Boehringer Ingelheim

Gemeinsame Tagung von 3 AGs
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G. Nehmiz

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

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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

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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

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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

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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

Aims of Phase II

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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

Aims of Phase II

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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
  - ↑patient exposure, cost and time ①

  vs.

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

Determination of N in Phase II by optimization approach

Determination of N in Phase II by optimization approach

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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

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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

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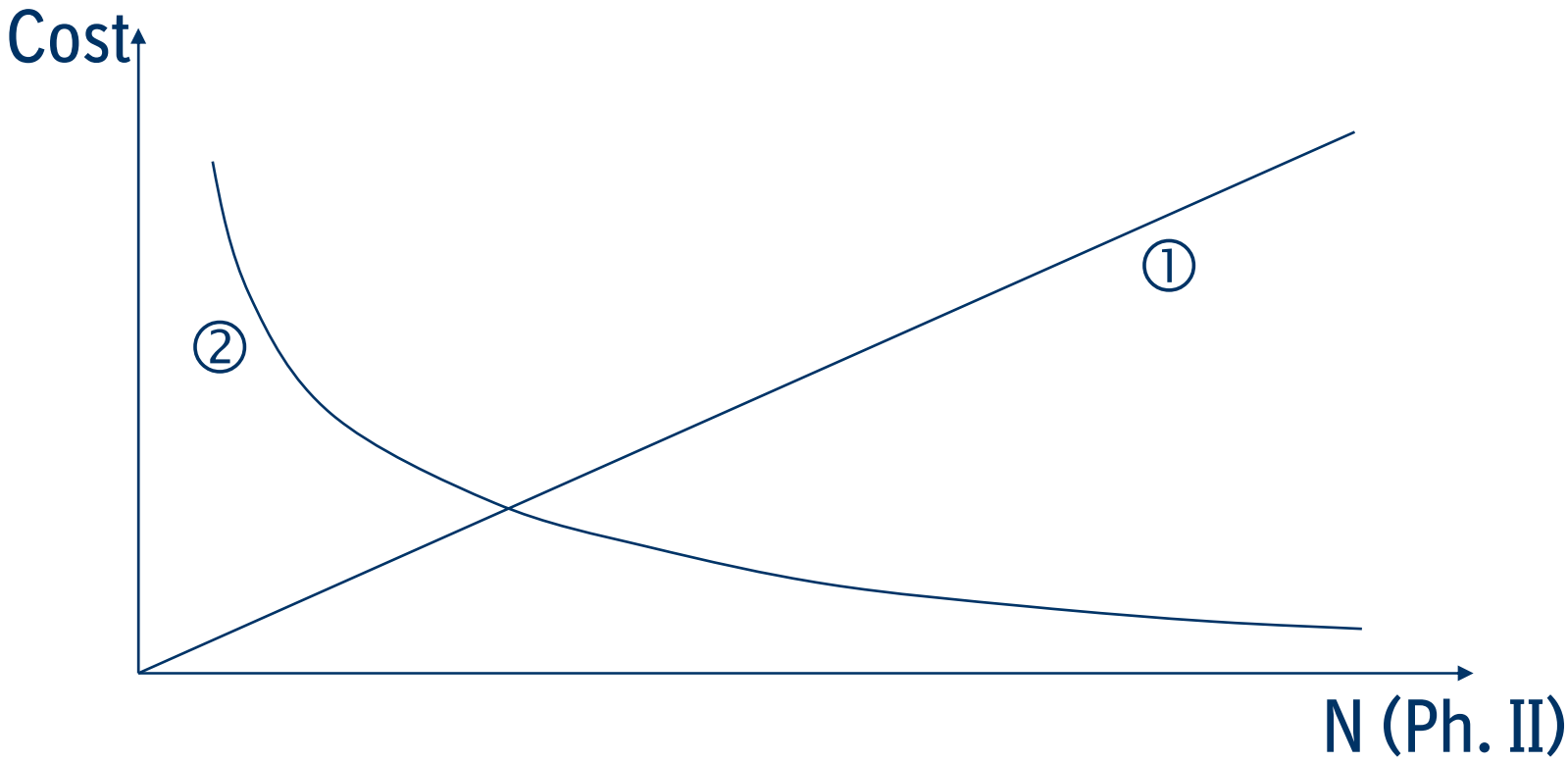
Qualitatively:



Determination of N in Phase II by optimization approach

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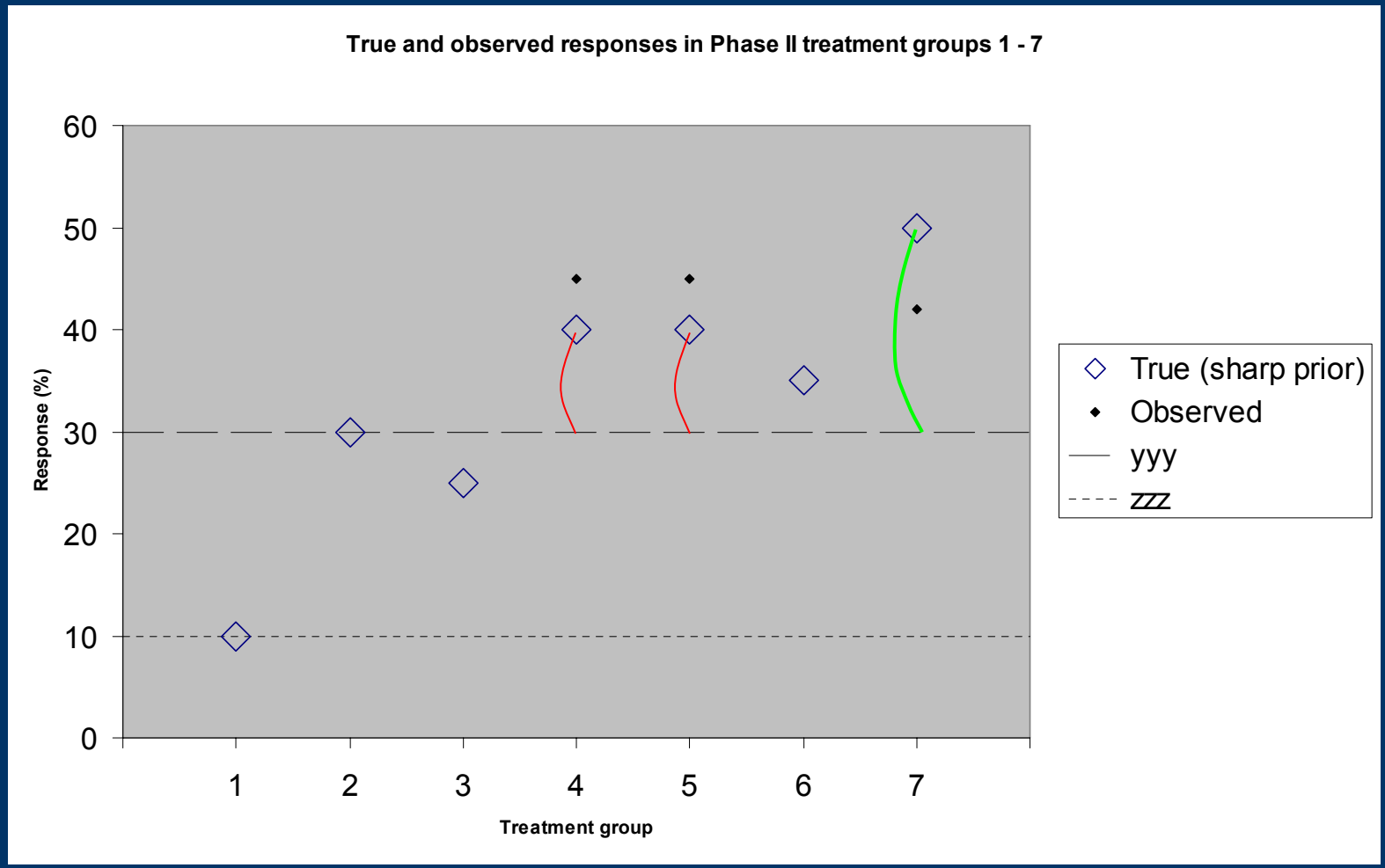
- Phase II of xxx will have several (ca. 7) treatment groups of equal size
- Of these, the 1 or 2 best treatments will be selected for Phase III
- Problem: The treatment that is in fact the best one might not show up as the best one or among the 2 best ones and will – inadvertently – not be selected, 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



Determination of N in Phase II by optimization approach

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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

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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

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Function ② 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 ① and ② has a minimum.

Determination of N in Phase II by optimization approach

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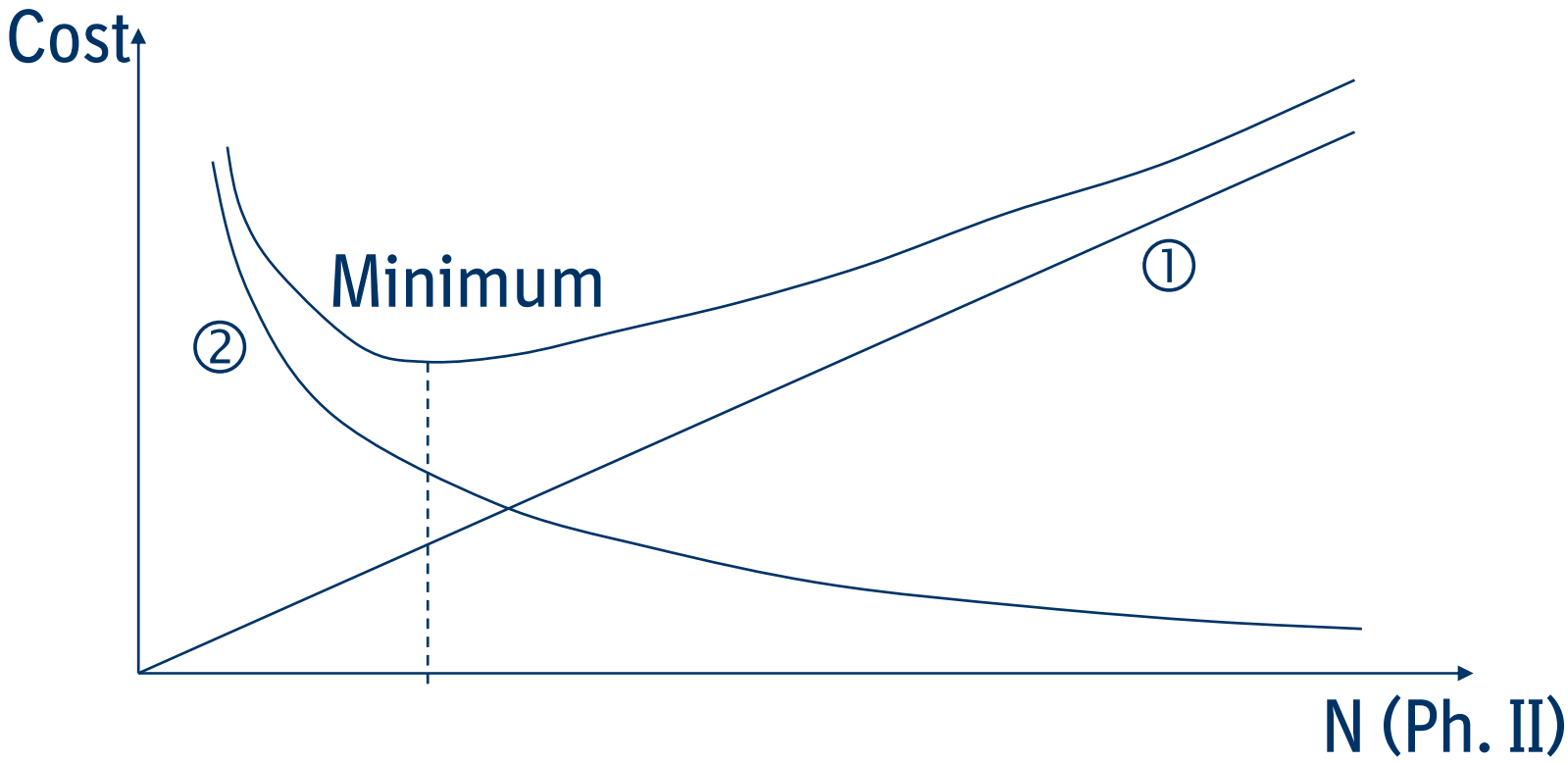
To repeat the qualitative picture:



Determination of N in Phase II by optimization approach

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Quantitatively, function ② 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

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Determination of N in Phase II by optimization approach

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

Ref.: Casagrande/Pike/Smith 1978

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Determination of N in Phase II by optimization approach

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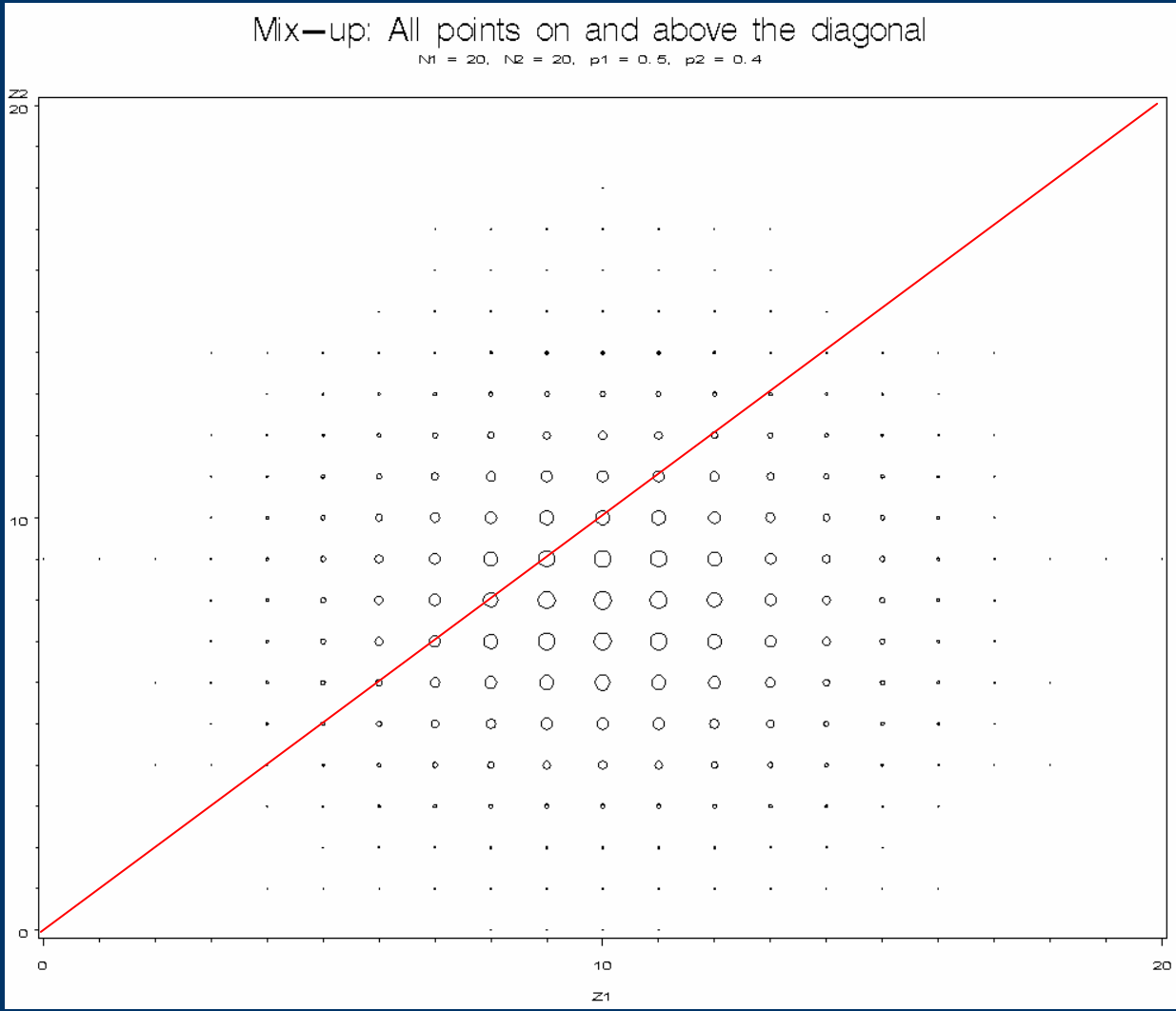
The mixup probability depends from N_{II}. In the simple case of fixed assumed response proportions p_1 and p_2 for each treatment, it is the product of 2 Binomial distributions, summarized on and above the diagonal line. Analytic calculation is possible, no simulation necessary.

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



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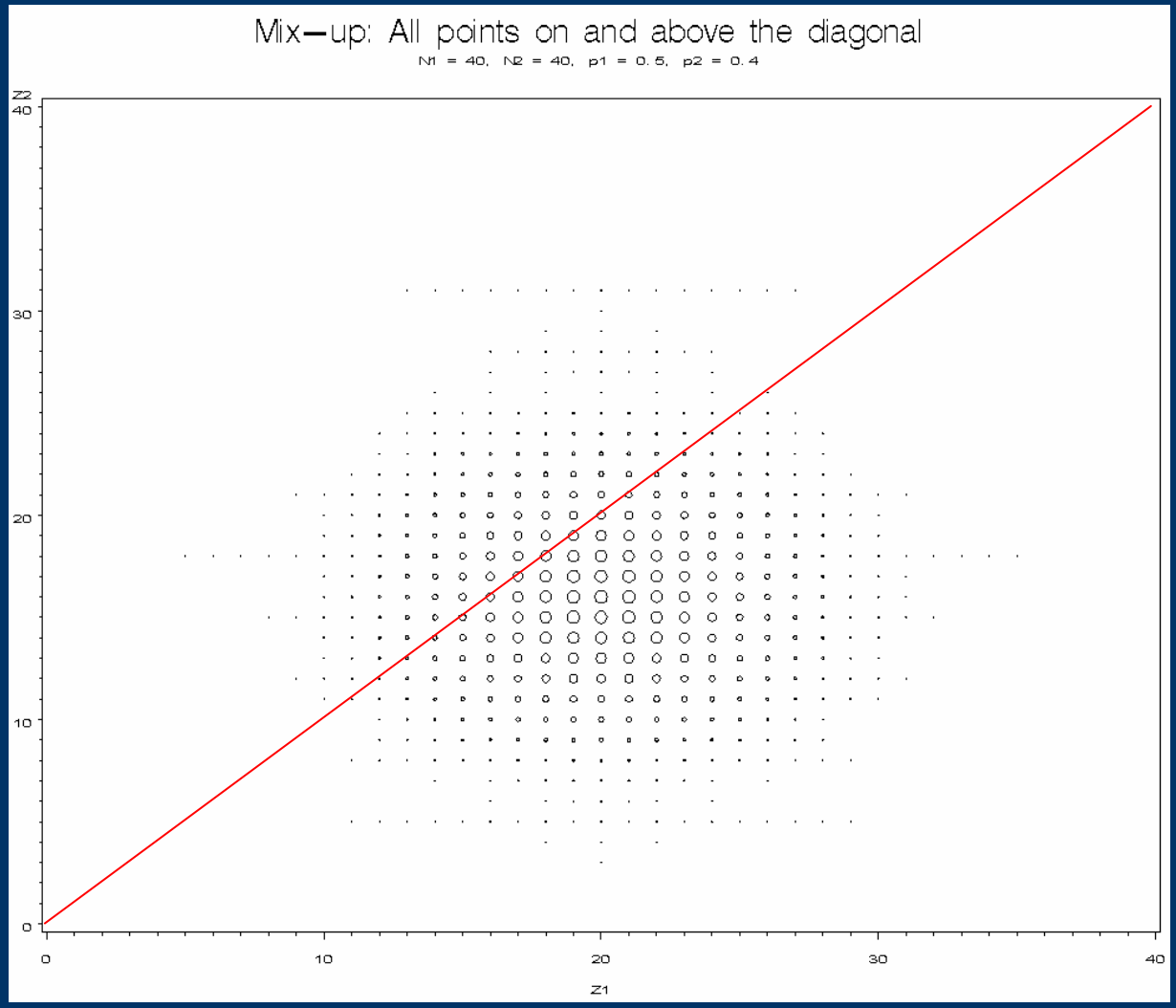

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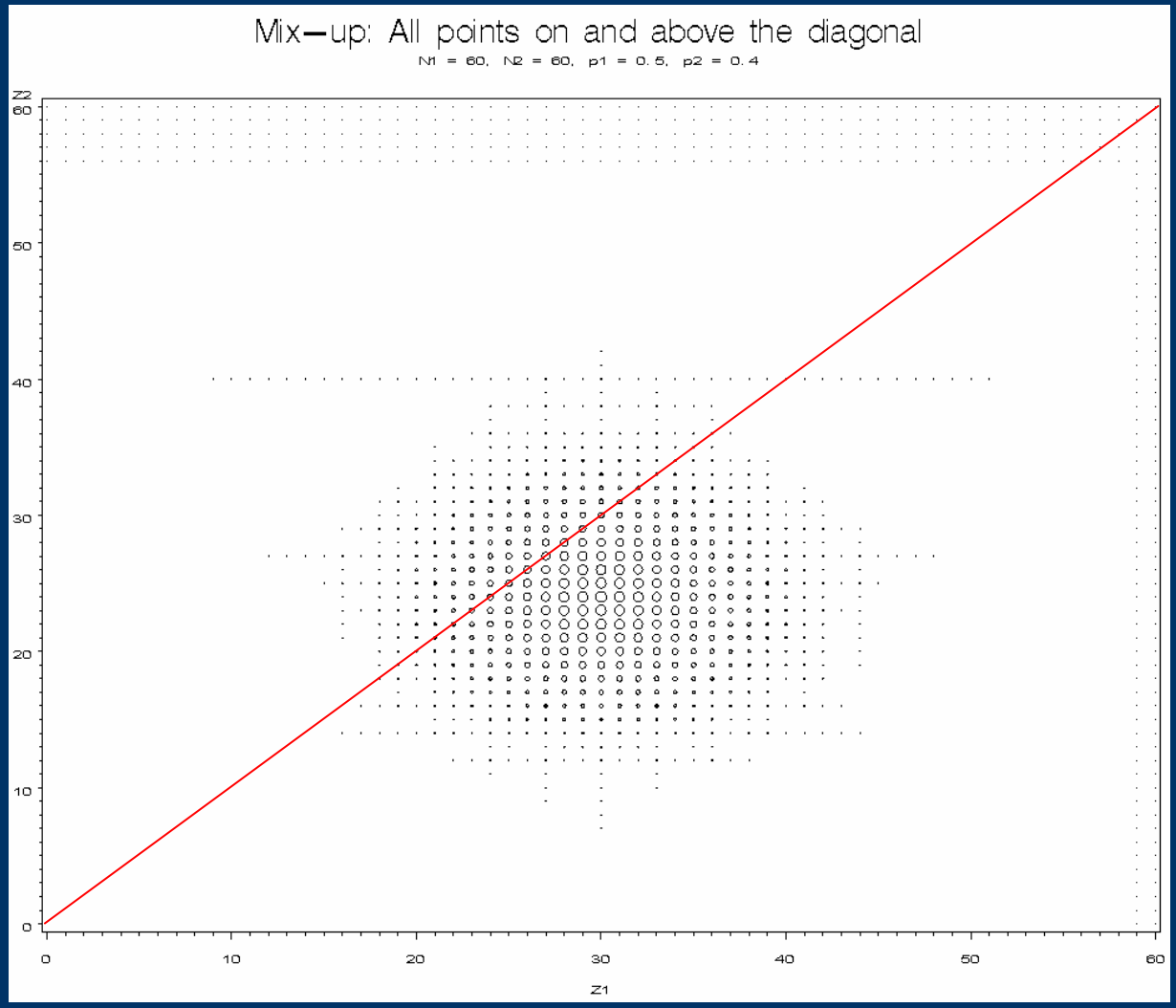

Determination of N in Phase II by optimization approach

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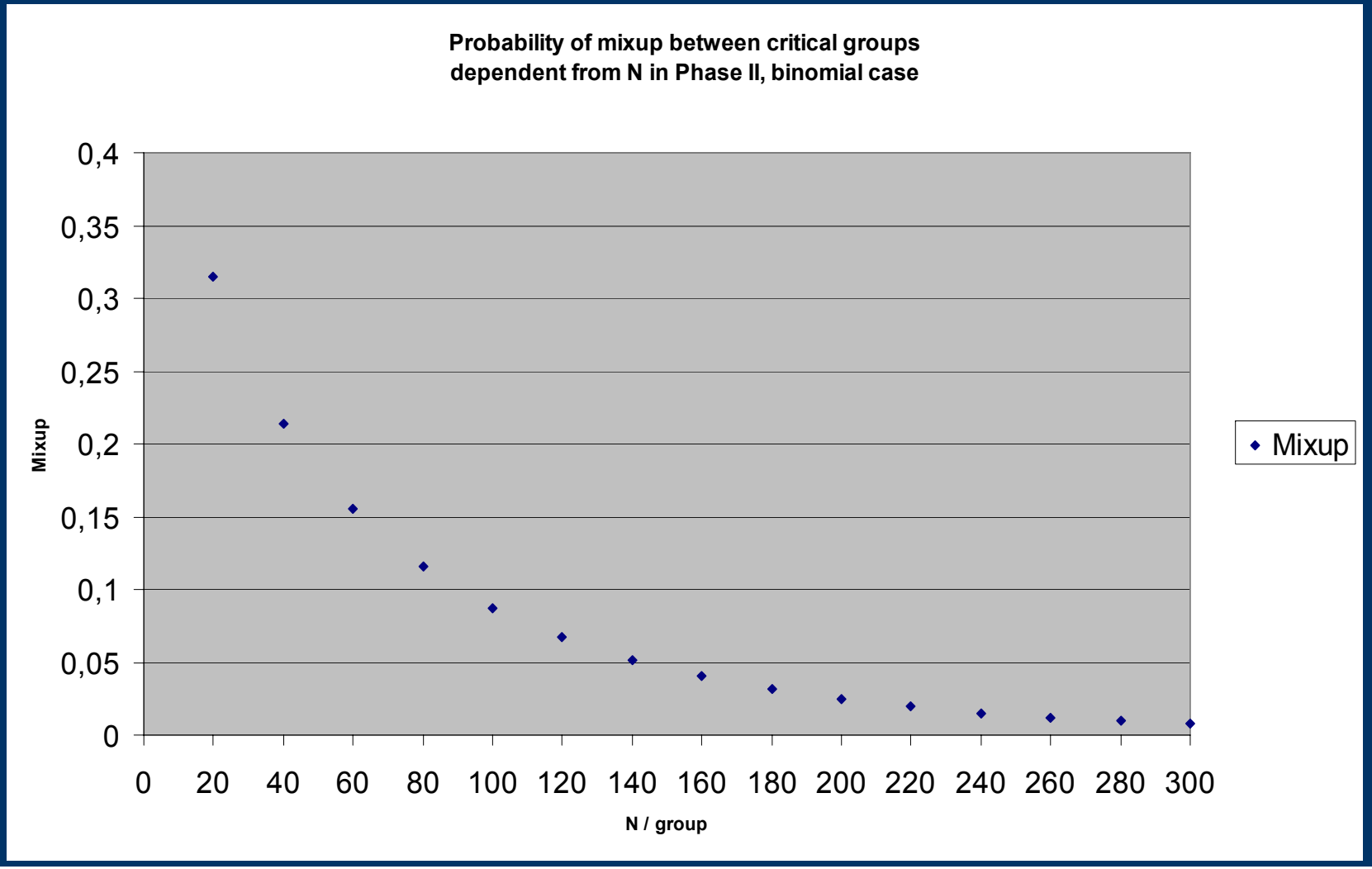
The mixup probability from Binomial distribution (p1=0.5, p2=0.4):



Determination of N in Phase II by optimization approach

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Quantitatively, function ② 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

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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

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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

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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 ② with N_{II} as independent variable as well

Both functions, ① and ②, have the same unit, “patients”, and can be added to each other

Both functions of N_{II} are convex (function ① is linear, function 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

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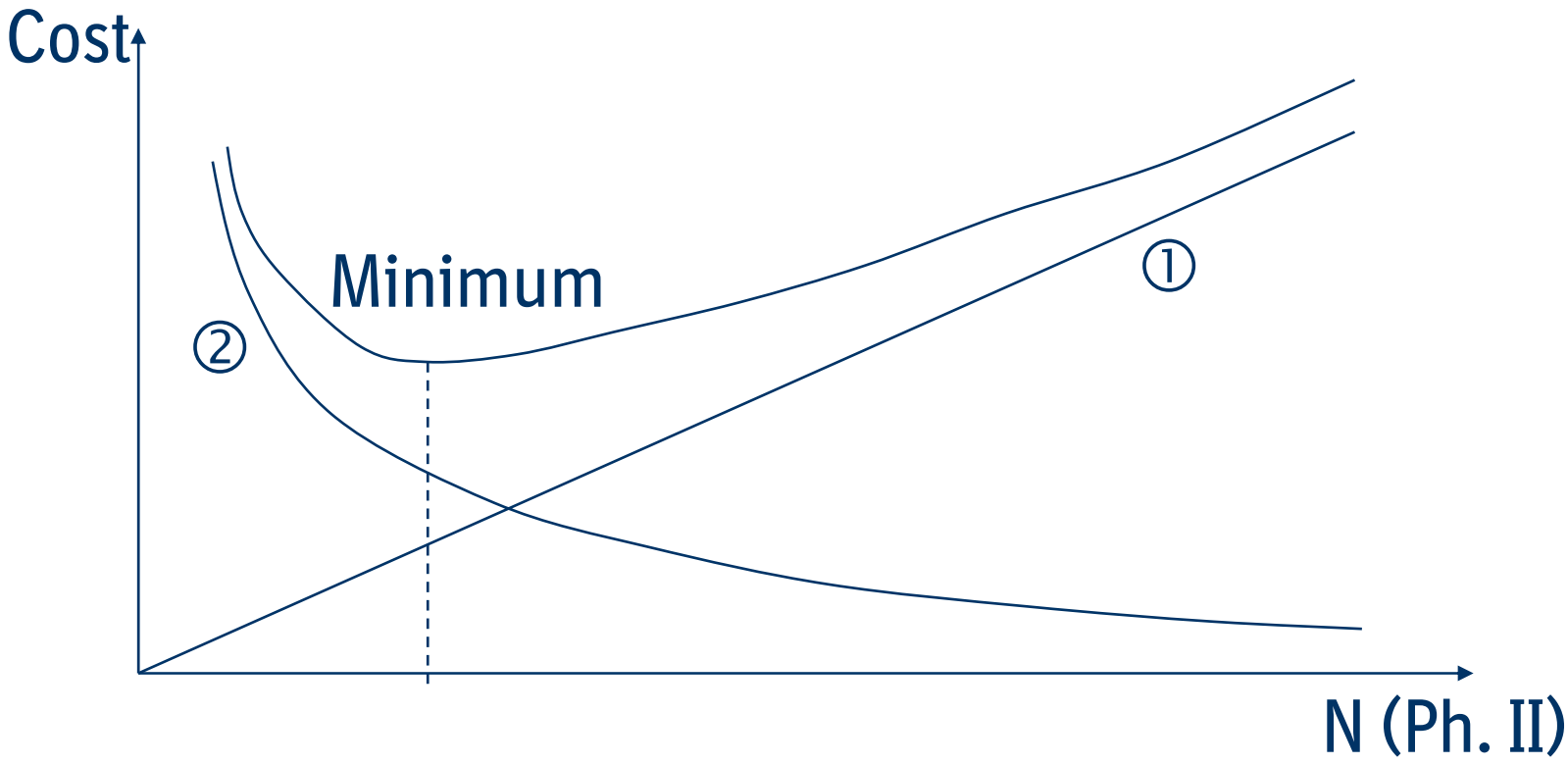
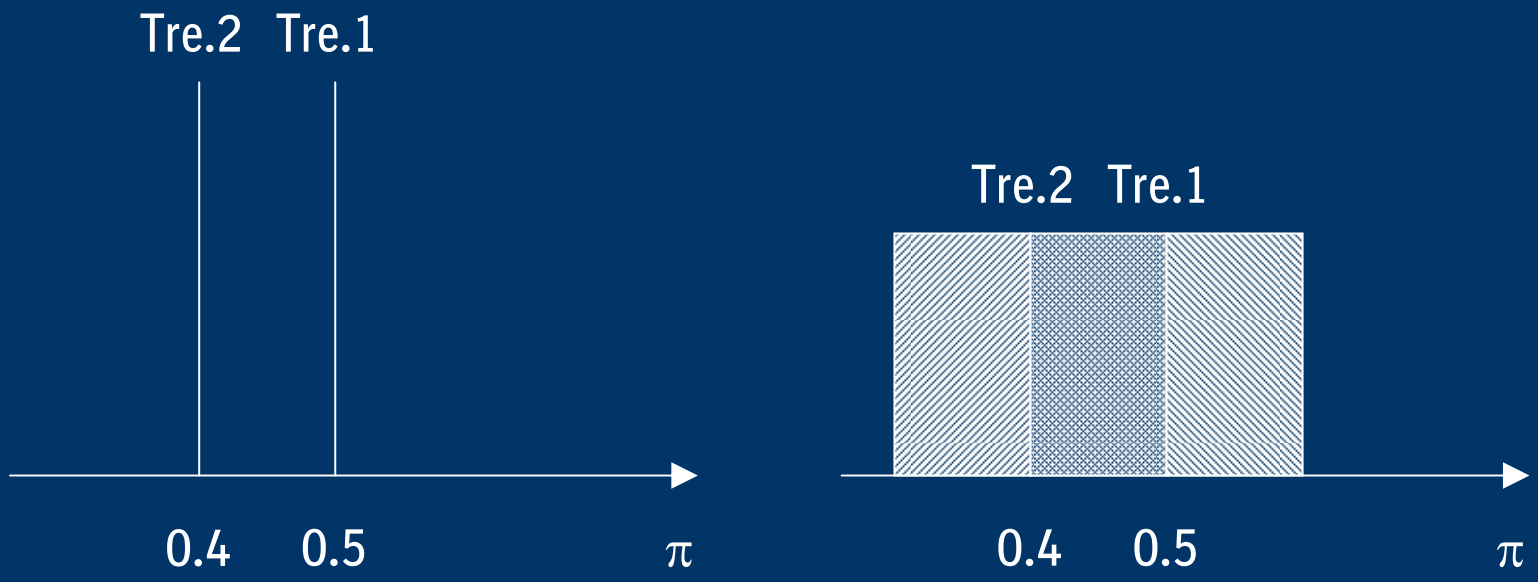
To repeat the qualitative picture:



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

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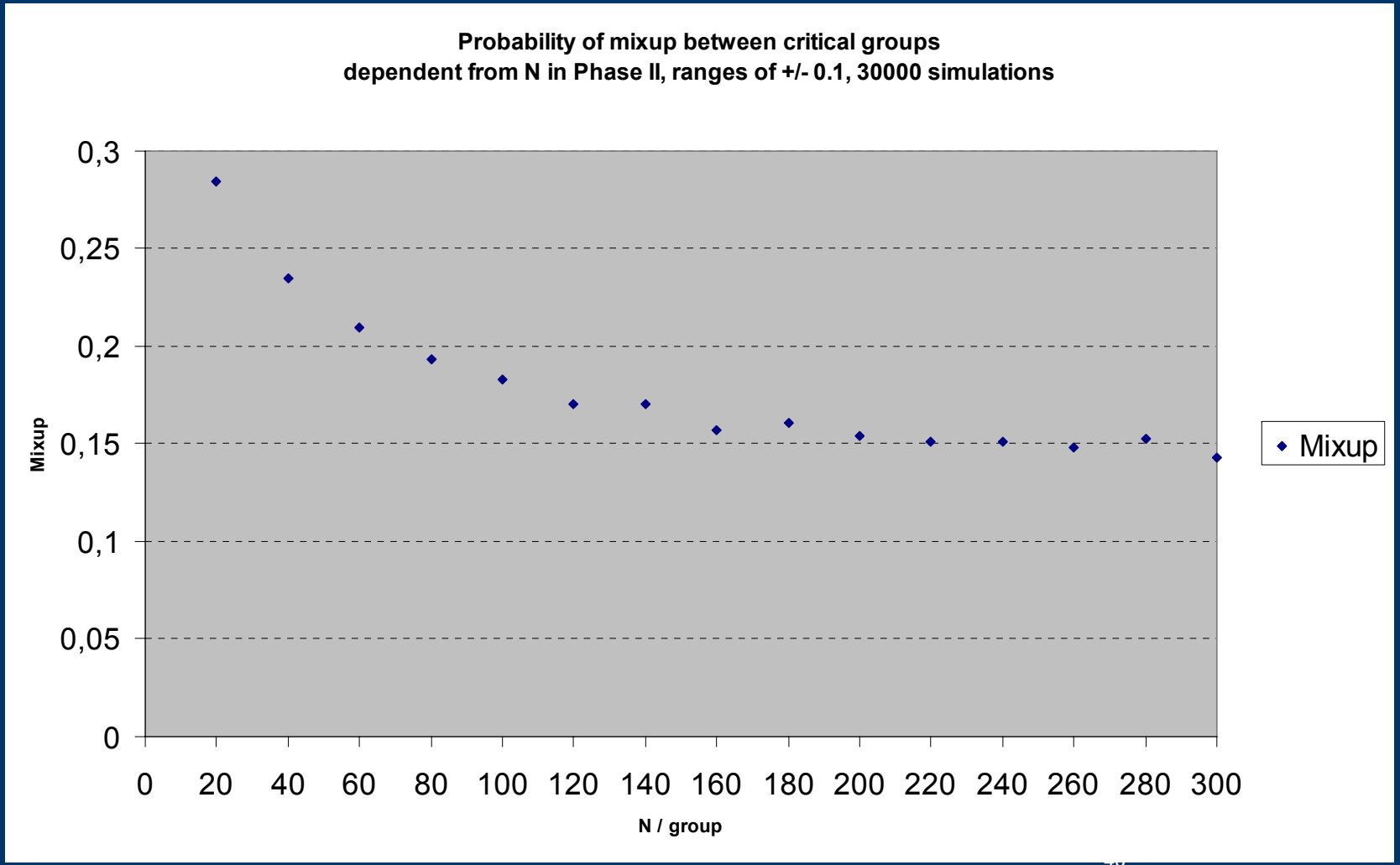
The mixup prob. from mixture of Bin. Distr. (p1=0.4-0.6, p2=0.3-0.5):



Dependence from prior distribution

Any other information about the to-be-expected effects of the treatments can be included here (e.g. meta-analysis results).

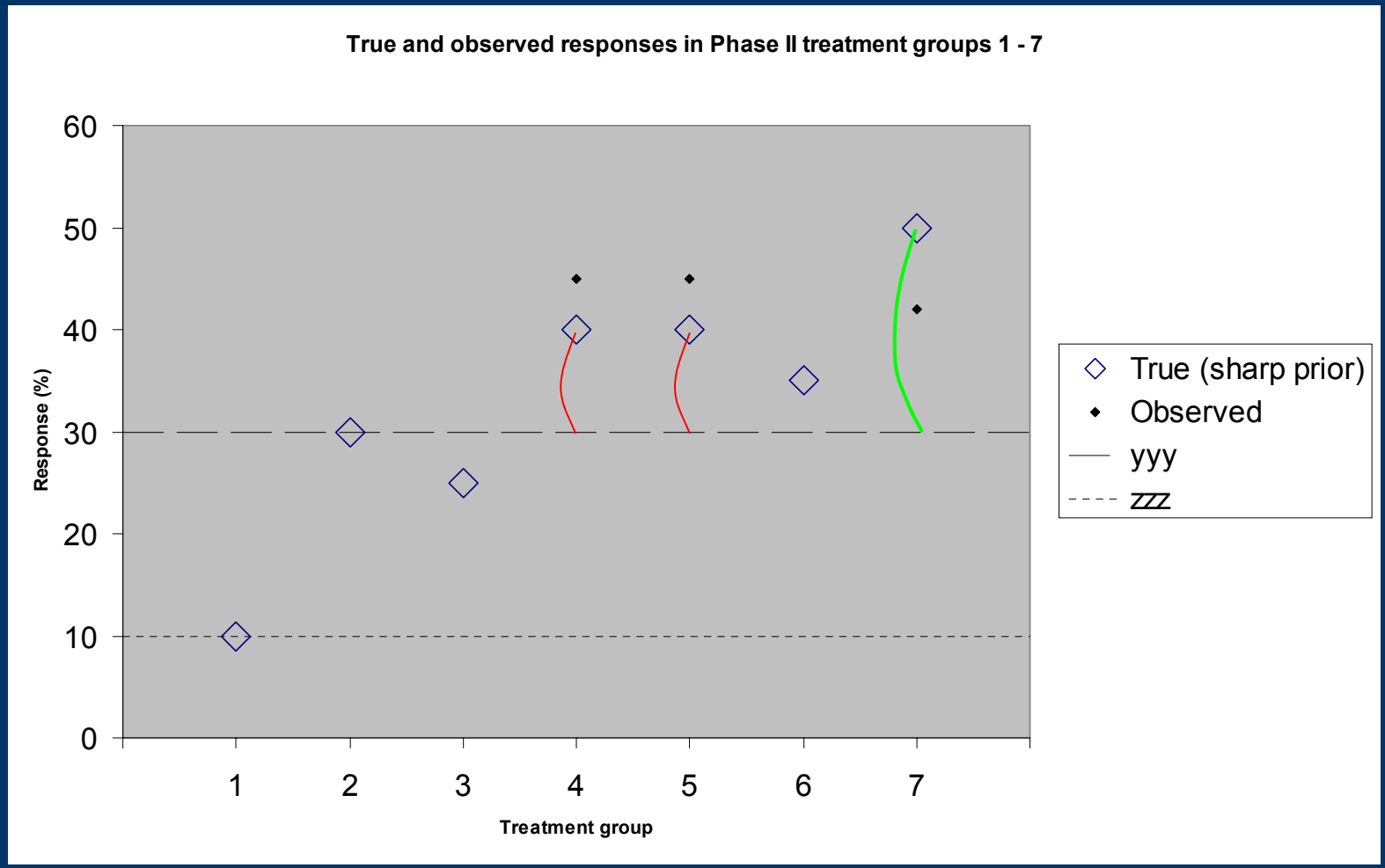
Resulting sample size for Phase II

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



Resulting sample size for Phase II

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

Group 1: ...	3 mo – response	10% (range	0-20)
Group 2: ...	3 mo -	30% (	20-40)
Group 3: ...	6 mo -	25% (	15-35)
Group 4: ...	6 mo -	40% (	30-50)
Group 5: ...	3 mo -	40% (	30-50)
Group 6: ...	6 mo -	35% (	25-45)
Group 7: ...	6 mo -	50% (	40-60)

- 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

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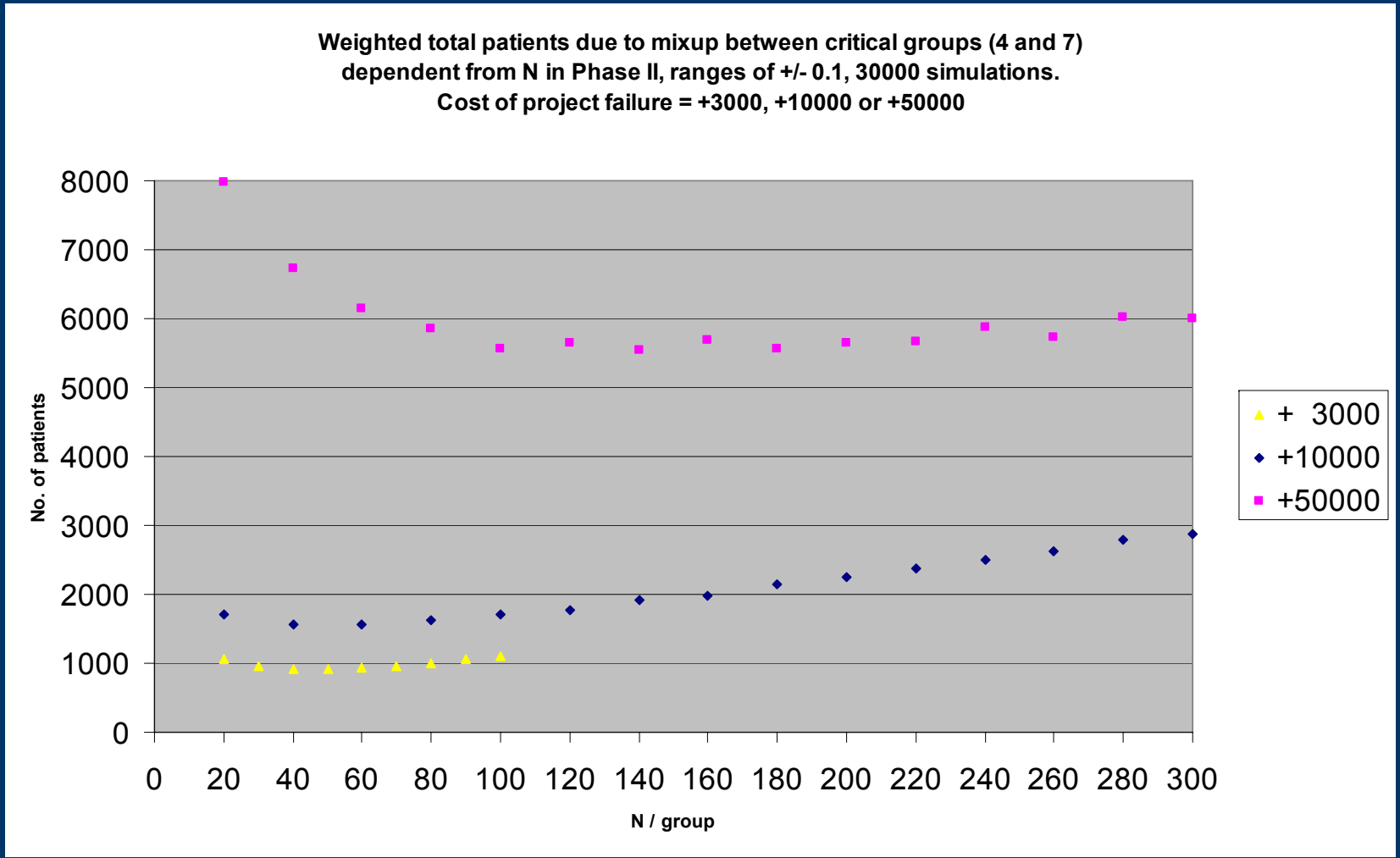
Overall summary:



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

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

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