tr>
<th>End point</th>
<th>Phase IIb</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20</td>
<td>40</td>
<td>3 months</td>
</tr>
<tr>
<td>ACR50</td>
<td>60</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td></td>
</tr>
<tr>
<td></td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

(1) SC = safety criteria  
(2) ACR20, ACR50 binary outcome which indicates a 20% or 50% improvement over a given time period
## Effectiveness

- Two data sources
  - Phase 3 trials for biologics (snippet of data below)
  - Early 1 month Phase 2a trial

<table>
<thead>
<tr>
<th>Drug</th>
<th>Regime</th>
<th>N</th>
<th>1 Month ACR50</th>
<th>3 Months ACR50</th>
<th>6 Months ACR50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anakinra</td>
<td>Placebo</td>
<td>121</td>
<td>NA</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>30mg day</td>
<td>119</td>
<td>NA</td>
<td>NA</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>75mg day</td>
<td>116</td>
<td>NA</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>150mg day</td>
<td>116</td>
<td>NA</td>
<td>9</td>
<td>22</td>
</tr>
<tr>
<td>Anakinra</td>
<td>MTX</td>
<td>251</td>
<td>NA</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>100mg day</td>
<td>250</td>
<td>NA</td>
<td>33</td>
<td>43</td>
</tr>
<tr>
<td>Etanercept</td>
<td>MTX</td>
<td>228</td>
<td>10</td>
<td>61</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td>25mg 2wk+MTX</td>
<td>231</td>
<td>44</td>
<td>95</td>
<td>133</td>
</tr>
<tr>
<td></td>
<td>25mg 2wk</td>
<td>223</td>
<td>35</td>
<td>79</td>
<td>92</td>
</tr>
</tbody>
</table>
Effectiveness Prediction Functions

- Use Phase III data set to estimate
  - Odds ratios between different treatments at the same time points
    - by a mixed-treatment-comparisons meta-regressions
  - Predict probability of ACR event at 3 or 6 months from 1 or 3 months
    - By logistic regression with random-effects
  - These can be functions of different treatment and disease duration

- Use Phase IIa study to predict the probability of ACR given new treatment compared to MTX

\[
\begin{align*}
\pi_M(1) & \rightarrow \pi_M(3) & \rightarrow \pi_M(6) \\
\pi_E(3) & \rightarrow \pi_E(6) \\
\pi_N(1) & \rightarrow \pi_N(3) & \rightarrow \pi_N(6)
\end{align*}
\]
Safety Criteria Functions (SCx)

3 month withdrawal probabilities if given MTX + biologic treatment at dose $d$

$$\pi_{sc1}(3,d) \quad \text{Probability of withdrawing because of SC1}$$

$$\pi_{sc2}(3,d) \quad \text{Probability of withdrawing because of SC2}$$

$$\pi_{sc3}(3,d) \quad \text{Probability of withdrawing because of SC3}$$

6 month withdrawal probabilities are twice 3 month probabilities
Safety concern 1 distributions

Elicited because there is no data

\[ \pi_{sc1}(3, d) = \lambda(1 - \exp(-d\beta)) \]

- Probability of withdrawing because of SC1 safety if given MTX + biologic treatment at dose d after 3 months

- Relative risk of withdrawal if given MTX + \{M1\}mg compared to MTX + \{H\}mg
  - \( \frac{1 - \exp(-\{M1\}\beta)}{1 - \exp(-\{H\}\beta)} \sim \text{Beta}(16.1, 8.2) \)

- Risk of withdrawal if given MTX + \{M1\}mg
  - \( \gamma(1 - \exp(-\{M1\}\beta)) \sim \text{Beta}(2.2, 59.7) \)
Elicitation

- Suppose we wish to elicit a distribution for a risk
- The experts judge the percentiles of the risk to be
- Find a and b to minimize

\[
(F_{a,b}(0.1) - 0.05)^2 + (F_{a,b}(0.2) - 0.5)^2 + (F_{a,b}(0.35) - 0.95)^2
\]

CFD of a beta distribution

Find a Beta(5.8, 22.3) distribution
Study simulation model

*How decisions, information and values are linked*

![Diagram showing the relationship between various factors in a study simulation model.](image-url)
Clinical Trial Simulation vs Bayesian Clinical Trial Simulation

Clinical trial simulation
- Can estimate expected results from complex trials
- **But parameters are fixed**

Bayesian clinical trial simulation
- To compute PoS we must also simulate parameters
- This is done in the same loop and needs no extra simulated trials
- **Average over the unknown parameters**
Probability of success depends on design

*Could pick a design that gives maximum PoS*
### Study results

*Dig into where studies are failing*

<table>
<thead>
<tr>
<th>End point</th>
<th>Sample size</th>
<th>Exposure</th>
<th>Sample size</th>
<th>Non-inferiority margin</th>
<th>PoS</th>
<th>Fail Non-inferiority</th>
<th>Fail Superiority</th>
<th>Fail Safety</th>
<th>PoS (Registration)</th>
<th>Fail Non-inferiority</th>
<th>Fail Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20</td>
<td>80</td>
<td>3 months</td>
<td>200</td>
<td>0.8</td>
<td>7.8%</td>
<td>91.8%</td>
<td>42.6%</td>
<td>5.2%</td>
<td>4.7%</td>
<td>1.7%</td>
<td>0.16%</td>
</tr>
<tr>
<td>ACR20</td>
<td>80</td>
<td>6 months</td>
<td>200</td>
<td>0.8</td>
<td>6.8%</td>
<td>89.9%</td>
<td>40.1%</td>
<td>2.2%</td>
<td>4.7%</td>
<td>1.5%</td>
<td>0.02%</td>
</tr>
</tbody>
</table>

- The overall probability of successful drug registration is the same in both cases
  - But a 6-month study has a slightly smaller chance progression from Phase 2b to Phase 3
  - This is good as it stops the program before the expensive study

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*Bayesian clinical trial simulation | Richard Nixon | 2010 March 24*
Impact of larger Phase IIb trials

*Size of the Phase IIb is key driver of PoS*

![Bar chart showing the impact of different size Phase IIb trials on the overall chance of success.](chart.png)

- **100 patients per arm**: 11.0%
- **150 patients per arm**: 12.0%
- **200 patients per arm**: 13.0%
- **250 patients per arm**: 14.0%
Sensitivity analysis: the Tornado Diagram

Not calculated during this work, but are a useful way of assessing which uncertainties have most influence on value.

Value of alternative when all other uncertainties are at their 50th percentile levels, and Uncertainty X is at its:

- 10th %ile level
- 50th %ile level
- 90th %ile level

Uncertainty X

Uncertainty W

Uncertainty X

Uncertainty Y

Major value drivers and risk sources

Lesser or negligible risk sources
What does decision analysis bring to trial design?

- Comprehensive approach that evaluates many different combinations
- Considers interactions of options
- Accounts for uncertainty in assumptions
- Evaluation of tradeoffs beyond statistical power