**Introduction**

Neurological conditions include some of the most prevalent of modern life, primarily due to demographic transitions and developing global economies.1 One 2016 estimate found that this disease area was the most common cause of DALYs and second most common cause of deaths globally.2 Despite being one of the most disabling disease areas, neurological drug development has proven more challenging than other areas of drug development, with some indications lacking any established disease-modifying standard of care (SOC).3 The difficulties in the development area start with the basic science, where we understand relatively little about disease pathology. When these theories are brought into preclinical studies, they additionally suffer from a reliance on animal models that vary significantly in their neuronal makeup from humans and have trouble ensuring that the drug is transported across the blood-brain barrier.3,4 Together, these issues mean that new treatment options for CNS disorders are brought into clinical trials with less of an understanding of the treatment and disease than in other indications. Once in clinical trials, development then faces challenges of measuring the impact of treatments on the CNS, using endpoints that lack validation as surrogates for clinical outcomes, and the long accumulative nature of the impairments that need years to be measured.5 Additional challenges include the risk of intervening in an organ system- the brain- where personal identity and decisional capacity originate.3

These factors together create an area of drug development where investment in the field has a low chance of success (between 6-9%).6–8 One review found that CNS drugs were half as likely to be approved as other indications.8 However, neurological disorders are not a monolith characterized by failure to develop effective treatments. While nearly all AD drugs have failed,9 several classes of medications are available to treat other neurological diseases such as Relapsing Multiple Sclerosis and migraine.3 Over time, R&D expenditures have increased in all areas of medical research, but there has not been an associated increase in approvals in neurologic drug development overall.This has resulted in diminished investment in neurological drug development6,7 and lower numbers of applications for funding by the NIH for neuroscience research.10 Although the probability that a trial in some neurological disorders will find a successful drug historically is very low, positive results would have a massive impact on the experience of millions of patients.1 This emphasizes the need for innovation and research on how to bring drugs to approval in this disease area.

Generally, drug development follows a phased approach (1-4), each with a different goal and an increasing cost and number of patients involved. Briefly, phase 1 (P1) trials focus on gathering pharmacokinetic data and safety information for the treatment in humans. Phase 2 (P2) trials usually aim to collect safety and dose relationships while also gathering preliminary information on the efficacy of the new treatment using surrogate endpoints.11 P2 trials are sometimes separated into 2a (which look mainly at safety, tolerability, and proof of concept),12 and 2b (which test for efficacy). Next, phase 3 (P3) trials aim to determine whether there are enough safety and efficacy signals to move forward to approval. Finally, phase 4 (P4) trials are typically run post-approval to widen the approved population. These goals can vary across disease areas, and the phase priorities are occasionally flexible.11

There are calls for new and creative ways of modifying the drug development process to get these drugs to patients faster and to increase the incentives for companies to invest in their development without putting large numbers of patients and money into futile trials.7 For example, when interventions have shown exceptional promise in P2 trials, some commentators called for bypassing P3 trials and going directly to approval without this extra layer of evidence gathering.13 Other designs, such as phase 1/2 or 2/3, create seamless transitions from phase to phase, using fewer patients, time, and resources – at least in the ideal.14–19 In neurology, other techniques for speeding up drug development include shortening P2 trials,15 using basket or platform trials,12 historical controls,20 pragmatic P3 trials,21 enrichment designs,22 adaptive trials,23 and futility designs.23,24

The present thesis will focus on a method less widely characterized and understood, which we call “P2 bypass.” This is defined for our purposes as the practice of initiating P3 trials without positive efficacy evidence from a P2 trial investigating the same treatment in the same disease area. In these cases, the P3 trials may rely on data from other indications or drugs to infer information for their trial. For example, P3 trial investigators can extrapolate from trials looking at a similar drug in the same indication25 or the same drug but a similar indication.21,26 Alternatively, investigators sometimes run P2 trials but persevere after obtaining a nonpositive result on their clinical outcomes or run P2 trials that are not aimed at investigating efficacy. We will use all these cases to mean P2 bypass. There are many documented instances of P3 trials that bypassed P2 in neurology.21,27–29

A previous study completed by the present author suggests that in other disease areas, P2 bypass is common. For example we found that 47% of P3 cancer trials bypass P2 trials. However, the drug development landscape is vastly different in neurology. For example, there are significantly fewer, and longer clinical trials in neurology than in cancer, and the treatments investigated are often marginal and palliative.30 Contrary to oncology, where bypassing may be due to encouraging early safety or efficacy signals, bypassing P2 trials in neurology may be influenced by an absence of biomarkers, low “pipeline density,” the lack of surrogate endpoints3,31 and desperation to find treatment options for a population with little to no treatment options, a practice termed “hail Mary.”21,32 Other reasons companies might bypass P2 evidence include the “academic industrial complex,” market pressures, intense competition between companies, or the vast potential for payoff if successful.27 Bypassing P2, if a treatment proves effective, would likely speed reduce the time it takes for the treatment to be approved. However, some reviews highlight the importance of P2 trials in neurology drug development and admonish against bypassing P2 trials.5,26,33 This is because P3 trials that bypassed P2 are initiated with a lower amount of evidence available to optimize dose, safety, efficacy, and population details. This may limit the chance that the P3 trial will be successful. Alternatively, other reviews introduce P2 bypass as a viable trajectory to limit drug development time in neurology.34

In what follows, we will describe the current literature on important variables typically explored in P2 trials in neurology, along with how the data can be used to make go/no-go decisions for P3 trials and to shape subsequent trials. This will be followed by a discussion of how bypassing P2 trials may impact the research trajectory and the welfare of trial participants.

**The purpose of P2 trials in neurology**

To understand the usefulness of bypassing P2 trials, it is first important to understand the role of P2 trials in traditional neurological drug development. Together with P1 trials, P2 trials make up what some commentators call the “learn zone”35 of drug development, where researchers can collect data that has “a significant impact on future trial size, expense, and risk.”11 P2 trials in AD have been called a “necessary step in drug development.”19 In addition guidance from the FDA states that “sponsors assess P2 results to determine if the preliminary results are sufficiently promising to justify a phase 3 study”34 Therefore, bypassing P2 trials and the information gained from them may impact the future of the drug development trajectory. Three variables typically investigated in P2 trials often inform the design of future trials: dose/schedule, preliminary efficacy, and population details.

Dose and schedule

The first task of a typical P2 trial in neurology is to find a roughly optimal dose and schedule for administering the drug.25,26,36–39 This is a stage where, using many doses (under the maximum tolerated dose found in P1 trials), researchers can begin to see a dose relationship in the safety and efficacy endpoints.11 Firstly, this information can help ensure that the a safe dose is moved forward to P3 testing. In CNS disorders this is a critical step because drugs treating these conditions are often taken for prolonged periods, such that safety issues might emerge with chronic exposure. As well, CNS drugs can affect the core of who we are and cause adverse psychiatric outcomes, such as suicidal behavior.3,11 Many doses are changed (mostly lowered) after FDA approval due to safety concerns.40,41 One study investigating these dose changes found that dose changes were most common in neurological drugs. This finding clearly shows the importance of meticulously investigating dose and safety relationships prior to approving a new treatment.42 A prominent example is in AD with verubecestat. There was a significantly worse cognitive outcomes and safety profiles in the experimental arm of the P3 trial after bypassing P2.43 It has also decidedly important for trials investigating treatments for stroke like magnesium and statins.23

Secondly, dose optimization is used to find effective dose relationships. One review investigating P3 trials in TBI argues that equivocal dose optimization results from P2 trials may have contribute to nonpositive P3 results. These authors suggest that P2 trials should be used to optimize dose before progression to P3 to increase the likelihood that the P3 trial is successful.36 It is important to use a high enough dose that it is efficacious but low enough to limit toxicity. Rather than the MTD, it may be ideal for the “lowest effective dose” to be the one brought through testing.44 Reviews of P3 trials that were non-positive for AD45,46 and TBI47,48 have discussed the role that the lack of dose optimization may have had on the outcome.

Efficacy

The second task of a P2 trial is to begin to evaluate whether the drug has the desired impact on the condition. Ideally, these trials would use clinical endpoints so that researchers can determine if the treatment impacts the livelihood of patients with the condition. However, in some chronic neurological diseases, relying on clinical effects would significantly prolong clinical trial duration.25,26,39,49 For example, a useful endpoint to investigate treatments for patients with RMS is annualized relapse rate, but this endpoint typically takes years to measure. In these cases, P2 trials may use endpoints that are surrogates for the clinical outcomes. These surrogate endpoints are often chosen without evidence that they are sensitive or reliable predictors of clinical outcomes,3,31 though they can be powerful when validated because of their ability to decrease trial duration.35 These endpoint are especially widespread in AD drug development, where the lack of validated surrogate endpoints to use in P2 trials may lead to the initiation of P3 trials without any indication that there is a clinical relationship.32 Reliance on these endpoints may hurt the chance of positive results in P3 trials, as was the case with Semagacestat34 and Solanezumab.27

Because of these difficulties, investigating clinical efficacy is often not the primary goal of P2 trials in neurology.25 In these cases, trials may rely more on “proof of concept” endpoints. These can be an important step to provide evidence that the treatment is at least working how it is hypothesized. These endpoints simply show that the drug has the desired effect on a target, which sponsors assume will have the desired therapeutic effect, and can be a vital minimum level of efficacy to show in early trials.44,50,51 For example, several P3 trials have been initiated for treatments in ALS52 and AD53 without showing proof of concept before initiation, and were ultimately non-positive. However, researchers are unclear on the type of efficacy evidence (proof of concept, surrogate, or clinical) that should be used to indicate that the intervention can be brought into P3 trials in neurology.

Relevant patient populations

Finally, the above variables are all investigated and optimized within a patient population of interest. There can be vast heterogeneity between patients of the same condition, such as differences in patients’ line of treatment, subgroup disease classification, genetic status, and disease severity.12,54 Determining which type of patients to optimize the treatment to can take trial and error. Sometimes, sponsors expand patient populations beyond those which have been investigated in P2 trials. However, this practice may jeopardize the generalizability of the supporting evidence for a trial or clinical application. In particular, the prior safety evidence may not indicate how patients with more severe disease will respond.33,37 Nevertheless, broadening the population may be necessary to ensure that patients beyond a restrictive trial population can benefit from a later approval.11 Alternatively, investigators can further restrict a population from a P2 trial using evidence from subgroups. However, when these analyses are not preplanned, extrapolation from subgroup populations to guide the design of P3 can lead to nonpositive results,14,44,49 shown by examples in RRMS,27 PMS,26 and AD.27,49

Together, the information learned from P2 trials can help generate knowledge on the “intervention ensemble”, the package of variables surrounding the treatment that must be researched to make it clinically meaningful.55 Information on the variables above can also guide “go/no-go” decisions for further testing to limit waste in drug development.12,51 For example, P2 trials can be used to weed out drugs that are not likely to be successful early in the development process.26,49

The amount and quality of evidence that is needed to make the decision to initiate a P3 trial remains unclear. One analysis from 2015 found that P3 CNS drugs were almost 50% less likely to move from the P3 trial to approval than all other indications but that P2 and P1 trials were not more likely to be unsuccessful. This indicates that P3 trial initiation in neurology may be ill-informed.56 Current guidelines in ALS25, PMS26, and AD44,49 suggest that P3 trials can be initiated without apparent clinical efficacy but not without proof of concept, dose information on safety, and the population defined. This step may be an important method of “derisking” the P3 trial from negative outcomes.44 In these cases, P3 trial designers will learn from other aspects of the P2 trial to optimize the intervention ensemble. On the other hand, in cases where P2 trials have clinical efficacy endpoints but get a non-positive result, researchers will learn from other aspects of the P2 trial to optimize the intervention ensemble but may have also been given reason to believe that the treatment may not be efficacious and to stop further investment (a no-go signal).

Transition…

**Impact of bypassing P2 trials on the research trajectory**

The decision to initiate a P3 trial and to expose large numbers of patients to a new drug should be backed by the greatest chance for success because of limited resources and to protect patient welfare.5 In what follows, I will review how the decision to bypass P2 may impact efficiency in drug development, both in cost to develop a new drug and the number of patients involved, and the risks and benefits for patients involved in the P3 trial.

Efficiency

When researchers find out that a treatment does not change clinical outcomes for a population of patients it is not a “failure”, but rather a powerful tool to learn more about a disease and treatment target.45,57,58 However, the stage of the development process in which a treatment is abandoned can profoundly impact the cost, time and number of patients involved in the endeavor. For example, in the case where a P3 trial is nonpositive and bypassed P2, resources may have been a wasted by the sponsor’s failure to first perform a P2 trial. Researchers have proposed that bypassing P2 trials would only be reasonable if the number of drugs starting in the pipeline was limited and there were unlimited resources for researchers to use in clinical trials. This way, screening out ineffective drugs would be unnecessary, and there was no cost to researching ineffective therapies.59 The reality of drug development is far from this ideal.

The cost of running a P2 or P3 trial differs significantly. Although it is hard to estimate the average costs of different phase trials because reporting of such is weak,60 one paper estimated that the median cost of a P2 trial was $8.6 million and that P3 trials cost $21.4 million.61 Using a similar estimate for AD development, finding an ineffective drug in a P3 trial that rather than in a P2 trial could double the cost of development and the time it takes to find this result.1 Suppose there is a nonpositive result in P3 after bypassing. In that case, investigators may not know if this result was due to truly ineffective drugs or the lack of evidence on the intervention ensemble. The later would require more testing and add to the cost and time to bring that treatment to approval. However, this practice would save money and time if the P3 trial is positive after bypassing a P2 trial compared to the case where a P2 is run and followed by a P3 trial.

In addition to research costs and time to development, patients are an essential resource to consider. There is no evidence to the best of our knowledge describing the average number of patients in P2 or P3 trials in neurology nor the number of hours that these participants contribute of their time. Still, a P3 trial will likely use greater amounts of both resources. Participating in clinical trials is not without its costs and burdens for patients.62 A few studies have investigated the amount of time different treatments require of patients in clinical care.63–65 One found that 10% of living days involved seeking care for cancer patients.65 This amount of time has not been estimated for participation in clinical trials, but it is sure to be higher due to exposure to research methods and assessment. This donation of patient time, especially for patients who are made vulnerable by their conditions, should be optimized for the greatest possible return on investment.

Risks and benefits to patient participants

In addition to designing efficient research trajectories, researchers should consider how bypassing a P2 trial impacts the risks and benefits afforded to patients who participate in the following P3 trial compared to patients participating in P3 trials based on P2 trials. The potential benefit for a pharmaceutical company and future patients cannot be exchanged for the decline in welfare for the patients involved.

One way to conceptualize protecting risk and benefit for patients in trials is to consider the concept of clinical equipoise as described by Freedman. He argued two tenets of clinical equipoise must be fulfilled to justify randomizing patients in a clinical trial rather than providing them with the standard of care. These are 1) disagreement amongst experts on whether the experimental or control treatment will be better for patients and 2) the trial's ability to quell this disagreement.66 Bypassing P2 trials has implications for both.

To the first point, P3 trial approval decisions should include a discussion as to whether the existing data has given us reason enough to believe that the experimental arm may be better for patients than the standard of care. A trial that does not have affirmative evidence available before its initiation may be associated with higher risk and diminished benefit. A P3 trial that bypassed P2 also may suffer because it is based off a lower level of evidence on the intervention ensemble. In this case, the expert community, with access to data (or lack thereof), would likely have little reason to believe that the experimental treatment could be better for patients than the SOC. Thus, equipoise may be threatened for a P3 trial designed to enroll a large number of patients with little prior evidence. For example, our paper on oncologic drug development found that those trials not supported by P2 trials had significantly worse survival outcomes.

To the second point, a non-positive P3 trial that bypassed P2 may be less capable of changing expert opinion. This is because the non-positive result could be due to an ineffective treatment or the lack of intervention ensemble optimization . One review of go/no go decisions in CNS development said it well: “from a scientific perspective, its optimal only to make “Go” decisions when one is clear that results of a study will prove interpretable about the potential of an intervention in the absence of a positive finding.”51

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**Conclusion**

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The dismal neurologic drug development landscape calls for empirical analyses of different development trajectories to find the optimal way to develop novel neurological drugs within the constraints of limited resources, such as money or patients. One such trajectory, bypassing P2 trials, is a possible method for speeding up development to get drugs to patients faster. In the following chapter, we will first estimate the prevalence of bypassing in ten neurologic conditions. Secondly, we will investigate how bypassing positive clinical evidence impacts p3 trial success and “how much information is sufficient to proceed to P3 without excessive risk of failure?”19

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