Contemporary Clinical Trials 57 (2017) 69–86

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

Optimizing adaptive design for Phase 2 dose-finding trials incorporating long-term success and financial considerations: A case study for neuropathic pain

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A B S T R A C T

In this paper, we propose an adaptive randomization design for Phase 2 dose-finding trials to optimize Net Present Value (NPV) for an experimental drug. We replace the traditional fixed sample size design (Patel, et al., 2012) by this new design to see if NPV from the original paper can be improved. Comparison of the proposed design to the previous design is made via simulations using a hypothetical example based on a Diabetic Neuropathic Pain Study.

1. Background

The accelerated use of adaptive design in clinical trials has provided drug research and development a more flexible and effective approach to better distributing resources and fitting patients' needs. The increasing popularity of the adaptive design has led to a number of successful launches of new medications.

Comparing to a fixed arm design, an adaptive design allows better evaluation of the dose-response profile with a given sample size especially under the circumstance when only one Phase 2 study will be conducted before heading to Phase 3 and hence several dose levels need to be tested in the Phase 2 study. An adaptive design also provides balance between required sample size and study feasibility/costs offering opportunity to stop "early" based on the futility or success criteria. For example, a traditional parallel arm dose-ranging neuropathic pain study with 3 dose levels (6 mg/12 mg/18 mg) of an experimental drug (ED) requires sample size of > 400 subjects, which would be challenging in terms of both time for full enrollment and related expenses. In contrast, an adaptive randomization study with the same sample size allows for inclusion of additional interim dose levels (9 mg and 15 mg). Or adopting an adaptive design will result in a significant reduction in sample size if fewer doses are tested. Moreover, an adaptive design offers enhanced characterization of the dose-response profile and hence provides more informed dose selection for Phase 3 trials and actual safety information at potential Phase 3 dose levels.

Nevertheless, the extensive adaptive design research mainly focuses on the logistics of the trial itself lacking the global view which should incorporate both drug innovation and finance considerations. With the high availability of approved medications on market across almost all therapeutic areas these days, a successful launch of a new medication does not merely rely on its efficacy and safety, but marketing and financial considerations also play a definitive decisive role. In other words, in clinical trials, cost-effectiveness is crucial in optimizing the study design. A variety of researchers have contributed their work to this topic. Patel and Ankolekar [6] introduced a Bayesian approach to incorporate economic factors in sample size determination and design for clinical trials and portfolio of drugs. Burman et al. [2] proposed a decision analytic approach to calculate the sample size from a perspective of maximizing company profits. Mehta and Patel [5] used net revenue and net present value (NPV) for sample size re-estimation in confirmatory trials. Patel et al. [7] expanded the NPV concept to design a Phase 2 trial choosing a dose selection method and planning future Phase 3 trials. In their paper they used a traditional fixed sample size design to optimize expected net present value (eNPV) of the product. Our paper is an extension of their work. In this paper, we introduce an adaptive design to optimize the probability of Phase 3 success and eNPV of an ED for diabetic peripheral neuropathic pain. We replace the tradition fixed sample size Phase 2 dose-finding design used in Patel et al. [7] with an adaptive randomization design and evaluate

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http://dx.doi.org/10.1016/j.cct.2017.03.011
Received 5 January 2017; Received in revised form 16 March 2017; Accepted 20 March 2017
Available online 04 April 2017

the impact of several Phase 2 design features on the probability of Phase 3 success and the eNPV.

2. Introduction on neuropathic pain trials

We demonstrate the ideas and considerations by designing a Phase 2 neuropathic pain dose-finding trial as an illustration. The design frame and process that we propose can be easily generalized to studies in other therapeutic areas.

2.1. Efficacy endpoints

The neuropathic pain is a complex and chronic condition that is usually caused by damaged or dysfunctional nerve fibers sending wrong signals to the somatosensory system. The efficacy measure for the considered neuropathic pain study is the patient reported Numeric Rating Scale (NRS) ranging from 0 to 10 where 0 represents no pain and 10 represents severe pain. The primary efficacy endpoint is the average of NRS over a certain period of time prior to a scheduled study visit, typically 4 to 7 days. The pain intensity is recorded and monitored periodically. A typical Phase 2 neuropathic pain study's duration is usually 12 weeks.

2.2. Safety

As compared to efficacy, safety might be more challenging to be explicitly expressed due to various types and severity of adverse events (AEs). To quantify safety so that it can be taken into consideration during the design phase, we simplify and evaluate safety as the non-tolerability rate representing the frequency and severity of AEs emerged with the ED of neuropathic pain. The non-tolerability will raise concerns on the safety of the ED and will have impact on the final Go/No-Go decision. However, they will not be counted in early stopping for either failure or success.

3. Key concepts of a cost-effective adaptive design

3.1. Dose-response models for efficacy

We model the dose-response curve with a normal dynamic linear model (NDLM) [1]. The NDLM is a flexible and robust model for capturing non-monotonic curves. Let $i = 1, \ldots, k$ be the subject indices. Let subject i have dose $d_i = 0, 1, \ldots, D$, in which the placebo control is labeled as $d = 0$, the active comparator is labeled as $d = D$, and in-between are ED doses. The amount of dose for $d_i = d$ is denoted as ν_d, where $d = 0, 1, \ldots, D$. Denote Y_i as the change from the baseline to the endpoint in the response. Assume θ_d is the mean response for Y_i for dose $d_i = d$. The following error structure is assumed for Y_i:

$Y_i \sim \theta_d + N(0, \sigma^2)$.

The prior distribution for the first ED dose, $d = 1$, is $\theta_1 \sim N(\mu_1, {\upsilon_1}^2)$, and

$\theta_d \sim N(\theta_{d-1}, {\tau_{d-1}}^2)$ for $d = 2, \ldots, D-1$, where ${\tau_d}^2 = \tau^2(\nu_{d+1} - \nu_d)$.

The prior distribution for the "drift" parameter in the NDLM is

$$\tau^2 \sim IG\left(\frac{\tau_n}{2}, \frac{\tau_\mu^2 \tau_n}{2}\right).$$

The prior distribution for the error term is

$$\sigma^2 \sim IG\left(\frac{\sigma_n}{2}, \frac{\sigma_\mu^2 \sigma_n}{2}\right),$$

where σ_μ and τ_μ are the prior means for σ and τ, and σ_n and τ_n are means of σ and τ that are based on n observations. The gamma distribution is given by.

$$f(x; k, \theta) = x^{k-1} \frac{e^{-x/\theta}}{\theta^k \Gamma(k)}.$$

The placebo control is modeled separately with prior distribution

$\theta_0 \sim N(\mu_0, \upsilon_0^2)$.

The active comparator is also modeled separately with prior distribution

$\theta_D \sim N(\mu_D, \upsilon_D^2)$.

Of note, we leverage and implement inverse gamma (IG) as the prior distributions for variances. The choices of parameters for the IG prior distributions shall be carefully considered as they can have impacts on inferences drawn from posterior distribution as pointed out by Gelman [3].

3.2. Longitudinal models for efficacy

We design the trial with multiple visits instead of a single visit at a fixed time after randomization. Then, a longitudinal model will be employed to enable final observations to be imputed for those subjects that only have intermediate responses. Separate longitudinal models might be fitted to various doses. Nevertheless, the models should be in the same form but can have different parameter values (e.g. one set of parameters for placebo arm and a different set for the ED arms). The same priors can be used for all models.

We use the simple linear regression model to accommodate the correlation between final observations and intermediate responses. A common model is used for each ED dose and a separate model for the placebo and one for the active comparator arm.

The primary end point is modeled as:

$Y_i | y_{it} \sim \alpha_t + \beta_t y_{it} + N(0, \lambda_t^2)$,

where t is the visit number, y_{it} is the response at visit t and α, β and λ have the priors:

$\alpha_t \sim N(\alpha_\mu, \alpha_\sigma^2)$,

$\beta_t \sim N(\beta_\mu, \beta_\sigma^2)$,

$$\lambda_t^2 \sim IG\left(\frac{\lambda_n}{2}, \frac{\lambda_\mu^2 \lambda_n}{2}\right).$$

3.3. Safety evaluation

As mentioned in Section 2.2, safety is quantified and expressed as overall non-tolerability rates. Non-tolerability rates commonly increase as the dose is up-titrated. Non-tolerability rates should be approximated based on historical data or reliable sources such as notable publications or agencies' guidance. Table 1 displays three common safety scenarios in terms of overall non-tolerability rates.

3.4. Clinically significant minimum utility for both efficacy and safety (CSMU)

To take efficacy and safety into account for decision making

Table 1
Three sample safety profiles.

Safety scenario	dose				
	Placebo	Low dose	Medium dose	High dose	AC
Low	10%	10%	15%	20%	17.5%
Moderate	10%	15%	20%	30%	20%
High	10%	20%	30%	40%	35%