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# Design Archetypes
## for Phase II Clinical Trials in Central Nervous System Disorders

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**Abstract**

An over-arching framework is proposed to guide the design of phase II studies in CNS disorders. Archetypes are considered for scenarios where dose-response is highly relevant in clinical practice, as in the symptomatic treatment of acute disorders. Archetypes for scenarios where dose-response is less relevant, as in disease modification for neurodegenerative disorders, are beyond the present scope. Primary design archetypes are determined by axes of development that are defined by optimism for success (probability of efficacy) and signal detection (magnitude of the anticipated effect size). The fast- to-registration primary archetype uses a dose-response study as the first efficacy, i.e., proof of concept (PoC), study and is appropriate when the prospects for signal detection and the optimism for efficacy are higher. These conditions may exist when the anticipated effect size is large and when either testing a drug with a proven mechanism of action or when a favorable biomarker result was obtained in Phase I. The fast-to-PoC primary archetype tests one dose to establish PoC before assessing dose-response and is appropriate when the optimism for efficacy and the prospects for signal detection are lower. These conditions may exist when testing a drug with a novel mechanism *and* the anticipated effect size is smaller. Secondary archetypes are used to mitigate the trade-offs between the quick-kill-fast-to-PoC approach and the quick-win-fast-to-registration approach, and are key areas where adaptive designs can be beneficial.

Key Words: Clinical Trial, Clinical Trial Design

**Introduction**

The focus of this paper is on optimizing the design of Phase II studies for psychiatric disorders. Phase II studies play an important role in drug development because optimizing the design of such studies must be done in conjunction with optimizing Phase III / IV studies, and the Phase II plan implies certain goals must be reached in Phase I to support the subsequent studies. In addition, given that Phase II is the middle of the three phases required for marketing approval, it is a focal point for achieving objectives sequentially, in parallel, or seamlessly via adaptive approaches.

The usefulness of various phase II designs has been extensively examined for some diseases, such as cancer [1,2]. In psychiatric disorders, there have been elaborate examinations of trial-design features, such as blinded lead-in periods [3-6], placebo response and its impact on drug-placebo discrimination [7–11], assessment scales and sensitivity of scales and subscales [6, 12-18], relationships between other design features, analytic methods, and outcome [6, 19-23], as well as general design discussion and examples of novel designs [24-28]. However, most of such examinations have used data from or focused on confirmatory studies. Comparatively little has been written about how well certain phase II designs inform subsequent trials in psychiatry and other central nervous system (CNS) disorders.

This notwithstanding, the need for improved Phase II studies is obvious. At present, only about 9% of CNS drugs that enter phase I testing survive to launch [29]. Approximately 50% of the failures are a consequence of failures to demonstrate efficacy in Phase II,

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which is a 15% increase in failure rate over the previous decade [29]. Meanwhile, failure rate of CNS drugs in Phase III is about 50% [30], with problems in drug-placebo discrimination and increased placebo response increasing at an alarming rate [31]. Together, these findings clearly point to high rates of false negative and false positive rates in phase II as a major obstacle in CNS drug development. In fact, improving Proof-of-Concept (PoC) clinical trials is the most important factor required to improve the attrition rate in drug development [30].

In a recent consensus paper on the design of PoC trials of antidepressants, the authors concluded that PoC trials of antidepressants should be small, focusing on a single hypothesis [32]. Whether or not this conclusion applies more broadly across psychiatry and CNS disorders, and if so, how then to assess other hypotheses of importance, is the motivation for this paper.

The objective is *not* to provide specific recommendations for particular disease states or compounds. Rather, the goal is to discuss an over-arching framework based on underlying principles that form the basis for individual decisions. The companion papers address specific issues of importance in PoC trials: the use of active comparators, first in the context of a positive control to assess assay sensitivity and then as a direct comparison of the test drug versus standard of care.

**Considerations in Phase II Development**

The goals of Phase II development include: (1) exploring the use for the targeted indication, i.e, establishing PoC; (2) and estimating the dosage for subsequent studies, i.e., addressing the dose- response relationship [33, 34].

Although there is a large volume of literature on general aspects of assessing dose-response [37-43], including applications specific to Psychiatry and CNS disorders [44-45], the implications of these considerations on overall drug development has only rarely been addressed [46]. Another goal of phase II that has emerged in recent years but that is not mentioned in the ICH guidelines is to provide an early assessment of how the test drug compares with a standard of care. This topic is covered in one of the companion papers.

One way to approach Phase II development is to achieve each of the goals of establishing PoC and assessing dose-response in separate studies. For test drugs that are not effective, sequential studies that first establish PoC and then only after a positive result proceed to test other objectives, can be more efficient. Resources are not wasted studying multiple doses of a test drug, none of which are useful.

However, the sequential approach may also be slow and inefficient for test drugs that are effective. For example, it could take many years to plan and conduct sequential PoC and dose finding studies in Phase II, and the treatment arms from the PoC study will likely again be tested in the dose finding study. The sequential study approach might be classified as a cheap quick kill, slow, expensive win approach.

Another way to approach Phase II is to conduct a single study focusing on dose finding that is also used to establish PoC.  As previously noted, for test drugs that are not effective, this approach is inefficient.  But if the drug is effective, more information is obtained sooner and at lower cost than by going through the sequence of PoC, followed by dose finding.  Therefore, this approach might be classified as a cheap, quick win, expensive slow kill approach.

Therefore, speed and spend, (time vs. money) must be optimized so as to optimize the development plan.  Implicit in this discussion is that the optimum design hinges on whether or not the drug is effective, a characteristic of course unknown when phase II studies are designed because establishing this is one of the objectives.  Hence, understanding and mitigating the trade-off between speed and spend is an important aspect of Phase II development

How drugs are used in actual clinical practice may also influence Phase II development. In some scenarios, ample opportunity to fine-tune dosing on an individual patient basis exists.  For example, in symptomatic treatments to manage chronic disease, such as depression, dosing can start low and go slow.  That is, to see if a lower dose provides adequate treatment, and if not to then try a higher dose [35].  The key issue here is that dose-response is relevant in the treatment of individual patients.

In other instances, such as Alzheimer's disease (AD), little flexibility may exist to adjust dosing-based efficacy.  In AD, progression is slow.  Therefore, drugs intended to modify

the disease and delay its progression require long evaluation periods. By the time a patient is identified as not responding adequately to the initial dose, it may be too late to consider alternatives.

The focus of this paper is on those scenarios where dose-response is a highly relevant concept in individual-patient treatment.

**Axes of Development**

In scenarios where dose-response is relevant in clinical practice, mitigating the trade-offs between the efficient-kill-inefficient-win of the sequential approach versus the inefficient-kill-efficient-win of a dose finding study as the PoC study is important in developing a successful clinical plan. Optimizing developmental can be approached by considering two factors, termed here axes of development. These axes apply regardless of the relevance of dose-response but, as noted in a subsequent section, the implications of the axes depend on the relevance of dose-response.

The axes of development are: (1) the optimism for success; and (2) signal detection. Optimism is essentially the probability that the test drug is effective. Signal detection refers to assay sensitivity, which is the ability of a study to detect a true difference between treatments [36]. Not surprisingly, assay sensitivity is strongly influenced by the magnitude of the treatment effect. A third axis, external factors, is also important. External factors are those features not related to the characteristics of the test drug that

can influence development decisions. Examples of external forces include logistic and financial considerations, patent expirations, anticipated launches of competitors, etc.

While the external forces are important, they are mostly idiosyncratic to each compound. Our focus is on the over-arching principles that influence all compounds. Hence, external factors are beyond the present scope. Therefore, the two key questions to pose when considering development of drugs for which dose-response is relevant in clinical practice are:

1) What is the probability that this drug is effective?

2) What is the assay sensitivity for this disease state / drug class?

Optimism for efficacy can be measured on a continuum as the probability of technical success, p(TS). However, it is also useful to categorize optimism as high or low. Optimism may be considered high if the mechanism of action of the test drug has previously been established or if a favorable biomarker result indicative of efficacy has been obtained in Phase I. Optimism might be considered low if the mechanism of action is novel. Of course, there may be other factors which produce a high p(TS), such as robust results in a series of validated animal models, even if the mechanism is novel.

Likewise, signal detection can also be measured on a continuum based on anticipated effect size. However, it is again useful to categorize this axis as high or low. Although the distinction is arbitrary, a cut off for high versus low signal detection is chosen as an effect size of 0.5.

With drugs that have comparatively larger effect sizes, assay sensitivity is generally not problematic and differentiation from placebo can reliably be obtained with small sample sizes. With drugs that have comparatively smaller effect sizes, differentiation from placebo requires larger sample sizes and assay sensitivity is often considered poor.

Refined discussions of the axes of development should be done based on the continuum. But for gaining an overview of how these factors influence development the 2x2 cross tabulation of optimism and signal detection as high or low is useful. This categorization is presented in Table 1. The drug development implication for each of these four categories is included in the table. For example, with a proven mechanism, it is more likely a beneficial effect (signal) exists than for a novel, unproven mechanism; and, if the effect size is large it will be easier to detect the signal. Other points are more subtle, such as when the signal is smaller assessing dose-response is likely to be more difficult.

Table 1.  Axes of development and their drug development implications.

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| Signal detection | | Signal unlikely to exist. | Signal likely to exist. |
|---|---|---|---|
| | **High** <br> ($\Delta >= 0.5$) | Signal unlikely to exist. <br> Easy to find signal if it exists <br> Showing dose response possible. | Signal likely to exist. <br> Easy to find signal if it exists <br> Showing dose response possible. |
| | **Low** <br> ($\Delta < 0.5$) | Signal unlikely to exist. <br> Not easy to find signal if it exists <br> Showing dose response difficult. | Signal likely to exist. <br> Not easy to find signal if it exists <br> Showing dose response difficult. |
| | | **Low** | **High** |

**Optimism**

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To illustrate, consider scenario A where the maximally effective dose ($E_{max}$) yields an effect size of 0.60; in scenario B, $E_{max}$ yields an effect size of 0.30. In scenario A the dose yielding 50% of the maximal effect ($ED_{50}$) by definition has an effect size of 0.3 and the difference between $E_{max}$ and $ED_{50}$ is also an effect size of 0.3. In scenario A, the difference between doses is as great as the difference between $E_{max}$ and placebo in scenario B.

In scenario B, all the differences are small, especially the between-dose differences. Hence, larger sample sizes are required to achieve a commensurate level of reliability on the same evaluation. A dose ranging study in scenario B would require a very large sample size, which might be a poor investment if it were as yet not proven that any of the doses had a beneficial effect.

**Design Archetypes for Scenarios Where**
**Dose-response is More Relevant in Clinical Practice**

The implications outlined in Table 1 suggest three primary design archetypes.

1)   ***Fast-to-PoC.*** This archetype focuses on an efficient, quick kill. If optimism is low, the drug is more likely to be ineffective than to be effective. Hence, it makes sense to focus on a design that quickly, cheaply, and robustly tests whether or not the drug has any beneficial effect. It also makes sense to not try and show a dose-response early in development if it is more likely that no doses are effective

and/or if showing dose-response in effective drugs is unlikely, owing to small effect sizes.

2) ***Fast-to-registration.*** This archetype focuses on an efficient, quick win. If success is more likely, it makes sense to focus on a design that quickly gets to the ultimate goal of a regulatory approval, including understanding dose-response, if the anticipated effect size is sufficiently to such that showing dose response is possible.

3) ***Fast-to-peak-value***. This primary archetype is much like fast to registration, but multiple indications (or a single broad indication) are simultaneously considered. For example, fast to peak value may require two or more Phase II studies to support the two or more simultaneous Phase III programs.

Given the similarities between fast-to-registration and fast-to-peak value, discussion is focused on only the peak to registration archetype, with straight-forward extrapolation to the fast to peak value archetype.

These primary archetypes can be mapped to the axes of development presented in Table 1. For example, fast-to-registration fits well for scenarios where signal detection and optimism are both high - the upper right quadrant of Table 1. Fast-to-PoC fits well for scenarios where signal detection and optimism are both low – the lower left quadrant of Table 1. However, further elaboration is needed to understand how to best map primary archetypes to those scenarios where one of the axes is low and the other is high.

One characteristic of a good development plan is minimization of the trade-offs between the primary archetypes. A quick-kill paradigm makes sense if optimism is low, but some of those drugs will be effective. A quick-win paradigm makes sense if optimism is high, but some of those drugs will not be effective. Hence, consideration must be given to ways of minimizing the trade-offs between a quick-win-slow-kill approach and a quick-kill- slow-win approach. This is also particularly important when one of the axes of development is low and the other is high.

Minimizing these trade-offs and determining the proper archetype for scenarios where one axis is high and the other is low is accomplished via selection of an appropriate secondary archetype. The secondary archetype will often be a hybrid of the two primary archetypes; consequently, this is a fertile area for adaptive designs. For simplicity in describing the following secondary archetypes, define a PoC study as 2-arm, focusing on a high dose or a flexible dose of the test drug versus placebo; and define a dose ranging study as including placebo and at least 3 fixed doses of the test drug.

1. *Separate PoC and dose finding studies in Phase II.* This scenario is slow because it employs two sequential trials and is inefficient because treatment arms from the PoC study (high dose and placebo) are repeated in the dose ranging study. However, this approach discharges risk at low cost because a decision for further development is based on the first, small trial.

2. *PoC in Phase II, with a dose finding study in Phase III.* Secondary archetypes 1 and 2 involve the same studies. However, the availability of pivotal clinical-trial material or some bridging strategy results in the dose ranging study in secondary archetype 2 counting as one of the pivotal studies in Phase III required for regulatory approval.

3. *PoC in Phase II, with multiple studies using overlapping doses in Phase III to assess dose response.* This approach can be especially useful when effect sizes are small and therefore the number per arm needed to assess dose response is large.

4. *An adaptive Phase II study focusing first on PoC and then after a positive signal is found at an interim analysis patient allocation is altered to focus on dose finding.* This approach can be implemented by initially randomizing only to the maximum dose and placebo, and after the interim then randomizing to placebo and lower doses. However, this plan generates confounding of dose and time. Therefore, it may be more prudent to initially over-randomize to the highest dose but allocate some patients to intermediate and low doses. Then, after the positive interim, over-randomize to the intermediate and low doses while keeping the allocation percentage to placebo constant.

Secondary archetypes for a fast to registration approach may include the following:

1. *Single dose finding study in Phase II.* This is useful in the high signal detection scenarios when effect sizes are larger. Large effect sizes mean that sample size per arm for a given power is small. The 2- to 3-fold increase in total sample size typically needed

for a dose ranging study versus a PoC trial may be, for example, the difference between total enrollment of 200 patients and 80 patients, respectively. The additional 120 patients may be justifiable to obtain dose-response from the same study that establishes PoC, especially if it is likely that the drug is effective.

2. *Skip Phase II altogether.* A biomarker or healthy volunteer model is used in Phase I to establish PoC and dose-response. While such a scenario may be difficult to achieve, the advantages in speed and spend are compelling.

3. *Adaptive Phase II study focusing first on PoC and then focusing on dose response.* This is essentially the same scenario as examined for secondary archetype 4 in the fast to PoC primary archetype.

*Example scenarios*

The following example scenarios are illustrations of how to use the axes of development in choosing design archetypes, not specific recommendations.

Scenario 1. The test drug is being developed as a potential therapy for the pain associated with diabetic peripheral neuropathy (DPNP). Results from a validated biomarker in phase I have increased optimism for success. The anticipated effect size based on previously approved drugs is greater than 0.50, and there is little evidence in the literature for failed trials. This is the scenario depicted by the upper right quadrant of Table 1.

With the positive biomarker result, greater certainty exists that the test drug is effective. With a fairly large effect size, showing dose-response with reasonable sample sizes is possible, intermediate doses can contribute to signal detection, and total sample size will not be large. For this scenario, a fast-to-registration archetype using a single dose finding study in Phase II may be optimal.

Scenario 2. This scenario is the same as scenario 1, except that there is no biomarker and hence with a novel mechanism p(TS) is low, but the anticipated signal, if it exists, is expected to be large. This is the scenario depicted in the upper left quadrant of Table 1.

Given that p(TS) is lower than in scenario 1, greater need exists to focus more heavily on signal detection, but if an effect exists it is likely large, such that the sample size per arm is small and intermediate doses may contribute to signal detection. In this scenario, an adaptive approach that initially over-randomizes to placebo and high dose until the interim analysis (focus on PoC), and then over-randomizes to lower doses (focus on dose-response) may be optimal.

Scenario 3. The test drug is being developed as an antidepressant. It has a novel mechanism of action. There is no validated biomarker or healthy volunteer model result from phase I to increase p(TS). The historical effect size for antidepressants is small, and this disease state is well known for high rates of placebo response and poor assay

sensitivity, leading to high failure rates of clinical trials. This is the scenario depicted in the lower left quadrant of Table 1.

With a novel mechanism, in the absence of other data from a validated biomarker or healthy volunteer model, it is unlikely that the drug will be effective. And even if it is, with a smaller effect size showing a dose response is unlikely, or at least the sample size to do so would be large.

For this scenario, the key idea is to maximize the probability of signal detection given that the signal will be hard to find and that the probability of showing dose response is low. A fast-to-PoC primary archetype using a two-arm study, testing a high dose, perhaps via flexible dosing, may be optimal. Dose-response can be evaluated in Phase III, using multiple studies with overlapping doses. For example, Phase III study 1 might contain low dose, middle, dose and placebo; Phase III study 2 might contain middle dose, high dose, and placebo. Each study has placebo and middle dose. If the designs are as identical as possible, the overlapping doses and similarity in design facilitate pooling and minimize bias in comparing doses across the studies.

Scenario 4. As in scenario 3, the test drug is being developed as an antidepressant. In this scenario, it is a modified version of an approved compound that is hoped to have better pharmacokinetic properties and fewer drug-drug interactions than the approved compound. Here, in contrast to scenario 3, the mechanism is proven, but the anticipated signal is again small. This is the scenario depicted in the lower right quadrant of Table 1.

With a proven mechanism p(TS) is high, but with a smaller effect size and poor assay sensitivity, demonstrating dose-response is unlikely, or at least required sample size per arm to do so would be large. As in scenario 3, the key idea is to maximize the probability of signal detection given that the signal will be hard to find and given that the probability of showing dose response is low. Hence, the same approach as for scenario 3 may again be appropriate. However, it may also be appropriate to consider the adaptive approach outlined in scenario 2, where initial randomization focuses on signal detection and after a positive interim result randomization is altered to focus on dose response.

## Discussion

Improving the quality of PoC studies has been cited as the most important factor in reducing the attrition rate in drug development. However, the design of PoC studies is a complex and difficult topic, with many factors that must be addressed. Understanding of fundamental principles may be useful guides in design decisions to overcome these difficulties.

This paper has focused on scenarios such as acute phase clinical trials and symptomatic treatments, where dose-response is relevant in treating individual patients. It is proposed that the axes of development, defined by optimism for success and signal detection provide the over-arching framework from which individual design decisions can be made. Although each of these attributes is on a continuum, it is easier to appreciate them in a binary manner as outlined in Table 1.

The axes of development lead to primary design archetypes. The key distinction between primary archetypes is whether the first efficacy study should focus on establishing PoC (fast to PoC) or on evaluating dose-response (fast to registration). Secondary archetypes are used to minimize the trade-offs between the efficient-kill,-inefficient-win-fast-to-PoC archetype and the inefficient-kill-efficient-win-fast-to-registration archetype.

The archetypes presented in this paper are not intended to be an all-encompassing list, but rather a short list of general approaches. The design archetypes are also not intended to provide specific recommendations. Rather, the focus is on the key concepts that provide the over-arching framework from which decisions can be made.

External factors, such as logistic and financial considerations, patent expirations, anticipated launches of competitors, etc. may influence design decisions. These topics were not addressed because they tend to be idiosyncratic to individual development programs. Nevertheless, the principles outlined in this paper may be useful for addressing external factors. For example, if logistic or financial considerations limit the size of a study, forcing a fast-to-PoC approach on what would otherwise be a fast-to-registration scenario, the secondary archetypes may be useful in mitigating the trade-off from being forced into a smaller than desired first efficacy study.

Adaptive design of clinical trials is a rapidly evolving area that cannot be adequately covered in this paper. Extensive examination of adaptive designs and their relevance to

drug development are available [47]. However, as noted in several of the secondary archetypes, adaptive designs may play an important role in PoC trials. For example, an adaptive design may mitigate the trade-offs between a quick-kill-fast-to-PoC approach and a quick-win-fast-to-registration approach. Another example for utility of adaptive designs lies with early comparisons to a standard of care (SoC). An active comparator may be included via an adaptive design, where an interim analysis is conducted when the sample size is sufficient for establishing PoC, or for establishing dose-response, depending on the primary archetype; if the interim result is positive, enrollment to placebo, the active comparator and the relevant dose(s) of the test drug is continued until the desired operational characteristics for the test drug versus SoC contrast is been achieved. This topic is covered in greater detail in one of the companion papers.

The other companion paper discusses use of active comparators as a positive control to assess assay sensitivity and other ways to improve assay sensitivity. The issues and use of active comparators either as a benchmark for comparing to SoC or as a positive control can be layered on top of the basic design archetypes discussed in this paper.

Drug development in general, and the proper design of PoC clinical trials faces many challenges, requiring many solutions and approaches. Perhaps the secret to success is knowing that there is no secret to success – that everything must be done well in order to get the right data to make the right decision. If such is the case, then a clear understanding of key over-arching principles may be a useful starting point.

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