Abstract

Increasing failure rates and growing costs call for more efficient drug development programmes. Innovative clinical programme and trial designs as well as advanced analysis strategies, coupled with more rigorous quantitative assessment of their ability to reliably answer the key development questions, constitute an important aspect in the improvement of modern drug development. A framework for the quantitative assessment of the relative merits and risks of alternative programmes and trial and analysis options is discussed, delivering critical input to inform portfolio- and programme-level decisions. This framework, called clinical scenario evaluation (CSE), is described and illustrated by an example comparing different design options for a phase II dose-finding study with active comparator. CSE helps to improve drug development by providing a solid basis for decision-making in the relative assessment of competing strategies and enabling more efficient execution of the subsequent clinical development plan.

Keywords
Clinical scenario evaluation (CSE), drug development, critical path, innovative designs, robustness, uncertainty, risk assessment, informed decision-making

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Finite resources and growing expenditure per single approved drug are increasing the necessity for more efficient drug development programmes. Increasing failure rates require them to be more robust against incorrect assumptions and unforeseen operational challenges. Identifying a robust clinical programme in the presence of high uncertainty is both a need and a challenge. This is also recognised by regulatory stakeholders through activities such as the Critical Path Initiative\(^1\) and the subsequent Opportunity List\(^2\). Novel clinical programmes, including possibly innovative trial designs and advanced analysis strategies, coupled with more rigorous quantitative assessment of their ability to reliably answer the key development questions, constitute an important aspect in the improvement of modern drug development. Quantitative determination of the relative merits and risks of an alternative programme, trial and analysis options – a framework we refer to as clinical scenario evaluation (CSE) – is critical input for informing portfolio- and programme-level decisions. Consequently, CSE facilitates more robust, integrated drug development strategies. This framework requires collaboration and transparency between the key internal stakeholders, including clinical, drug supply, biostatistics and pharmacology teams. Eventually, this also requires collaboration with external stakeholders, such as regulatory agencies and key scientific opinion leaders, to ensure mutual reassurance and acceptance of the clinical development plan and its subsequent execution.

Clinical Scenario Evaluation

The concept of CSE as described by Benda et al.\(^3\) provides a framework that can be applied at the different hierarchical levels of complexity within drug development, namely:

- development programme;
- clinical trial design; and
- the analysis levels.

Irrespective of the level at which CSE is applied, the framework aspires to a common set of principles:

- Identify the key (clinical development) objectives.
- Clearly define alternative/competing options (clinical programmes, trial designs, statistical analysis strategies) to address these objectives, e.g. an adaptive confirmatory dose-selection trial compared with separate phase II and III trials.

New Clinical Development Options

The revolution in biomedical sciences and increasing methodological advances are making more and more clinical development options possible, e.g. through the availability of biomarkers, new information technologies or advanced innovative clinical trial designs. A natural mechanism for understanding the relative efficiency of competing drug development options is to compare and contrast them in a structured up-front evaluation (framework) in which underlying assumptions are varied to assess, for example, the ability to select the appropriate dose. The upside of this integrated approach is a more in-depth understanding of one’s current drug development knowledge, uncertainties and corresponding risks associated with decisions made surrounding the clinical development plan. Consequently, CSE facilitates more robust, integrated drug development strategies. This framework requires collaboration and transparency between the key internal stakeholders, including clinical, drug supply, biostatistics and pharmacology teams. Eventually, this also requires collaboration with external stakeholders, such as regulatory agencies and key scientific opinion leaders, to ensure mutual reassurance and acceptance of the clinical development plan and its subsequent execution.
Clinical Scenario Evaluation – A Framework for Evaluating Competing Development Strategies

- Identify a range of clinical assumptions, from optimistic through to pessimistic, with respect to reaching the objectives. This is necessary in order to assess when executed the robustness of a selected approach to deviations from assumptions at the planning stage. For example, a steep dose–response relationship may be considered optimistic compared with a flatter one.
- Specify what to measure (metrics) in order to assess the relative benefits of one option against others, for example how likely a clinical programme is to correctly select a dose and successfully demonstrate effectiveness. The metrics are needed for a balanced and reasonable yet critical comparison of the different strategies.
- Assimilate all knowledge acquired from the CSE evaluations and additional contextual information, knowledge of competitors, for example, to support informed decision making.

The key components of these CSE principles are depicted in Figure 1.

**Value Proposition**
A basis for decision-making derived from the relative assessment of competing clinical development options is needed. In general, a CSE endeavour should include the traditional approach and should quantify the relative merits and risks of the competing strategies. This transparency forms a basis for better understanding and supports informed decision-making. The relative value of investing in, for example, a more innovative drug development is therefore more easily ascertained via the benchmarking naturally built into the CSE.

Mutual confidence in the acceptance of innovative, possibly more efficient clinical development strategies is required. Key external stakeholders, such as regulatory authorities, investors, etc., require adequate information to be made available for sufficient understanding and ultimately confidence in permitting the ‘replacement’ of traditional approaches with more efficient ones. The assimilation of knowledge generated via CSE supports the necessary dialogue with external (and internal) stakeholders in building mutual confidence in the new propositions. More stable and robust clinical programme execution should be obtained with CSE. Through CSE, the clinical development options are subjected to ‘stress-testing’, ensuring that decision-makers understand the robustness and – perhaps more importantly – the sensitivity of a chosen strategy to deviations from the initial planning assumptions. The chosen strategy will usually deliver acceptable robustness to reasonable deviations in assumptions, hence avoiding unnecessary time spent on corrective actions when observing deviations in assumptions during the programme execution.

**Case Study – Phase II Dose-finding with an Active Comparator**
To fix ideas, consider an example depicting an intermediate level of complexity within the CSE framework: a case study focusing on a method that stabilises the expected outcome of a dose-finding clinical trial. This example is placed in a common setting, developing a therapy for which there is pre-existing market competition.

**Motivation and Background**
A new drug with a new mode of action is being investigated in the treatment of acute pain. There are existing marketed products as well as competitor products still under development. Additionally, based on feedback from marketing and sales, there is high consumer expectation of clear differentiation without loss of efficacy against medications already available within this indication. Following the basic steps outlined above, the key drug development objective is to identify the dose beyond which the new drug provides a better efficacy outcome than the competitor drug.

**Clinical Setting**
A successful proof-of-concept using only a high dose has been established in early development. Consequently, the dose–response shape and its relation to the existing marketed therapy is unknown. A phase II dose-finding study is planned to determine the relevant dose range out of which one or several doses can be put forward to phase III. Differentiation to market competition for the new product will be strongly dependent on the selected dose range. Therefore, this phase II study needs to ensure high confidence in the dose(s) identified for phase III evaluation – aligned with the aforementioned key drug development objective.

**Clinical Study Objective**
A main goal of this study is to estimate with sufficient confidence the dose of this new therapy that is at least as good as the competitor with respect to pain reduction, assessed on a visual analogue scale. This ‘confidence’ will be measured using the precision of the estimated dose.

The required sample size depends critically on:

- the dose–response relationship;
- the efficacy of the active control; and
- the intrinsic variability of the clinical end-point.

Some knowledge regarding the second and third points is available from historical information, i.e. via a mixture of previous in-house studies and published literature involving the active control. However, the dose–response relationship of the new compound is unknown. As mentioned previously, confidence in the selected dose will be measured via the precision by which it is estimated. This precision heavily depends on the underlying dose-response relationship itself, which is unknown.

**Components of the Clinical Scenario Evaluation**
Following the conceptual framework in Figure 1, the trial options under consideration are:

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**Figure 1: Clinical Scenario Evaluation Framework**

- Various assumptions
- Assumption 1
- Assumption 2
- Assumption 3
- Assumption 4

- Clinical scenarios
- Measure via metrics

- Metric 1
- Metric 2

- Incorporation of context information, e.g. market competition, portfolio risk, etc.

- Measuring competing clinical scenarios

- Informed decision-making

- Programme/trial analysis options
- Strategy 1
- Strategy 2
- Strategy 3

- Strategy 4
- Strategy 5

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**Development: Trial Design and Protocols**

- **A ‘traditional’ fixed trial design:** five doses of experimental drug (with one ‘low’ dose) and the comparator drug (at the marketed dose). A placebo control was considered to be unethical in this specific setting. In order to benchmark against this design, best-guess estimates for the underlying assumptions (above) were made based on all available information at the planning stage.

- **The competing design option:** a two-stage flexible dose-finding study. The purpose of the first stage is to provide an opportunity to re-assess design assumptions to ensure adequate precision in the estimated dose that is at least as good as the comparator. At this interim assessment, the total number of additional patients for the second stage and the doses to which these future patients would be allocated may be updated to increase the chance of achieving the primary study objective. Several variants on this design option were considered within the actual CSE to provide the optimal choice for number of patients in the first stage. This also optimises the confidence (information) with which design adaptations are made relative to the overall maximal study sample size. Although these options are clearly important components within the overarching CSE, for simplicity they are not discussed in further detail here.

In **Figure 2**, the relative merits of the two-stage design versus the traditional fixed design are depicted. In each panel in Figure 2 the dose–response relation is given with corresponding confidence intervals. For simplicity, the reference horizontal line defines the targeted benefit to the comparator. The vertical drop-down lines define the confidence around the dose achieving the targeted benefit compared to the comparator. In reality, actual calibration to within-trial control mean response is more complex; however, the example in this case study should suffice for illustration. The upper panel of Figure 2 illustrates the case when the assumptions for the fixed design (assumption 1), i.e. best guesses at the planning stage, were correct. In this case, the confidence around the estimated dose achieved the target precision. In reality, deviation from the planning assumptions, e.g. a flatter dose–response relationship (assumption 2), may be encountered. In this case, the fixed design – given by the bottom left-hand illustration – does not achieve the targeted degree of confidence. However, the two-stage flexible design would mitigate the risk by re-assessing the necessary total sample size and also the doses to which all future patients should be assigned in order to achieve the targeted degree of confidence – as defined in the bottom right-hand illustration.

The flexible design may somehow appear intuitively obvious; however, these design adaptations may in themselves have undesirable operating characteristics, e.g. a tendency to systematically over/under-estimate the target dose, thereby producing a bias.

The assumptions for this case study were manifold:

- the underlying dose–response relationship, e.g. log-linear, E$_{max}$ sigmoid;
- the intrinsic variability of the clinical end-point; and
- the mean response of the active comparator and mean response of the highest acceptable dose, both on a relative scale to the lowest experimental dose.

The metrics used in the case study were related to:

- Validity, as measured by the closeness of the actual frequency with which the design will correctly identify the true target dose within the estimated confidence interval of the target dose to nominal frequency (for example 95%). The principle in constructing such confidence intervals has already been illustrated in Figure 2.
- Robustness of the design to deliver targeted confidence, as measured by the precision of the estimated dose.

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**Figure 2: Flexible Two-stage Dose-finding Study**

- Assumption 1
- Stage 1
- Stage 2
- Estimate sufficiently precise
- Stop trial
- Assumption 2
- Increase sample size to allocate dose groups
- Target dose confidence interval
- Reference
- Dose
- Response
- Target dose confidence interval
- Reference
- Dose
- Response

**Figure 3: Distribution of Possible Precision Outcomes Relative to the Target Precision for Two Design Options**

- Fixed
- Flexible
- Distribution (%)
- Efficacy range
- Efficacy range

**Figure 4: Average Sample Size of the Flexible Design Relative to the Fixed Design**

- Assumption made for fixed design
- Relative average sample size (%)
- Efficacy range
- Efficacy range
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- Cost of study execution. This is summarised rather simplistically using the total sample size requirements. In the case of the fixed design, this is a cost determined at the planning stage. For the flexible design, the total number of patients is not fixed in advance (by design) and therefore the average total number was used. Although this seems perhaps too simplistic in some settings, e.g. because of additional associated operational costs due to the flexible design, here these additional costs were considered negligible relative to total patient costs.

**Informed Risk Assessment and Decision-making**

Evaluation of the flexible two-stage design compared with the traditional design should allow a transparent basis on which to compare and contrast the relative merits and thus decide which design to implement. The traditional design is simple and straightforward, provided the dose–response relationship and underlying variability have been guessed correctly. In this case, it will be a very efficient solution. The challenge is the number of unknowns and the risks associated with running this simple study based on possibly highly mis-specified assumptions. The new flexible design provides an opportunity to review and update the design assumptions, which should provide protection against mis-specification of assumptions and ensure the required confidence (precision) for the estimated dose range, or at least minimise deviation from the target degree of confidence. This adaptive design is a risk-mitigation strategy, since the design should be robust to reasonable mis-specification of assumptions, i.e. decreasing the chance of an unsuccessful trial result. This design will be more complex operationally/logistically; however, the ‘price of robustness’ versus an operationally unsuccessful trial result. It is therefore not as robust as the flexible design.

**Clinical Scenario Evaluation Case Study Result**

The CSE was performed using extensive computer simulations revealing the following results:

- Validity: there was no detectable difference between the two main design options under any of the assumptions considered.
- Robustness: Figure 3 shows the distribution of the confidence interval width relative to the target width. This targeted level of precision is given by the horizontal line at the 100% mark. The x-axis reflects the range of assumptions on the mean response of the highest dose relative to the lowest one. The central value (40) corresponds to the initial assumption used for the fixed design. The solid boxes contain the central 50% of the simulation outcomes. The lines (whiskers) cover the range of outcomes excluding the extreme cases, i.e. 1% on either end. The flexible design considerably decreases the possible range for imprecision. To the left, the fixed design yields a much larger range and deviates further from the target precision. It is apparent that, in the planning phase, the fixed design delivers less confidence in getting a precise study result. It is therefore not as robust as the flexible design.
- Cost: Figure 4 depicts the average sample size of the flexible design compared to the fixed design’s preplanned sample size. The x-axis corresponds to that of Figure 3. Under the assumptions made for the fixed-design plan, the average number of subjects used in the flexible trial would increase by about 8%. This means that if one were absolutely sure about one’s assumptions, the fixed design would be more efficient than the flexible design. The higher sample sizes to the left and the lower right illustrate the mechanism of sample size adjustment under mis-specification.

Whereas the first metric shows that the two options are equally valid, a cost trade-off is shown between robustness and cost. However, in practice the additional cost would be well spent in the light of a priori uncertainty.

**Value of the Clinical Scenario Evaluation**

Logistical challenges of an interim analysis represent another cost. The CSE helps to put these expenses into the right perspective by ensuring well-informed decision-making on the clinical study design. The new method can reliably be applied. Study results become more predictable and useless study results can be avoided or, at least, limited. The subsequent clinical programme can be better planned regarding long-term timelines and project schedules.

**Conclusion**

The framework of a CSE helps to improve drug development by providing a solid basis for decision-making in the relative assessment of competing strategies under a range of underlying assumptions. It creates confidence in innovative, more efficient methods both internally and externally. Clinical programme execution is made more stable and robust against underlying uncertainties. Such a framework requires clear terminology to define its different components – the assumptions, the competing options and the metrics that are used to assess and compare these options. Following this, CSE helps to develop and structure a holistic approach for optimising drug development. The identification of relevant competing options is paramount. A wide range of underlying assumptions should be considered to support robust decision making. The metrics used to evaluate the different options should capture the likelihood of achieving the programme goals initially defined. CSE enhances discussion with internal and external stakeholders, fostering a common understanding and a productive interaction between the different contributors, ultimately leading to a more efficient drug development process.

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