Modelling and Simulation of the incidence of adverse events in clinical trials

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Introduction

- Drug Y is an improved version of a marketed drug X
- A specific adverse event is related to supra-efficacious drug levels and is expected for drug Y as well.
- In planned clinical trials with drug Y, we want to control the incidence of the adverse event, to balance efficacy and safety
- PK/PD model using data of drug X (~2500 patients, 10 trials)
- Predict adverse event in clinical trials with Y (based on a pharmacokinetic and pharmacological rationale)
How to model adverse events?

A typical patient AE profile

Dichotomize at the end of the trial
Binary Data Analysis

Dichotomize during the trial
Time-to-event/Hazard Modeling

Complete profile day-by-day
Repeated Binary Data Analysis

Complete profile as state changes
Recurrent Event Analysis, Markov Models,...
The Data of Drug X

- Double-blind placebo controlled trial with 3 doses

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Drop-out(%)</th>
<th>AE(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>98</td>
<td>67(68)</td>
<td>13(13)</td>
</tr>
<tr>
<td>10 mg</td>
<td>99</td>
<td>51(51)</td>
<td>10(10)</td>
</tr>
<tr>
<td>20 mg</td>
<td>103</td>
<td>54(51)</td>
<td>25(24)</td>
</tr>
<tr>
<td>30 mg</td>
<td>100</td>
<td>52(52)</td>
<td>29(29)</td>
</tr>
</tbody>
</table>

\[
AE = \frac{\text{# of patients with at least 1 AE-episode}}{\text{# of patients randomized}}
\]
Kaplan-Meier plot for time to first AE

![Kaplan-Meier plot](image-url)
Cumulative hazard

![Graph showing cumulative hazard over time for different doses of a medication, with Placebo, 10 mg, 20 mg, and 30 mg treatments represented by different lines.](image-url)
What measure of drug exposure?

- No scientific rationale available
- As the adverse event develops over time, an integrated measure of long term exposure was chosen

Individual - Average Steady-State Concentration ($C_{av_i}$)

$$C_{av_i} = \frac{\text{Dose}}{\text{Cl}_i/\tau}$$

$Cl_i : \text{Individual Clearance}$
$\tau : \text{Dosing interval}$

Bayesian Individual Predictions
Population PK model
**Cumulative hazard x Exposure**

<table>
<thead>
<tr>
<th>Cav (µg/ml)</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>13.3% (13/98)</td>
</tr>
<tr>
<td>[0-.25]</td>
<td>12.7% (8/63)</td>
</tr>
<tr>
<td>[.25,.35]</td>
<td>13.8% (8/58)</td>
</tr>
<tr>
<td>[.35,.45]</td>
<td>28.6% (10/35)</td>
</tr>
<tr>
<td>[.45,.60]</td>
<td>28.0% (14/50)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>27.4% (17/62)</td>
</tr>
</tbody>
</table>
Incidence of AE x Exposure

![Graph showing the incidence of AE (Adverse Events) against exposure levels. The x-axis represents Median Cav (micg/ml) ranging from 0.0 to 0.8, while the y-axis represents the percentage of AE with values up to 25%. The graph exhibits a sharp increase in AE incidence at a Median Cav of 0.4 micg/ml.]
Modeling the AE risk

\[ \log \lambda(t, c_i) = f(t) + g(t, c_i) \]

- \( t \): time since trial start
- \( c_i \): individual average steady state concentration

**Time dependency**

\[ f(t) = \beta_0 + \beta_1 t \]

**Drug effect - logistic**

\[ g(c_i) = \frac{\theta_1}{1 + \exp\left(\frac{\theta_2 - c_i}{\theta_3}\right)} \]

- \( \theta_1 \): maximal effect
- \( \theta_2 \): EC50
- \( \theta_3 \): scale parameter (steepness )

**Drug effect - threshold**

\[ g(c_i) = I(c_i > \theta_1) \cdot \theta_2 \]

- \( \theta_1 \): threshold for risk increase
- \( \theta_2 \): log risk increase
Functional form for various $\theta_3$
Likelihood profile for $\theta_3$
Threshold versus logistic model
($\theta_3=1$)
Implementation in SAS 8.2

```sas
id time cav event;
1  1     12  0
1  2     12  0
1  3     12  0
...
1  60    12  0 = censored at Day 60
2  1     65  0
2  2     65  0
2  3     65  1 = has AE at Day 3
...
```

```sas
proc nlmixed;
parms a=-4  b=-0.04  emax=1  ec50=3  scale=4;
loghaz=a+b*time+emax/(1+exp(ec50-cav)/scale);
p=exp(loghaz);
model event~binomial(1,p);
run;
```
Model Validation

AE incidence (%) in 5 independent clinical trials with drug X (total ±2000 pat.). Each point is a different dose, each color a different trial.
Clinical Trial Simulation for Drug Y

- Population PK model

\[ \text{Cl}_i \]

- PK/PD-model

\[ \text{Cav}_i \] \[ (\lambda_{AE})_T \]

- Drop-out-model

\[ (\lambda_{DROP})_T \]

Simulation Model

- for subject = 1, ..., N
- for t = 1, ..., d
- \( \text{AE}(t) \sim \text{Bin}(1, \lambda_{AE}) \)
- \( \text{DROP}(t) \sim \text{Bin}(1, \lambda_{DROP}) \)
Incidence of AE in the population

Simulation of 2000 patients/dose, no drop-out, 8-week trial

% with AE - Diff. with Placebo

Median

5% - 95% percentile

Total Daily Dose, mg

PAGE 2004, Uppsala, 17-18 June 2004
AE Incidence (%) in planned trials

Simulation of 1000 trials, 100 patients/dose, drop-out, 8-weeks

Dose 0 mg
Dose 3 mg
Dose 9 mg
Dose 15 mg
AE Incidence (%) in planned trials

Simulation of 1000 trials, 100 patients/dose, drop-out, 8-weeks
Conclusions

- Hazard modeling is a flexible tool to model the occurrence of side effects in clinical trials.
- In the example presented here, the risk for a specific adverse event showed a steep (~on/off) relation with the patient-specific average steady state concentration.
- Modeling allowed synthesis of data of a large number of studies of a marketed drug.
- Clinical Trial Simulation allowed to study what can be expected in planned clinical trials, and optimize the dose range to study.