An optimization approach for the early phases of drug development

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The clinical development of drugs until registration consists usually of 3 phases, which build on each other. Phase I (tolerability in healthy volunteers), Phase II (mechanismus in patients, dose selection) und Phase III (efficacy in patients). We ask critically which kind of information a Phase II trial should deliver, in order to support Phase III planning. Then we investigate how, based on these thoughts, the planning of Phase II is affected.

Up to now the „result“ of Phase II was considered to be a statement about the existence of a dose-effect trend or about whether certain contrasts would be proven to be different from 0. This, however, does not support any extrapolation to effect sizes that are to be expected in Phase III, nor to the degree of certainty with which they can be expected. Likewise, dose selection is not supported quantitatively.

We investigate now the probability that in Phase II an actually sub-optimal dose shows, by random error, the best results and is selected for Phase III; the consequence is that the power of the Phase III trial is unintentionally reduced and the risk to obtain a non-significant result (failure of the whole project) is increased. The damage resulting from the project failure is, consequently, to be weighted with the probability of false selection and with the resulting loss of power.

The probability of wrong selection decreases with increasing sample size in Phase II, N_{II}, and an N_{II} exists above which the decrease is so small that the weighted damage resulting from the project failure also decreases to an unrelevant extent. On the other hand, the costs of Phase II – which occur with certainty – increase linearly with N_{II}. In order to find the optimal N_{II}, the costs of Phase II and those of the failed project are brought on one common scale and then calculated in dependence from N_{II}. Here it has proven to be intuitive to use as the unit fort he common scale a sum of real and fictitious patients.

An – anonymised – example with a binary endpoint (binomial distribution with – at first – fixed parameter values p_1 and p_2) shows that a too “lean” Phase II is not optimal.

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