Case Study: Feasible Phase II Design for Critical Decision Making

Introduction

In this case study example, a Phase II Proof of Concept study was planned to assess the probable effectiveness of a new drug to be given in addition to standard antibiotic therapy in patients with a serious bacterial infection. The proposed study design was multi-centre, double-blind, randomised and placebo-controlled. The primary endpoint was Time to Clinical Stability (TCS). A mean time to TCS of 5 days was expected on control and the study had been sized to include N=245 patients to test the hypothesis that the addition of drug would accelerate TCS to at least 3.5 days with 80% power and a Type I error of 2.5% 1-sided.

The study was intended to support the next critical step in development decision making in terms of proceeding to Phase III or not. The Sponsor asked for statistical help in assessing the sample size and design with this in mind. Of particular note was finance for the study which was to be raised through venture capitalists.

Evaluation of Options

Critical in early Phase II studies is understanding (i) what purpose the study will serve in terms of the next step in development decision making and (ii) what level of risk the Sponsor is willing to accept in terms of (a) continuing development of an ineffective drug and (b) discontinuing development of an effective drug.

Routinely, Phase II studies are sized with (a) = 2.5% and (b) = 20% meaning, essentially, for the hypothesized clinically relevant difference, there is a 97.5% chance of a correct 'No Go' decision that drug is ineffective and an 80% chance of a correct 'Go' decision that drug is effective. However, these levels of risk are typically those chosen for confirmatory regulatory Phase III studies. A case for considering different levels of risk for a Phase II decision making study can be made, levels that ease the burden of the required sample size but nonetheless are acceptable to the Sponsor.

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With this in mind, two strategies were examined statistically:
A. PoC Phase II study with a range of Go/No Go options
B. PoC Phase II with an interim look

A. PoC Phase II study with a range of Go/No Go options

Table 1 provides options for a Phase II PoC trial with varying levels of confidence regarding decision making.

Table 1. PoC Phase II study with varying levels of confidence for decision making

						Go / No Go Criteria	
Option	Prob correct 'No Go' decision	Prob correct 'Go' decision	Mean TCS control (days)	Mean TCS drug (days)	Total Patients Req'd	Go if observe drug/control less than	No Go if observe drug/control greater than
#1	97.5%	80.0%	5.0	3.5	245	0.78	0.78
#2	95%	80.0%	5.0	3.5	193	0.79	0.79
#3	90%	80.0%	5.0	3.5	205	0.84	0.84
#4	86.8%	80.0%	5.0	3.5	120	0.82	0.82
#5	81.4%	82.4%	5.0	3.5	100	0.84	0.84

Option #1 (highlighted) represents the initial protocol design. In this option with N=245:

- If the observed ratio of mean TCS on drug to mean TCS on control is ≤ 0.78, so at least 22% lower on drug than on control, equating to at least a 1.4 day shortening of TCS on drug compared to an expected 5 days on control, then a 'Go' decision can be made with an 80% chance that decision is correct.
- If the observed ratio of mean TCS on drug to mean TCS on control is > 0.78 then 'No Go' decision can be made with a 97.5% chance that decision is correct.

Alternatively with option #4 (highlighted), a saving in N of approximately 50% can be made with a study of 120 patients if the Sponsor is willing to accept an 87% chance of making a correct 'No Go'. With this option, the trigger for a decision would be an observed ratio of mean TCS on drug to mean TCS on control ≤ 0.82, equating to at least a 1.1 day shortening of TCS on drug compared to control.

B. PoC Phase II with an interim look

The options above can be further refined by considering the insertion of an interim analysis. A decision rule can be then employed at the interim to either proceed to the end of the study if interim data are promising or terminate the study early (with potential cost savings) if the data are weak. Statistically this rule has to be engineered to that the overall probabilities of making correct 'Go' and 'No Go' decisions maintained at an acceptable level.

For example, consider a Phase II PoC with N=100, 120 or 140 patients as in Table 2.

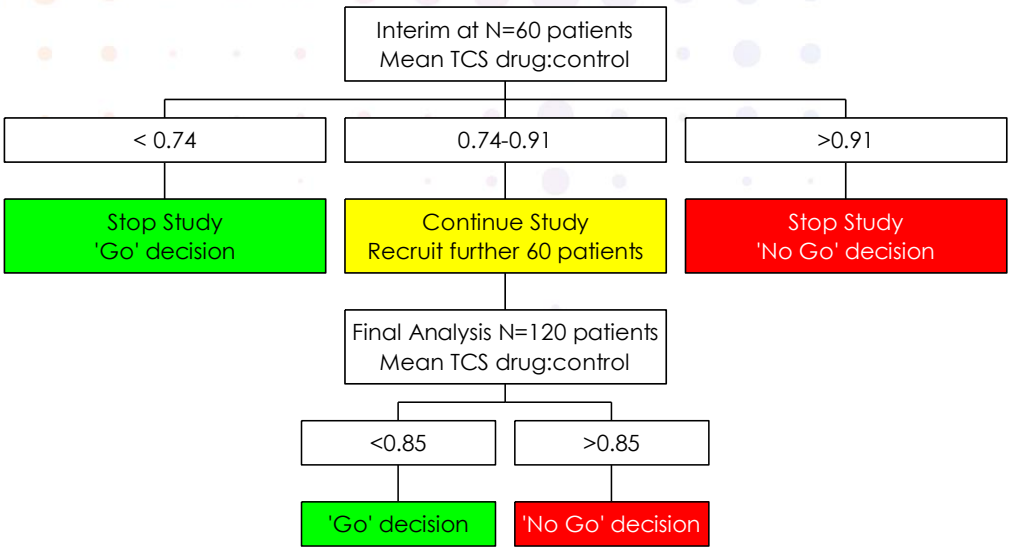
Table 2. Phase II PoC designs with an interim look

Number of patients		Interim criteria for mean TCS drug: contol		Final criteria for mean TCS drug: contol	Drug hag no true effect		Drug improves TCS for 5 to 3.5 days	
Interim	Final	Stop if ≤	Stop if ≥	Go if ≤; No Go if >	Pr (stop at interim)	Overall trial Prob No Go	Pr (stop at interim)	Overall trial Prob Go
60	100	0.74	0.91	0.85	64.4%	79.9%	58.8%	78.7%
60	120	0.74	0.91	0.85	64.4%	80.2%	58.8%	80.2%
60	140	0.74	0.91	0.87	64.4%	80.3%	58.8%	81.3%

An option therefore might be to conduct a 120 patient Phase II with an interim at 60 patients. The study would:

- Stop for efficacy if the ratio of mean TCS on drug to control was ≤ 0.74, so mean TCS at least 26% lower on drug than on control, equating to at least a 1.3 day shortening of TCS on drug.
- If drug was truly effective, then there is a 59% chance of an early efficacy stop
- stop for futility if the ratio of mean TCS on drug to control was >0.91, so no better than 9% shorter on drug than control, equating to less than an 0.5 day shortening of TCS on drug.
- If drug was truly ineffective, then there is a 64% chance of an early futility stop
- If the ratio of mean TCS on drug to control at the interim falls between 0.74 and 0.91, then a further 60 patients would be recruited.
- With all 120 patients, if the final ratio of mean TCS on drug to control ≤ 0.85, then the decision is a 'Go', otherwise it's a 'No Go'.
- Overall this design would provide an 80% chance of correctly concluding the drug was ineffective and an 80% chance of correctly concluding the drug was effective.

A schematic of the design is shown below.



Conclusion

In this case example, the Sponsor opted for N=120 with an interim at 60 patients. The Sponsor recognised that the Phase II decision making setting is inherently different to the Phase III confirmatory setting. They were happy to accept appropriately calibrated levels of decision making risk with well defined 'Go' and 'No Go' criteria. In taking this option for Phase II the Sponsor saved 50% on the original sample size and also allowed an early stop option for either efficacy or futility, being an option particularly welcomed and supported by the funding VC group.

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