An optimization approach for the early phases of drug development
Overview

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Aims of Phase II
Aims of Phase II

Usually there are 3 phases in clinical drug development:
- Phase I: Safety in healthy volunteers
- Phase II: Mechanism in patients, and dose selection
- Phase III: Efficacy in patients.

The aim of Phase II in the xxx project is
- to support the selection of the treatments (dose level, duration, combo partners) that go in Phase III.
Aims of Phase II

What is the primary medical view on a Phase II trial:
- the single trial alone
- the trial as integrated part of the development project?

This determines
- the questions that can be answered by the trial
- the adequate analysis methods
- the necessary N to obtain precise results.
Aims of Phase II

For consideration of the single trial alone speaks:

- Extrapolation to Phase III unclear anyway (e.g. population, con-meds)

- Use of established analysis methods (data description, CIs, p-values) and planning methods (power)

- Clear “signals” provided through low p-values, which can be used for marketing (external and internal) and for go / no-go decisions

- More comfort for investigators at time of publication
Aims of Phase II

For consideration of the **project context** speaks:

- Uncertainty of extrapolation to Phase III made quantitative
- Balance between savings in Phase II and risk for Phase III shown explicitly and quantitatively
Aims of Phase II

Selection of the right treatment(s) to be used in Phase III:

Single trial alone:
Comparisons between treatments:
- “Some differences are certainly non-0 but others are not”

Trial in project context:
Estimation of the probability of correct selection:
- “A reasonable selection is likely”
Aims of Phase II

⇒ Sample size determination in Phase II:

**Single trial alone:**
Power calculation to detect differences

**Trial in project context:**
Determination of an N for which it can be expected that the probability of the correct selection is sufficiently high
Aims of Phase II

We continue within the project context.
Aims of Phase II

Analysis methods within the project context:

- Low p-values give yes/no answers to a question that is relevant (if at all) only for a “final” trial

- Confidence intervals indicate which size of the difference can reliably be excluded – this is not a relevant question, either

- Publication: CONSORT rules prescribe to report the method of sample size determination, not the power calculation

Ref.: Moher/Schulz/Altman 2001
Analysis methods within the project context:

- Describe our knowledge of the unknown parameters (response rates with xxx) as random variable, the range of which becomes narrower when the project proceeds (Bayes approach)

- Start with only imprecise, external information, then become more precise when data accumulate

- The aim of the subsequent Phase III trial remains a “submissible” result, i.e. one with a low p-value vs. the control treatment yyy
Analysis methods within the project context:
- Forget p-values, show plausibility intervals for unknown parameters
- Replace power considerations by an optimization of $N_{II}$ regarding
  - $\uparrow$patient exposure, cost and time ①

  vs.

  - $\uparrow$risk of wrong selection for Phase III due to too imprecise knowledge acquired in Phase II ②

Aims of Phase II
Determination of N in Phase II by optimization approach
Determination of N in Phase II by optimization approach

Find the balance between the following:

- ↑ patient number

**vs.**

- ↑ risk of wrong selection for Phase III due to too imprecise knowledge acquired in Phase II

There is an optimum beyond which a further increase of $N_{II}$ would **not** **relevantly increase** the correctness of the selection **anymore**; the small gain in power of Phase III due to more precise selection would be out-weighed by the efforts for the higher $N_{II}$

How can we find this optimum?
Determination of N in Phase II by optimization approach

Find 2 functions that have $N_{II}$ as the independent variable:

- The effort to perform Phase II – function ①

and

- The surplus risk for the company to end up with a failed Phase III due to wrongly selected treatments due to too imprecise knowledge acquired in Phase II – function ②
Determination of N in Phase II by optimization approach

Qualitatively:

Cost

N (Ph. II)

①

②
Determination of N in Phase II by optimization approach

Phase II of xxx will have several (ca. 7) treatment groups of equal size

Of these, the 1 or 2 best treatments will be selected for Phase III

Problem: The treatment that is in fact the best one might not show up as the best one or among the 2 best ones and will – inadvertently – not be selected, leading to a loss of Phase III power and to an increased risk of project failure

The problem is here illustrated with the comparison vs. yyy, it becomes less severe for the comparison vs. zzz.
Determination of N in Phase II by optimization approach

True and observed responses in Phase II treatment groups 1 - 7

- True (sharp prior)
- Observed
- yyy
- zzz
Determination of N in Phase II by optimization approach

Qualitatively:

Function 1 considers costs of patients in Phase II.

It goes up linearly with $N_{II}$.

It considers also costs due to treatments not selected later.

It does not consider costs due to delay of Phase III and of submission / registration through an unnecessarily large and long Phase II – time-planning for recruitment is currently independent of trial size (e.g. 1 year for Phase III).

It cannot consider any medical risk for patients due to exposure to xxx.
Determination of N in Phase II by optimization approach

Function ② considers costs due to surplus failure risk of Phase III after wrong selection.

E.g. we plan for 50% response in Phase III but select after Phase II a treatment that has in reality only e.g. 40% (but we do not know that!). Consequently, the probability of a failed trial / project will go up.

It is not a remedy to start with the 40% from the beginning (enormous over-power in case of correct selection).
Determination of $N$ in Phase II by optimization approach

Function $\hat{d}$ approaches 0 due to diminishing overlap between treatments for large $N_{II}$

It decreases more strongly for smaller $N_{II}$ and becomes asymptotically flat

Therefore, the sum of $\hat{c}$ and $\hat{d}$ has a minimum.
Determination of N in Phase II by optimization approach

To repeat the qualitative picture:

Cost

Minimum

N (Ph. II)
Determination of N in Phase II by optimization approach

Quantitatively, function \( \hat{d} \) is determined by the following:

- The decrease of power in Phase III due to incorrect selection
- The probability with which this occurs (depends from \( N_{II} \))
- The loss to the company due to the failure of the project.
Determination of N in Phase II by optimization approach

Quantitatively, function $d$ is determined by the following:
- The decrease of power in Phase III due to incorrect selection
- The probability with which this occurs (depends from $N_{II}$)
- The loss to the company due to the failure of the project.
Determination of N in Phase II by optimization approach

The decrease of power in Phase III due to incorrect selection is immediately clear (Casagrande formula).

Ref.: Casagrande/Pike/Smith 1978
Determination of N in Phase II by optimization approach

Quantitatively, function $d$ is determined by the following:

- The decrease of power in Phase III due to incorrect selection
- The probability with which this occurs (depends from $N_{II}$)
- The loss to the company due to the failure of the project.
The mixup probability depends from $N_{II}$. In the simple case of fixed assumed response proportions $p_1$ and $p_2$ for each treatment, it is the product of 2 Binomial distributions, summarized on and above the diagonal line. Analytic calculation is possible, no simulation necessary.

Question: Which degree of mixup is tolerable? Further weighting is necessary, a fixed limit (5%? 20%) is not meaningful.

Ref.: Wakana/Yoshimura/Hamada 2007
Determination of N in Phase II by optimization approach
Determination of N in Phase II by optimization approach

Mix-up: All points on and above the diagonal

N1 = 40, N2 = 40, P1 = 0.5, P2 = 0.4
Determination of N in Phase II by optimization approach
Determination of N in Phase II by optimization approach

The mixup probability from Binomial distribution (p1=0.5, p2=0.4):

Probability of mixup between critical groups dependent from N in Phase II, binomial case
Quantitatively, function $d$ is determined by the following:

- The decrease of power in Phase III due to incorrect selection
- The probability with which this occurs (depends from $N_{II}$)
- The loss to the company due to the failure of the project.
What is the unit of the “cost” variable (y axis)? Be careful not to add apples and pears to each other.

All costs are expressed in patient numbers.

The relevant quantity is the number of patients treated in Phase II and III together.

Number of groups in Phase II and number of patients in Phase III needs to be fixed in advance – [OK for now].

Project failure will be expressed as costs of additional patients, these will be weighted by the failure probability.
Determination of N in Phase II by optimization approach

The loss to the company is approximated by the following:

- Marketing forecasts provide the expected turnover and RoI after registration
- If the cost of treating 1 patient for the standard duration with standard medication is eee EUR (upper limit), then this is equivalent to treating 3,000 patients in a study
- These 3,000 patient-equivalents are a lower limit; other values have however to be investigated as well.
Determination of N in Phase II by optimization approach

This loss is to be multiplied with the excess probability with which it occurs, which is the decrease of Phase III power * the probability of wrong selection (dependent from $N_{II}$)

Now we have defined function $\circled{2}$ with $N_{II}$ as independent variable as well

Both functions, $\circled{1}$ and $\circled{2}$, have the same unit, “patients”, and can be added to each other

Both functions of $N_{II}$ are convex (function $\circled{1}$ is linear, function $\circled{2}$ is the product of a constant, a convex function and a constant), so the sum has a minimum which gives the optimal $N_{II}$. 
Determination of N in Phase II by optimization approach

To repeat the qualitative picture:
Dependence from prior distribution
Dependence from prior distribution

If the theoretical proportions of response in the critical treatment groups are not known precisely (e.g. only in a range), the distributions of $z_1$ and $z_2$ will be more dispersed, and the overlap between the 2 groups will become greater.
Dependence from prior distribution

The mixup prob. from mixture of Bin. Distr. \((p_1=0.4-0.6, p_2=0.3-0.5)\):

Probability of mixup between critical groups
dependent from \(N\) in Phase II, ranges of +/- 0.1, 30000 simulations

![Graph showing mixup probability vs. N/group](image-url)
Any other information about the to-be-expected effects of the treatments can be included here (e.g. meta-analysis results).
Resulting sample size for Phase II
Resulting sample size for Phase II

Basic assumptions:
- Phase II has 7 groups (used here as approximation), of equal size
- Phase III has 1420 patients
- Project failure is assumed as equivalent to the costs of 3,000, 10,000 or 50,000 additional patients – will be investigated as scenarios
Determination of N in Phase II by optimization approach

True and observed responses in Phase II treatment groups 1 - 7

- True (sharp prior)
- Observed
- yyy
- zzz
### Resulting sample size for Phase II

- The groups investigated in Phase II and the expected responses are:

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>Response</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>3 mo</td>
<td>10%</td>
<td>0-20</td>
</tr>
<tr>
<td>Group 2</td>
<td>3 mo</td>
<td>30%</td>
<td>20-40</td>
</tr>
<tr>
<td>Group 3</td>
<td>6 mo</td>
<td>25%</td>
<td>15-35</td>
</tr>
<tr>
<td>Group 4</td>
<td>6 mo</td>
<td>40%</td>
<td>30-50</td>
</tr>
<tr>
<td>Group 5</td>
<td>3 mo</td>
<td>40%</td>
<td>30-50</td>
</tr>
<tr>
<td>Group 6</td>
<td>6 mo</td>
<td>35%</td>
<td>25-45</td>
</tr>
<tr>
<td>Group 7</td>
<td>6 mo</td>
<td>50%</td>
<td>40-60</td>
</tr>
</tbody>
</table>

- Response with yyy: 30% (considered fixed)
Resulting sample size for Phase II

- The critical mix-up occurs between Group 4 (...) and Group 7 (...):

  Group 4: ... 6 mo - 40% (30-50)

  Group 7: ... 6 mo - 50% (40-60)
Resulting sample size for Phase II

- Simulate trial outcomes of Phase II: Direct simulation with SAS sufficient, no MCMC necessary. 30,000 simulations:

  Group 4: ... 6 mo - 40% (30-50)

  Group 7: ... 6 mo - 50% (40-60)

- Investigate overlap ➔ wrong selection for Phase III ➔ loss of power vs. yyy (= increased project failure risk)
Resulting sample size for Phase II

Overall summary:

Weighted total patients due to mixup between critical groups (4 and 7) dependent from N in Phase II, ranges of +/- 0.1, 30000 simulations.
Cost of project failure = +3000, +10000 or +50000
Resulting sample size for Phase II

Although the mixup probability is lower for fixed proportions, the resulting optimum is very similar.

The optimal Phase II sample size is 60 – 100.

Results can be transferred to other populations ("borrow strength").

Ref.: Pezeshk 2003, Stallard 1998
Summary

- An optimum for $N_{II}$ can be found
- It should not be too small, for early exclusion of large risks
- A higher project value ("blockbuster") moves the optimum to the right; it is relevant to find a lower limit for the project value
- A more difficult Phase II moves the optimum to the left
- The balance between speed and risk can be quantified
- The optimum did not relevantly depend from the prior distribution of the (assumed) effects but systematic investigation is worth-while here.

Ref.: Pezeshk/Gittins 2006
Discussion

- How robust?

- How communicable?
  - Investigators
  - Medical journals
  - Patients and ECs
References


