ASTIN: a Bayesian adaptive dose–response trial in acute stroke

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Understanding the dose–response is critical for successful drug development. We describe an adaptive design to efficiently learn about the dose–response and the ED95. A dynamic termination rule allows for early discontinuation either for efficacy or futility. The design was deployed in ASTIN, a phase II proof-of-concept trial of the neuroprotectant, neutrophil inhibitory factor (NIF), in acute stroke. We discuss the learning from this trial. Clinical Trials 2005; 2: 340–351. www.SCTjournal.com

1 Introduction

Developing new pharmacological therapies is expensive. Most projects fail, sometimes late in the development process, and therefore there is great value in enabling earlier and better decision making as to whether or not to continue with a drug development program. Incomplete understanding of the dose–response is recognized as a major problem in clinical drug development, potentially leading to inappropriate doses being taken into phase III.

We have implemented a design that continuously captures outcome data to allow early termination and improved learning about the dose–response. We describe the rationale for adaptive treatment allocation and dynamic termination rules, show results from simulating the design, and discuss lessons learned from implementing the design in ASTIN, an acute stroke trial.

2 Issues in dose selection

A standard Phase II dose-selection design is a randomized, parallel group trial with placebo and three, or four, active doses. Let the objective of such a trial be to determine the minimum dose with satisfactory effect (MDSE) [1]. In ASTIN this was defined as the ED95, the dose delivering 95% of the maximum efficacy. This corresponds to looking for a dose delivering almost maximal effect, but that minimizes the danger of unacceptable adverse events. To illustrate issues in dose selection, assume that in addition to a placebo (P) group there are three doses groups, low (L), medium (M) and high (H) (Figure 1).

Some problems associated with the standard design are immediately apparent. With a small number of doses the interval between successive doses is wide. Consequently, as in Figure 1A, there may be no effect at L, and a maximum effect at M, from which we might only conclude that the ED95 lies between the two doses. Similarly, in Figure 1B we learn that the ED95 lies between P and L, or in Figure 1C where we learn that it lies between M and H. This choice of doses is only suitable for determining the ED95 if the dose–response gently increases across the whole dose range (Figure 1D).

2.1 Improvements to a standard design

2.1.1 Increase number of doses

Phase II of drug development should be an exploratory, or learning mode of investigation, rather than a confirmatory, testing mode [2]. Since it is known that if the objective of a trial is to estimate some aspect of a dose–response function then, for a fixed total number of patients, it is better to have more doses, with fewer patients per dose, than fewer doses with more patients per dose [3] and we would recommend using as many doses as is feasible. In ASTIN we chose 15 doses and placebo, made possible because the study drug was delivered by infusion, allowing for dilution. However, even for treatments in tablet form, many more doses than are currently used could be contemplated, for example, by combining two tablets of strengths...
allowing any dose in the range of 0–8 to be studied. The advantage of increasing the number of doses is seen in Figure 2A – a narrower interval between doses allows the ED$_{95}$ to be better determined. Increasing the number of doses is an option only if we adopt a learning stance, via estimation, rather than a confirmatory stance, via testing, since, in the latter, whether we use 3 or 15 doses has little impact on the number of subjects needed in a single group to detect a difference of

Figure 1  Issues associated with traditional dose–response designs.

Figure 2  Issues in increasing the number of doses.
a given size. A second issue is illustrated in Figure 2B. Patients allocated to the first four doses, excluding placebo, are wasted, since their response will essentially be the same as the response of patients to placebo. Similarly, patients allocated to the top three doses will respond similarly to patients receiving the first dose on the plateau. Ideally, if the shape and the position of the dose–response function were known, then patients could be allocated to placebo or to the four doses spanning the steep portion of the dose–response curve. This would be true whether the position of the curve on the interval was as in Figure 2B or 2C.

2.1.2 Adaptive allocation

While at the start of a trial we may know little about the position of the curve within the dose interval, as the trial progresses, information accrues as to the response of patients to differing doses and we can learn about the position and use this information to adapt allocation. For example, if we learned that the dose–response curve was as in Figure 2B we could reduce the chance of allocating patients to the low doses or to the very high doses, whereas if it was as in Figure 2C, we would only need to allocate to placebo and the lowest four doses.

2.1.3 Early stopping

As part of learning about the shape of the dose–response curve we are also able to make decisions about stopping early. For example, if there is little or no evidence to show that the drug has a real effect, then we should stop, as continuing would be futile. Similarly, there may be enough evidence to identify a dose with sufficient efficacy, and an adequate safety profile, to warrant going into a Phase III trial.

2.1.4 Seamless designs

During the development of this design it was intended that if early stopping for efficacy took place, transition to the subsequent Phase III trial would take place seamlessly. There are clear advantages to such a proposal, both in terms of time to approval if the drug were effective, but also in terms of continuity of recruitment. This approach was not adopted for ASTIN, because of objections both from the regulatory authority as well as within the company.

3 The ASTIN design process

Assume that the study is already running and that information has accrued on the shape and location of the dose–response function, allowing adaptive randomization. The design process is illustrated in Figure 3, in which four distinct elements are identified: randomization, prediction, decision making, and dose allocation.

3.1 Randomization

A new patient entering the study is assigned to placebo or an active dose predetermined to maximize learning about that aspect of the dose–response function that is of interest. Patients are allocated at a minimum rate to placebo throughout the trial to protect against a drift in the patient population that can lead to biased estimates of the dose–response function. By maintaining a minimum allocation to placebo we can fit time as an explanatory variable in the analysis and ameliorate the influence of population drift.

3.2 Prediction

In acute stroke trials it is standard to measure a patient’s response to treatment three months post-stroke. Waiting 90 days to determine the response of an individual patient to a dose results in many patients needing to be randomized before you can have learnt how to optimally allocate them to a dose. One approach is to predict a patient’s outcome at 90 days based on early outcome, or a surrogate outcome. Figure 4 shows data taken from the Copenhagen Stroke Database (CSD) [4] that contains data from 1351 pharmacologically untreated stroke patients entering an acute stroke unit (ASU) in Copenhagen between September 1991 and September 1993. In Figure 4A the relationship between the Scandinavian Stroke Scale (SSS) score, the primary endpoint used in ASTIN, at admission...
to the ASU and the corresponding score at discharge from the ASU is shown. The SSS measures neurological function with a zero representing a comatose patient and a score of 58 corresponding to no neurological deficit. There is only a weak relation between the SSS scores at admission and discharge with mild stroke patients being discharged with little neurological deficit and severe stroke patients being discharged with a substantial residual deficit.

Figures 4B, 4C and 4D show similar relationships between the SSS scores at 1, 4 and 8 weeks post-stroke and the SSS score at discharge. As time progresses, there is an increasingly strong relationship between the SSS score at an intermediate time point and discharge. These data were used to establish a set of linear regressions to predict final outcome based on early measurements, called the longitudinal model. In order to use this model in ASTIN, we required immediate access to early response data. This was achieved by building an electronic data interface to the clinical sites.

3.3 Updating estimated dose–response

Following the prediction of final outcome based on early response, the estimated dose–response function was updated by Bayes theorem. A Bayesian analysis accounts for all sources of uncertainty, in particular the uncertainty associated with predicting patient outcome from early outcomes in an appropriate way when updating the estimate of the dose–response curve. It also allowed us to update the longitudinal model as data from ASTIN became available.

3.4 Decision making

Having updated the estimate of dose–response, we can now make decisions as to the future conduct of the trial. There are three possibilities. First, there may be sufficient evidence to decide there is no dose of NIF giving sufficient efficacy to take into a Phase III, leading to the halting of ASTIN and the development program. Secondly, there may be sufficient evidence to identify a dose with the appropriate risk/benefit profile, allowing ASTIN to be stopped and the planning of Phase III to begin. If neither of the above decisions can be made then ASTIN continues in adaptive allocation and learning about the dose–response function.

3.5 Dose allocation

If ASTIN continues, the dose to be given to the next patient can be determined by choosing that dose which maximizes learning about the aspect of the dose–response function that is of primary interest. Based on simulation we chose to use that dose which minimizes the predicted variance of the response at the ED$_{95}$, in other words the dose that we expect to
lead to the most precise estimate of the response at the ED95, a measure of its expected utility.

3.6 Dose–response model

In general terms, the requirements for a dose–response model are that it relates the expected response at a given dose to a set of parameters and possibly covariates. Usually dose–response models are restricted to be monotonic. In ASTIN, a more flexible model allowing nonmonotonicity was needed because of an indication from an early patient safety study that the dose–response curve for NIF might be nonmonotonic at high doses [5].

One of the hindrances to the use of Bayesian methods in practice has been the lack of appropriate computational tools. Recently, the development of numerical methods based on Markov chain Monte Carlo (MCMC) has greatly broadened the scope of practical Bayesian statistics. However, MCMC has a computational overhead that may be prohibitive because of the considerable simulation work that is necessary to carry before trials can be run. The dose–response model needed to allow a degree of analytic updating of the response curve and the calculation of the expected utilities of each dose.

There are a number of approaches that give both flexibility and efficiency including models based on splines and kernel regression. In ASTIN we chose the Normal Dynamic Linear Model (NDLM), which has the necessary characteristics. NDLMs were originally developed in time series [6] and combine two sources of variability: observational and system. Figure 5 illustrates a second-order polynomial NDLM. The diamonds represent observed individual responses, \( Y_{jk} \) at dose \( Z_j \). At dose \( Z_j \), a straight line is fitted through the observations, parameterized so that the expected value at \( z = Z_j \) is \( \theta_j \), the intercept, and the slope is \( \delta_j \). If the model were a simple linear model then the expected response at dose \( Z_{j+1} = Z_j + 1 \) would be \( \theta_j + \delta_j \) and the slope would remain \( \delta_j \).

The dynamic component of the model allows these model parameters to change. The model may be written as follows.

**Observation equation:**

\[
Y_{jk} = \mu_j + v_j, \quad v_j \sim N(0, \sigma^2)
\]

**System equations:**

\[
\mu_j = \mu_{j-1} + \delta_{j-1} + \omega_j, \quad \omega_j \sim N(0, \sigma^2)
\]

\[
\delta_j = \delta_{j-1} + e_j, \quad e_j \sim N(0, \sigma^2)
\]

This is a flexible family of response functions in which the multipliers \( W_j \) can be regarded as smoothing tuners with small values giving a smooth response function and large values a more erratic response function. Covariates \( X_k \) can be introduced by making the expected responses depend linearly on the covariates:

\[
E(y_{jk}|z = Z_j, X_k) = \mu_j = \theta_j + \beta \times X_k
\]

and by applying the NDLM to the \( \theta_j \) values. In ASTIN, baseline SSS was used as a covariate in modeling dose–response, although not in choosing the dose to which the next patient is allocated.

Figure 5 Application of a second-order NDLM to dose–response relationships.
3.7 Stopping rules

In a Bayesian framework there are essentially two ways of stopping a clinical trial, one based on decision theoretic principles and the other on an assessment of the posterior probability of clinical meaningful effects.

The difficulty with the decision approach is that as more updates are performed, the number of decision scenarios increases exponentially; secondly, the necessary calculations are computationally intensive because they are not analytically tractable. Berry et al. [7] report approximations that have been developed to make the calculations more feasible. However, in the implementation of ASTIN it was decided to use the second approach, in which the size of the effect at the ED95 relative to placebo was determined and the decision to stop was based on the magnitude of this effect.

The NDLM models response through the expected value of the response \( \mu_j \) at a number of doses \( (j = 1, \ldots, J) \) including placebo \( (j = 1) \). The dose–response curve is converted into a dose–effect curve by defining the expected difference to placebo as

\[
\psi_j = \mu_j - \mu_0 \quad (j = 2, \ldots, J)
\]

To stop, we require two clinical effect sizes. The first, \( \psi_1 \), is the smallest clinical effect that we would not wish to miss and the second, \( \psi_0 \), is the largest clinical effect that is not of interest. These define stopping criteria for satisfactory efficacy and futility. If the posterior interval for \( \phi_k \) where \( k \) indexes the dose closest to the estimated ED95, denoted ED95*, lies completely above \( \psi_1 \), then we would conclude that there is sufficient evidence that the effect at the ED95 is large enough to warrant going into a Phase III trial. Conversely if the posterior interval for \( \phi_k \) lies completely below \( \psi_0 \), we could conclude there is sufficient evidence that the effect at the ED95 is too small to warrant continuing ASTIN or the NIF development program. A hypothetical example in which there is sufficient evidence to start a Phase III program is shown in Figure 6.

4 Simulating the design

Having developed such a complex design, were we in a position immediately to implement it? The answer is no, since there were a number of interested parties to persuade that the approach was appropriate and feasible. We needed to choose the appropriate settings for the algorithm. We needed to assure ourselves that the design had an acceptable operating characteristic, not only in terms of false positive rates and false negative rates, but also in terms of the aspects of the design that were considered important. Could the algorithm learn appropriately? Could it accurately estimate the dose–response relationship? Did the adaptive allocation result in a sensible choice of doses? Could we stop early? Were there benefits compared to a traditional design? Answers to these questions were needed to convince senior management in the company that the design was worthwhile and acceptable to the regulatory authorities and to convince the regulatory authorities in both North America and Europe that the approach was scientifically sound, and that the computer systems that were developed were appropriately validated. All of this was achieved by simulation. In practice, the simulations were conducted in two stages. In the first stage a fractional factorial computer experiment was conducted to optimize the parameter settings for the algorithm. In the second stage the operating characteristic of the design was determined based on the parameters determined in the first stage.

To illustrate, Figure 7 displays a series of snapshots from a simulation of a single trial in which the true underlying dose–response (indicated by the solid diamonds) corresponded to a logistic-type curve giving a maximum benefit over placebo of eight points change from baseline on the SSS. In Figure 7A, the prior is shown, and it can be characterized as reflecting a belief that if a dose–response exists it is minimal and gradual, but that there is great uncertainty. Figures 7B to 7H show the updated estimate of the dose–response curve (solid line) and its associated uncertainty (dashed line) after 25, 50, 100, 200, \ldots, 500 patients. On each graph the circles denote the observed patient responses, the arrows the doses that have already been allocated, and the dotted line a locally weighted fit (LOWESS) through the observed responses. These figures suggest that the algorithm can accurately estimate the dose–response relationship in that the estimate converges to the truth and the uncertainty reduces rapidly. They also suggest...
that it can learn appropriately and consequently choose appropriate doses, which is illustrated by the low density of patients allocated to the bottom four doses – indeed the second dose remains unused – as well as to the doses on the plateau.

Hundreds of thousands of such simulations were conducted so that the algorithm could be appropriately tuned. One of the main items of interest was how the adaptive design would compare to a traditional design. Table 1 illustrates the results of

Figure 7  Simulation of a single clinical trial.
the simulations. If interest centered on identifying the ED95 from a curve that plateaued at 2, 3 or 4 points benefit over placebo, then for 80% power, approximately 2400, 1000 and 600 patients are required, respectively; for 90% the corresponding numbers are 3200, 430 and 800. For an adaptive design based on a maximum of 1000 evaluable patients, the false positive rate is controlled at less than 5%, while the effect “power” for 3 and 4 points is acceptably high with small numbers of patients. Of course, the comparison to the traditional design is not completely fair, because the use of traditional sequential designs would reduce the average numbers of patients.

5 The results of the ASTIN study

In ASTIN, patients who had suffered an acute ischemic stroke who arrived in the emergency room of the hospital within 6 hours of its onset and who had a baseline rating on the Scandinavian Stroke Scale (SSS) of between 10 and 40 points were eligible for entry. Details of the exclusion criteria can be found in Krams et al. [8].

The study was run by an executive steering committee and an Independent Data Monitoring Committee (IDMC), with an expert Bayesian statistician, who were responsible for ensuring the safety of the patients, the integrity of the study, monitoring the performance of the algorithm, and confirming decisions to continue or stop the study. A number of formal meetings of the IDMC were prespecified, for which reports were prepared by an independent statistician and the computer system was run independently of the sponsor by Tessella Ltd.

A total of 966 patients were randomized, of whom 26% received placebo. There was preferential allocation to the top three doses (Figure 8), and 40% of patients were allocated to them.

Figure 9 illustrates the course of ASTIN in terms of the estimate of the dose–response relationship. In the frame corresponding to Week 0 the prior estimate of the dose–response is shown to be flat with expectation of 10 points change from baseline on the SSS. This placebo effect size was estimated from the data in the CSD study. The following six frames show estimates of the dose–response at 8-week intervals up to 48 weeks. What is already apparent by 16 weeks is that response on placebo – 19 points – is far higher than anticipated from the CSD study, and this persists during the course of the whole study. At week 32, the placebo effect is still much higher than anticipated, but there is little indication of a true dose–response. At week 48, the first opportunity at which the IDMC could stop the trial, it was stopped for futility. At this point recruitment was halted, but the protocol required that the patients who had already been entered should continue to be monitored for the full 13 weeks of the study. The study was finally completed 66 weeks after it started, at which point there was little indication of a positive dose–response.

The final estimate of the dose–response is magnified in Figure 10 and there are a number of points to consider. First, as was noted above, the placebo response was far greater at 17 points than the anticipated 10 points. The trial was designed to detect a 3 point benefit over placebo, which clearly is far greater than the estimated effect at any dose. This final model contained a single covariate – baseline severity. After the trial was completed a number of predefined important prognostic covariates, including tPA, were added to the model, but none materially changed the final conclusions. There was also no indication of any issues with adverse events, or serious adverse events. The only dose-related effect that was seen was in the antibodies to neutrophil inhibitory factor (NIF) [8].

6 Post-trial learnings

At the conclusion of ASTIN, a number of investigations were undertaken to assess the running of the trial and the algorithm.
6.1 Operational investigations

Throughout the planning of ASTIN we anticipated a particular recruitment speed; in the event the achieved rate was double. Centers themselves were enthusiastic about the unique aspects of the design, a phenomenon reported in a previous adaptive design [9]. One consequence of faster recruitment is that learning cannot take place efficiently. Our investigations suggest that a lower recruitment rate would

**Figure 9** Posterior estimate of the dose–response function during the course of ASTIN. —— Posterior estimate; ---- posterior uncertainty.
have caused the trial to stop with fewer patients recruited. It would have been preferable to work with fewer centers, aiming at achieving the optimal recruitment speed after an initial ramp-up time.

A second issue relates to exchangeability of the centers. In ASTIN there were 100 centers worldwide. Fewer centers would not only have brought us closer to an optimal recruitment speed, it would most likely also have reduced variability.

6.2 Statistical investigations

6.2.1 Longitudinal model

Figure 11A shows the average actual response for patients who completed the trial (dashed line),
together with the average imputed responses from the longitudinal model (solid line) using the prior estimate of the longitudinal model from the CSD plotted over time. Clearly, the imputed values are considerably higher than the actual responses. Figure 11B shows the same plot using the imputed values obtained from the updated longitudinal model. Here we see that once the longitudinal model begins to be updated, the imputed values become closer to the actual observed responses, illustrating that the CSD prior was not very good. Why?

The parameterization of the longitudinal model that was implemented in ASTIN had the form

$$y_i = \alpha_i + \beta_{i+1}$$

where $y_i$ is the response at week $i$. There are two issues with this parameterization. First, the parameters of the longitudinal model ($\alpha_i$ and $\beta_j$) are linked, and if one pair of parameters is updated all the others are too. Secondly, each pair may be estimated in different categories of patients. To see this we consider the acute stroke unit in Copenhagen. The 1351 patients who went through the unit in the two years of collection did not all stay for the same time. Those most severely impaired by their stroke stayed there the longest. If such patients were used to predict the progress from say weeks 11 to 12, they are not necessarily representative of the whole population and the parameter-linkage will have an impact on all other parts of the longitudinal model.

6.2.2 The estimate of the ED$_{95}$

Consideration of Figure 10 might suggest that the ED$_{95}$ for ASTIN should be of the order of 110 mg. In fact the posterior estimate of the ED$_{95}$ was 54 mg [8]. Why?

Conventionally, the Bayes’ estimate of a parameter is its posterior mean and this was used in ASTIN. Figure 12 displays the posterior distribution of the ASTIN-ED$_{95}$ – it is clearly bimodal. It can be argued that in the context of futility a bimodal posterior distribution for the ED$_{95}$ is not unexpected, since the posterior estimate of the dose–response curve will consist of a series of random bumps. This raises some issues.

First, in the context of futility, the concept of an ED$_{95}$ is meaningless. Secondly, given that futility is a possibility – particularly with the history of stroke trials in neuroprotection – it is preferable to use the posterior mode, rather than mean. Alternatively, an estimate could be obtained from the posterior estimate of the dose–response curve itself rather than average of the ED$_{95}$ values from each individual MCMC iterate. This suggestion was considered during the course of ASTIN as the IDMC-statistician identified the anomaly pointed to above. IDMC-inspired investigations showed that an algorithm based on the average curve had essentially the same properties as the ASTIN-implemented algorithm and that the final inferences would not have been fundamentally changed.

7 Discussion

We have shown that adaptive designs with dynamic termination rules can be successfully implemented in phase II proof-of-concept trials, offering important advantages such as improved learning about the dose–response and potentially earlier stopping. In future applications it will be important to build more reliable longitudinal models and to better control recruitment speed, aiming for a rate that allows the system to perform optimally.

Up front investment is required to allow designing the trial, simulating its characteristics and implementing it. However, the payoff goes beyond applying a more informative design. Investigators participating in ASTIN were extremely interested in the trial methodology, and regulatory agencies reviewing our approach were supportive of the concept of adaptive treatment allocation and dynamic termination rules in phase II. We are currently engaged in implementing similar designs in areas beyond stroke.

References


