



Exploiting Seamless Adaptive Clinical Trials

A ‘Seamless Clinical Trial’ involves what would normally be two, consecutive, separate clinical trials being run back to back without a pause. Broadly the same protocol is used for both stages with some limited adjustments made at the end of the first stage based on the results obtained so far (for instance which doses to use in the second stage and how many subjects will be required).

This kind of trial design offers the opportunity to eliminate what is typically a 6-9 month hiatus between trials, and therefore shortens the time the overall development programme takes. If the compound is successful, this shortened development time increases the time during which the compound can be sold whilst still under patent protection.

To achieve this time saving, there is no pause in the recruitment of subjects, the same centres are used in both stages, and the ethical and regulatory approvals for the protocol obtained at the very outset of the trial must cover both stages of the trial.

A seamless trial might combine phase 2a (proof of concept) and phase 2b (dose finding), or phase 1 (safety study) and phase 2a, but it is the idea of combining phase 2b and phase 3 that has engendered most interest in the pharmaceutical community. These are usually the largest and most expensive trials in a drug’s development.

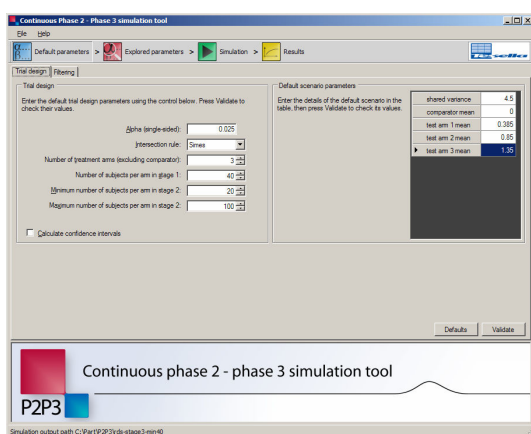
Combining data

At the point where the trial transitions from its first to its second stage, the first stage data is analyzed and some decisions regarding the second stage are taken. The most obvious decision is whether to continue the trial and, if so, to fix some of the parameters of the second stage; for instance “which of the doses used in the first stage should be used in the second stage?” and “how big should the second stage be?”.

Conversely, the two stages of a seamless trial can be simply analyzed, with only the second stage data being used as the basis of the submission to the regulators.

Researchers at the Medical University of Vienna have developed a statistical framework that allows first stage data to be combined with second stage data, whilst at the same time controlling the likelihood of making a false positive claim (a ‘type-1 error’) as required by the regulators. Being able to

combine the data from both stages in such a seamless trial offers the possibility of using fewer subjects in the second stage whilst still having the same probability of achieving a statistical significant result (the same 'power'). This will save phase 3 costs and save additional time. If the subjects recruited in the first stage are monitored for safety right up to the end of the second stage, then the combined trial will actually yield more safety data than if from equivalent separate trials.



However, whilst the statistical framework allows the probability of a 'type-1 error' to be controlled, it is no longer possible to simply calculate the likelihood of successfully showing that an effective compound actually works (the 'power'), or calculating how many subjects will be required. Furthermore, there are now new design questions to be answered, such as "what is the best split of subjects between the first stage and the second stage?" and "how many treatment arms should be retained into the second stage?".

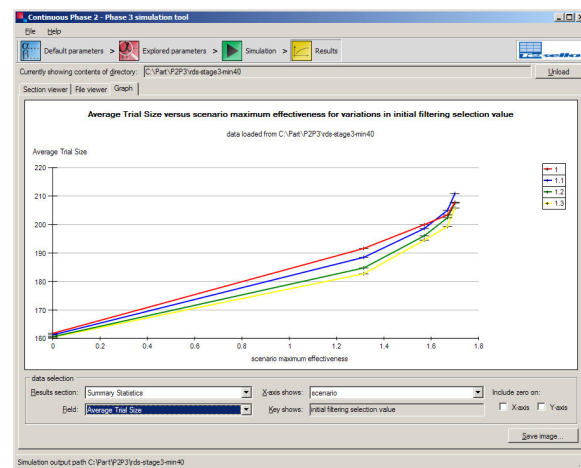
The only way to study the impact of these decisions on the likely outcome of the trial is to run simulations and analyze them using this new statistical method. Tessella has developed a software tool that does just this.

Tessella's 'Seamless Phase 2/3 Simulator'

Since 1998, Tessella has been helping to drive innovation in drug development by enabling the deployment of Adaptive Clinical Trials, and has developed the 'Seamless Phase 2/3 Simulator' to better equip the pharmaceutical community to carry out seamless drug trials.

Whether planning an actual seamless trial or simply evaluating the potential of seamless trial designs, it is essential to have the ability to simulate trials using seamless designs. This

is exactly what Tessella's 'Seamless Phase 2/3 Simulator' does.



The tool is organized to lead the user through the three steps of simulating a trial.

Firstly, the parameters of trial design (such as the required alpha, the number of treatment arms and the number of subjects to be allocated to each arm in each stage of the trial) are entered.

Secondly, the user can choose to explore the effects of changing up to two of the parameters over a range of values. For instance, the user can enter a number of scenarios with a range of different responses for each treatment arm and a number of different sizes for the first stage.

Finally, the user can run the simulations and view the results. A large number of results are collected from the simulations; these can be viewed in tabular form, viewed graphically or exported to files for importing into analysis tools such as Excel or SAS.



When are seamless phase 2/3 trials appropriate?

Embarking on a seamless phase 2/3 trial will be more expensive than starting on the phase 2 alone; in particular more compound must be manufactured and more investigating centres may be required at the outset. More importantly however, there will be no opportunity to re-design the protocol for phase 3 based on the data accumulated in phase 2. Regulators will need to be convinced that the risk of a re-design being required will be low.

There are, however, a number of situations where this risk is likely to be acceptable or even preferable to the alternative.

One example is when a pharmaceutical company already has experience of running clinical trials to study a particular disease. In this case, the likelihood of needing to change protocol is low. It may be that the company has already run trials in this disease or a similar type of compound. It may even have run trials with the same compound, but now wants to test it in a different way (eg. in a different patient population or in combination with another drug rather than in isolation). These are all circumstances in which both the company and the regulators might feel the risk is so small that a seamless design is practicable or even preferable.

It is also possible that a phase 2 study may have already been carried out, but not with sufficient data to be sure which is the best dose to use in phase 3. To be on the safe side the company might want to take two, or even three doses, into phase 3. However this may mean that the required phase 3 trial (using a conventional design) is too large. A seamless design can be used to introduce an interim look into the phase 3 trial (which is now really a seamless phase 3a/3b trial) at which the one dose to be carried on to the end is chosen.

A seamless phase 2/3 design could also be desirable when each subject must be studied for a considerable amount of time (eg. a year) in order to fully determine the effect of the drug. In this situation, the phase 2 trial often studies the subjects for a shorter period of time, and uses some early outcome or other predictor of what the subjects' final outcomes will be. This is clearly risky; more so than running a seamless phase 2/3 trial, where the full endpoint can be used for the phase 2 because of the time savings inherent in the seamless approach.

For more information on Tessella's experience in Adaptive Clinical Trials, please email info@tessella.com. For more detail on the mathematics behind Tessella's 'Seamless Phase 2/3 Simulator', please request a copy of 'Seamless Adaptive Clinical Trials: The Maths'.

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