**The Prevalence and Impact of Bypassing Phase 2 Trials for Pivotal Trials in Neurologic Drug Development**

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**Abstract**

Objective:

Pivotal trials for new neurologic drugs are often launched absent support from positive phase 2 trials. Such “phase 2 bypass” may degrade risk/benefit for phase 3 trials. Our primary objective was to determine the prevalence phase 2 bypass in neurologic phase 3 drug trials.

Methods:

We used ClinicalTrials.gov to create a sample of phase 3 trials investigating treatments for ten neurologic conditions and that completed between 2011- 21. To assess the prevalence of phase 2 bypass, we searched backwards to find preceding phase 2 trials involving the same drug-indication pairing. Secondarily, we investigated circumstances where phase 2 bypass was more prevalent, and whether phase 2 bypass was associated with adverse phase 3 trial outcomes.

Results:

We included 113 phase 3 trials in our sample, 46% of which bypassed positive efficacy evidence from a phase 2 trial. The prevalence of phase 2 bypass varied across indications, with bypass common in Alzheimer’s disease (63%) and least prevalent in relapsing-remitting multiple sclerosis (6%). Phase 2 bypass was not significantly more prevalent for industry funded or drug repurposing trials. Overall, phase 3 trials that bypassed in our sample were significantly less likely to be positive on their primary outcome and non-significantly more likely to have terminated early due to safety or futility than trials that were preceded by positive efficacy evidence from phase 2 trials.

Conclusion:

Almost half of neurologic disease phase 3 trials are launched absent supporting evidence from positive phase 2 trials. Our findings suggesting adverse impacts of phase 2 bypass on phase 3 outcomes are inconclusive due to confounding. We urge development of criteria defining when phase 2 bypass is ethically and scientifically justified for use by IRBs.

**French Abstract**

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**Contribution of Authors**

Chapter 1: HM wrote Chapter 1 and JK provided editorial assistance.

Chapter 2: Conceptualization: HM, RM, JKa, EA, LS, JKi. Data curation: HM, RM, KV, MM. Formal Analysis: HM. Supervision: JK. Writing - original draft: HM, JK. Writing - review & editing: All.

Chapter 3: HM wrote Chapter 3 and JK provided editorial assistance.

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**Introduction**

Drug development typically follows a regimented process. The prospect of efficacy is examined in early phase “exploratory” trials, and if a signal of efficacy is obtained, the drug is re-tested in more demanding, “confirmatory” trials. Yet occasionally, this timeline is compressed, with “confirmatory” Phase 3 (phase 3) trials launched on the back of equivocal, negative, or in the absence of direct clinical efficacy signals (i.e. no earlier phase testing, earlier phase testing with ambiguous results, or an earlier phase trial that is nonpositive on its efficacy endpoint).1 We call this phase 2 bypass. The present study will assess the prevalence and consequences for patients and research of running phase 3 studies in neurology lacking direct supporting phase 2 trial evidence.

Several reports have investigated the relationship between the presence of phase 2 efficacy evidence and phase 3 trial outcomes in cancer clinical trials and found that bypassing was associated with nonpositive phase 3 outcomes.2–4 Our own unpublished study suggests that 48% of phase 3 cancer trials are launched absent positive phase 2 evidence and that these trials that are not supported by phase 2 trials have significantly worse survival outcomes. However, the drug development landscape for cancer is very different than in neurology. For example, there are significantly fewer and longer clinical trials in neurology than in oncology, and the benefit gained is often marginal and palliative.5 In an approach termed a “Hail Mary”, companies are often investigating the same drugs, over and over again before they are abandoned.6 Contrary to oncology, where bypassing may be due to encouraging early safety or efficacy signals, bypassing phase 2 trials in neurology may be influenced by the lack of surrogate endpoints7,8 and an extremely high degree of unmet therapeutic need in neurological conditions. Despite these reasons for bypassing, guidelines in ALS and MS suggest that phase 2 studies should be required before phase 3 trial initiation.9,10

In neurology, phase 2 trials have often been used to optimize dose and schedule9,11–15 and to map out the safety and tolerability of the treatment regimen under investigation.9,11,13,15. In addition, these trials are often designed to show the proof of concept behind the treatment, such as investigating whether it has the desired biological effect9,1113 However, methods to provide proof of concept often rely on surrogate endpoints with little evidence that they are sensitive or reliable.7,8 Beyond proof of concept, showing signs of clinical efficacy in phase 2 trials is desirable, but often very difficult 9,11,15 For example, there are very few established clinical endpoints in early Alzheimer’s disease, partially due to the chronic nature of the disorder which prolongs the duration of clinical trials significantly compared to acute disorders.16 Due to the limitations associated with clinical endpoints, guidelines in ALS and AD research suggest that phase 3 trials can be initiated after using a phase 2 trial to receive information on safety and tolerability, dose, proof of concept, all without clear clinical efficacy signals.11,16

When phase 3 trials are initiated without direct clinical efficacy evidence from a phase 2 trial, phase 3 trials designers might rely on data from other sources to infer information for their trial. For example, phase 3 trial investigators can extrapolate data from trials looking at a similar drug in the same indication.11 Investigators may also initiate a phase 3 relying on data from same drug but a similar indication9, although it has been suggested that repurposing drugs in this manner should begin with a phase 2 trial in the new indication before phase 3 trial initiation. 1718

Alternatively, investigators sometimes do run phase 2 trials in the same indication but persevere after obtaining a nonpositive result on their clinical outcomes (or don’t have one). This is especially prevalent in AD drug development. Indeed, phase 3 trials for all of the following drugs were nonpositive on their clinical endpoints and were initiated after phase 2 trials that were nonpositive on their clinical endpoints, relied on post-hoc analyses, or did not have clinical endpoints: tarenflurbil16, solanezumab17, tramiprosate, and atorvastatin8.

The decision to run a phase 2 trial before a phase 3 trial has implications in both cost of drug development and patient burden. For instance, one simulation in AD showed an estimated 55% decrease in the cost of development when drugs are found to be unsuccessful in phase 2 trials rather than phase 3 trials,19 because the phase 2 can be used to weed out drugs that are not likely to be successful earlier in the development process.9,16 Although it is unclear if running a phase 2 trial followed by a phase 3 trial changes the time/cost/patient burden compared to trajectories that bypass, a simulation of timelines in pancreatic cancer predicts that phase 3 drug trials that are ended with futility analyses have longer development times and use more patients when they bypass phase 2 compared to not bypassing phase 2. 20

In what follows, we will create a sample of recent phase 3 neurology clinical trials to investigate 1) the prevalence of launching phase 3 trials that bypassed phase 2 trials, and 2) the relationship of supporting phase 2 evidence to risk-benefit for patients enrolled in phase 3 trials. Our study is intended to evaluate contemporary practices and inform judgments as to whether it is scientifically and ethically appropriate to bypass phase 2 trials.

**Chapter 1: Phase 2 Trials in Neurologic Drug Development**

**Introduction**

Neurologic conditions include some of the most prevalent of modern life, primarily due to demographic transitions and developing global economies.21 One 2016 estimate found that this disease area was the most common cause of DALYs and second most common cause of deaths globally.822 Although increasingly common, many neurologic diseases do not have any effective treatments.7 This dismal treatment landscape shows the need for innovative modifications to the drug development process to get treatments to patients faster and to increase the incentives for companies to invest in their development.

In the following chapter, we first review the drug development landscape for neurologic diseases and one method of designing trial trajectories to reduce the time it takes to get effective treatments to patients - bypassing phase 2 trials. Next, we will provide an overview of the rationale for running phase 2 trials before starting phase 2 trials in neurology. This will be followed by a discussion of how bypassing phase 2 trials may impact research trajectories and the welfare of trial participants.

1. **Neurologic drug development**

1.1 Challenges

Neurologic drug development has proven more challenging than many other areas of drug development, with some indications lacking any established disease-modifying standard of care (SOC).7 These difficulties start with the basic science, where we understand relatively little about disease pathology. When these theories are brought into preclinical studies, they suffer from a reliance on animal models that vary significantly in their neuronal makeup from humans. Additionally, CNS drug delivery is made more difficult than other targets due to the inability for anything other than small molecules to cross the blood-brain barrier.7,23,24 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 measuring the impact of treatments on the CNS, using endpoints that often lack validation as surrogates for clinical outcomes, measuring the long accumulative nature of the impairments, and determining how the chronic exposure to treatments will impact safety over time.25 Additional challenges include the risk of intervening in an organ system- the brain- where personal identity and decisional capacity originate.7

These factors together create an area of drug development where clinical development has a low chance of leading to an FDA approval (between 6-9%).26–28 One review found that CNS drugs were half as likely to be approved as other indications.28 Hurdles to development have discouraged companies from investing in developing treatments for these diseases26,27 For example… However, several classes of medications are available to treat other neurologic diseases such as relapsing multiple sclerosis and migraine.7 Historically, the probability that a trial in some neurologic disorders will show positive results is low. However, this outcome would have a massive impact on the experience of millions of patients.21 Research is needed to determine how various drug development strategies and trajectories may be useful to bring more effective treatments to patients with neurologic conditions.

1.2 Efforts to accelerate drug development

To reduce the risk of exposing patients to ineffective and/or unsafe treatments, modern drug development systems use a phased approach since the 1960s (1-4), with each phase increasing cost and number of patients enrolled. The goals of each phase vary across disease areas and the priorities of each are flexible.29 In neurology, phase 1 trials focus on gathering pharmacokinetic data and safety information for the treatment in humans. Next phase 2 trials usually aim to collect safety and dose relationships while also gathering preliminary information on the efficacy of the new treatment using surrogate endpoints.29 Phase 2 trials are sometimes separated into 2a (which look mainly at safety, tolerability, and proof of concept),30 and 2b (which test for efficacy). Next, phase 3 trials aim to determine whether there are sufficient signals that the drug is efficacious to move forward to approval. Finally, phase 4 trials are typically run post-approval to widen the approved population and/or gather additional safety data.

Although this four-step paradigm has been a mainstay for decades, many drug developers use different approaches. For example, when interventions have shown exceptional promise in phase 2 trials, some commentators have called for bypassing phase 3 trials and going directly to approval without this extra layer of evidence gathering.31 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.17,19,20,32–34 In neurology, other techniques for accelerating drug development include shortening phase 2 trials,19 using basket or platform trials,30 historical controls,35 pragmatic phase 3 trials,18 enrichment designs,36 adaptive trials,37 and futility designs.37,38 For example, recent trials investigating treatments for amyotrophic lateral sclerosis,39 Alzheimer’s disease,40 and Parkinson’s disease41 have used various innovative trial designs to improve drug development efficiency.

1.3 Phase 2 Bypass

The present thesis will focus on a practice less reliant on novel trial methodologies: abridgment of the phased approach to clinical development. In particular, we will focus on the practice of initiating phase 3 trials without positive efficacy evidence from a phase 2 trial investigating the same treatment in the same disease area (“phase 2 bypass”). In these cases, researchers initiating phase 3 trials may rely on data from other indications or drugs to infer promise for a particular drug-indication pairing. For example, phase 3 trial investigators can extrapolate from trials looking at a similar drug in the same indication11 or the same drug in a similar indication.9,18 Alternatively, investigators sometimes run phase 2 trials that are not primarily aimed at investigating efficacy but rather at investigating safety or pharmacokinetics. Finally, investigators may launch phase 3 trials relying on positive signals from secondary or subgroup analyses in an otherwise nonpositive phase 2 trial. There are many examples of phase 3 trials that bypassed phase 2 trials in neurology.18,42–44 This practice raises the question: how important are phase 2 trials for the future of a drug development trajectory? If they are, which types of evidence from them are the most relevant?34

A previous study by the present author suggests phase 2 bypass is common and potentially problematic in other disease areas. We found that 47% of phase 3 cancer trials bypass phase 2 trials and that the risk/benefit balance for participating patients was significantly diminished compared to phase 3 trials preceded by positive phase 2 trials. However, these trends may differ in neurology as the drug development landscape is vastly different. For example, there are significantly fewer clinical trials in neurology than in cancer, and trials typically run longer. In addition, the treatments investigated in neurology are often palliative rather than disease-modifying.5 Contrary to oncology, where bypassing may be due to encouraging early safety or efficacy signals, researchers who bypass phase 2 trials in neurology may be influenced by the lack of surrogate endpoints that could be used as a readout of promise in phase 2 trials,7,8 desperation to find new treatments for a population with little to no options,6,18 market pressures, intense competition between companies, and the vast potential for payoff if successful.42

Bypassing a phase 2 trial, if the treatment proves effective, would likely reduce the time it takes for a treatment to be approved. However, some reviews highlight the importance of phase 2 trials in neurology drug development and admonish against bypassing phase 2 trials.9,10,25 This is because phase 3 trials that bypass phase 2 are initiated with a lower amount of evidence available to optimize dose, safety, efficacy, and population details. This may limit the chance that a phase 3 trial will be successful. Alternatively, other reviews introduce phase 2 bypass as a viable trajectory to limit drug development time in neurology.45

1. **The purpose of phase 2 trials in neurology**

To understand potential justifications for bypassing phase 2 trials, it is first important to understand the role of phase 2 trials in traditional neurologic drug development. To understand the implications of bypassing phase 2 trials, we first have to attend to the moral and policy logic embedded in the system of regimentation that has historically governed drug development. The phasing of clinical development was first proposed by the FDA \*\*\*

Together with phase 1 trials, phase 2 trials make up what some commentators call the “learn zone”46 of drug development, where researchers collect data that has “a significant impact on future trial size, expense, and risk.”29 The information learned from phase 2 trials helps generate knowledge on the “intervention ensemble”, the package of variables surrounding the treatment that must be researched to make it clinically meaningful.47 In addition, guidance from the FDA states that “sponsors assess phase 2 results to determine if the preliminary results are sufficiently promising to justify a phase 3 study”45

In this section, we will describe the current literature on three elements typically investigated in phase 2 trials to inform the design of future trials: dose/schedule, preliminary efficacy, and population. We will then review how phase 2 findings can be used to shape subsequent trials and make go/no-go decisions for phase 3 trials.

2.1 Dose and schedule

The first task of a typical phase 2 trial in neurology is to find a roughly optimal dose and schedule for administering the drug.9,11–15 This is a stage where, using many doses, researchers can begin to see a dose relationship in their safety and efficacy endpoints.29 Dose optimization is important to find a high enough dose that treatments are efficacious but low enough to limit toxicity.

Information gained from phase 2 trials can help ensure that the a safe dose is moved forward to phase 3 testing. In CNS disorders this is critical 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.7,29 Many doses are changed (mostly lowered) after FDA approval due to safety concerns.48,49 One study investigating these post-approval modifications found that dose changes were most common in neurologic drugs.50 These findings show the importance of investigating dose and safety relationships prior to approving a new treatment. Phase 2 trials serve as an opportunity to do so before investing in a phase 3 trial. In addition, reviews of phase 3 trials investigating treatments for Alzheimer’s disease,51,52 traumatic brain injury,12,53,54 and stroke37 have postulated that the lack of prior dose optimization may have led to non-positive outcomes.

2.2 Efficacy

The second task of a phase 2 trial is to begin to evaluate whether the drug has promise for treating a condition. Ideally, these trials would use clinical endpoints so that researchers could determine if the treatment impacts the disease course of patients with the condition. However, in some chronic neurologic diseases, using clinical outcomes to measure efficacy would significantly prolong clinical trial duration or demand large sample sizes, thus defeating the purpose of phase 2 evaluation.9,11,15,16 In these cases, phase 2 trials may use endpoints that are surrogates for the clinical outcomes.7,8 For example, a useful endpoint to investigate treatments for patients with relapsing-remitting multiple sclerosis is annualized relapse rate, but this endpoint typically takes years to measure. Researchers instead use MRI measures of lesions to evaluate disease progression much quicker. Endpoints such as these can be powerful when validated because of their ability to decrease trial duration or sample size.46 However, many endpoints used as surrogates for efficacy may have never been shown to have a relationship with clinical endpoints, thus providing misleading information as to the efficacy of a new drug. Surrogate endpoints are especially widespread in Alzheimer’s drug development, where the lack of validated surrogate endpoints to use in phase 2 trials has led to the initiation of phase 3 trials without any indication that there is a clinical effect.6 Some commentators argue that reliance on these endpoints may have played a role in recent non-positive phase 3 trial results for Semagacestat45 and Solanezumab42 in Alzheimer’s disease.

Because of these difficulties, investigating clinical or surrogate efficacy is often not the primary goal of phase 2 trials in neurology.11 In these cases, trials may rely more on “proof of concept” endpoints. These endpoints simply show that the drug has the desired effect on a target, which sponsors assume will have the desired therapeutic effect. Proof of concept may be a vital minimum level of efficacy to show in early trials.55–57 For example, several phase 3 trials were initiated for treatments in amyotrophic lateral sclerosis58 and Alzheimer’s disease59 without showing proof of concept before initiation, and were ultimately non-positive.

2.3 Relevant patient populations

Finally, the above variables are all investigated and optimized within a patient population of interest. There can be vast heterogeneity of disease presentation and baseline characteristics between patients with the same condition, such as differences in patients’ line of treatment, subgroup disease classification, genetic status, and disease severity.30,60 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 phase 2 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.10,13 Nevertheless, broadening the population may be necessary to ensure that patients beyond a restrictive trial population can benefit from a later approval.29 Alternatively, investigators can further restrict a population from a phase 2 trial using evidence from subgroups. However, extrapolation from subgroup populations to guide the design of phase 3 can lead to nonpositive results,16,17,57 shown by examples in RRMS,42 PMS,9 and AD.16,42

2.4 Whether to initiate a phase 3 trial

Information on these variables (especially efficacy) in phase 2 trials can help guide “go/no-go” decisions for further testing in order to limit waste in drug development.30,56 For example, phase 2 trials can be used to weed out drugs that are not likely to be successful early in the development process.9,16 One analysis from 2015 found that phase 3 CNS drugs were almost 50% less likely to move from the phase 3 trial to approval than all other indications but that phase 2 and phase 1 trials were not more likely to be “unsuccessful”. These results indicate that phase 3 trial initiation in neurology may be ill-informed.61

However, researchers are unclear on the type of efficacy evidence (proof of concept, surrogate, or clinical) to use as an indicator that the intervention should be brought into phase 3 trials in neurology. Current guidelines in ALS11, PMS9, and AD16,57 suggest that phase 3 trials can be initiated without apparent clinical efficacy but not without proof of concept, dose information on safety, and a defined population. In these cases, phase 3 trial designers will learn from other aspects of the phase 2 trial to optimize the intervention ensemble. Similarly, researchers who run phase 2 trials that have clinical efficacy endpoints but get a non-positive result will learn from other aspects of the phase 2 trial to optimize the intervention. However, they have also been given reason to believe that the treatment may not be effective and to stop further investment (a no-go signal). More research is needed to understand how phase 3 trial results are impacted by the type of evidence available to guide their design.

1. **Impact of bypassing phase 2 trials on the research trajectory**

When researchers bypass phase 2 trials, there may be far reaching implications on the future of the drug development trajectory. In this section, we will outline two ethical concepts and how bypassing phase 2 trials may impact them.

* 1. Efficiency

Trials have not “failed” when researchers find that an experimental treatment does not improve patient outcomes as non-positive results are normal in the natural history of drug development. Rather, these instances can be opportunities to learn more about a disease and treatment target.51,62,63 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.

The first resources to consider are the cost and time it takes to bring drugs to approval. Researchers have proposed that bypassing phase 2 trials would only be reasonable if there were unlimited resources for researchers to use in clinical trials. This way, there would be no cost to researching ineffective therapies.64 The reality of drug development is far from this ideal as the cost of running a phase 2 or phase 3 trial differs significantly. Although reporting on average costs of different phases is sparce,65 one review estimated that the median cost of a phase 2 trial was $8.6 million and that phase 3 trials cost $21.4 million.66 In a review of trials investigating treatments for Alzheimer’s disease, the cost/time of a phase 3 trial was roughly double that of a phase 2 trial.1 Therefore, bypassing phase 2 trials would significantly save money and time to reach drug approval when phase 3 find positive results.

However, efficiency regarding (cost and time) of bypassing phase 2 trials differs depending on the outcome of the phase 3 trial. For example, suppose researchers bypass a phase 2 trial and the subsequent phase 3 trial is positive. In this case, bypassing a phase 2 trial likely saved money and time compared to running both a phase 2 and phase 3 trial. However, in situations in which researchers bypass phase 2 trials and the following phase 3 trial is nonpositive, resources may have been a wasted by the sponsor’s failure to first perform a phase 2 trial (provided it would have been possible to find the non-positive result in phase 2). In addition, 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.

All of these considerations must also be considered with the opportunity cost of moving slower to approval. Both in number of patients and the cost to treat patients with the standard of care

In addition, to research costs and time to development, patients are an essential resource to consider. There is no research, to the best of our knowledge, describing the average number of patients in phase 2 or phase 3 trials in neurology nor the number of hours that these participants contribute of their time. Still, a phase 3 trial would likely use greater amounts of both resources. This donation of time, especially for patients who are made vulnerable by their conditions, should be optimized for the greatest possible return on investment.

* 1. Risks and benefits to patient participants

One way to protect participating patients is to consider the concept of clinical equipoise. Freedman argued that two tenets of clinical equipoise must be fulfilled for researchers to justify randomizing patients to receive an experimental treatment rather than providing them with the standard of care out of a trial: 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.67 Bypassing phase 2 trials has implications for both.

To the first point, clinical equipoise reflects a view of what experts would believe regarding a new experimental drug compared to standard of care were they able to access the totality of relevant evidence and were they exercising competent evidentiary judgment. When deciding whether to approve a trial, institutional review boards (IRBs) should discuss whether existing data have given the expert community reason enough to believe that the experimental arm may be better for patients than the standard of care. When reviewing a phase 3 trial that bypassed phase 2, IRBs will likely have less available evidence to consider on the intervention ensemble, efficacy, and safety for the new treatment. In this case, the expert community, with access to data (or lack thereof), would likely have reason to question whether the experimental treatment could be better for patients than the standard of care. Likely, fewer informed experts would prefer the experimental arm over the comparator in P3 clinical trials. That would undermine clinical equipoise: there would be less division among informed experts. In some cases, this division would be insufficient to be considered to fulfill clinical equipoise.

To the second point, a non-positive phase 3 trial that bypassed phase 2 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.”56 Both tenets of clinical equipoise are at risk of being unfulfilled, therefore it is important for further research to investigate how this plays out in practice.

**Conclusion**

In the chapter above, we reviewed the various pieces of evidence that phase 2 trials provide researchers in neurologic drug development. We also discussed how bypassing phase 2 trials may have implications for efficiency in drug development as well as the risks and benefits afforded to patients participating in phase 3 trials. In the chapter that follows, we will focus on the efficacy variable to investigate how often efficacy evidence is bypassed and whether that impacts the results of subsequent phase 3 trials in neurologic drug development.

**Chapter 2:**

**Submitted Manuscript**

**The Prevalence and Impact of Bypassing Phase 2 Trials for Pivotal Trials in Neurologic Drug Development**

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**Introduction**

Drug development for neurologic disorders is slow, expensive and failure prone. Many neurological disorders are characterized by heterogeneous populations and slow progression, thus necessitating lengthy clinical trials and large populations.11,16,25,60 Uncertainties surrounding pathophysiology and the severe limitations of animal models further add to the challenges of developing effective treatments for neurologic disease.7,23,24

To reduce the expense and time associated with testing new neurologic drugs in patients, sponsors sometimes truncate clinical development by skipping or deprioritizing preliminary evaluation of a drug’s efficacy in phase 2 clinical trials. For example, investigational Alzheimer’s disease treatments Aducanumab44 and Gantenerumab69 were both advanced into pivotal phase 3 trials based on signals from phase 1 trials.Such avoidance of phase 2 testing may help researchers overcome the inherent limitations of statistical powering in phase 2 trials71 and the absence of validated surrogate endpoints for many neurologic conditions.7,8

However, forgoing phase 2 testing is controversial.9,10,17,25,45 Risk/benefit balance for phase 3 trials may be degraded when they are started without supporting evidence from phase 2 trials. For example, when sponsors bypass phase 2, they have less information for optimizing variables like dose or trial eligibility for the phase 3 trial.5 In addition, phase 2 trials provide sponsors an opportunity to eliminate flagging drug candidates before they are evaluated in longer and larger phase 3 trials.

In what follows, we define “phase 2 bypass” as the launch of phase 3 trials absent phase 2 testing for efficacy, or despite negative outcomes in such testing. Our team previously reported that nearly half of phase 3 trials for solid tumor treatments bypassed phase 2 trials and that trials that bypassed had significantly worse efficacy outcomes.8 In the present work, we assess the prevalence and impact of phase 2 bypass in neurologic drug development.

**Methods**

Overview

Our primary goal was to estimate the prevalence of phase 2 bypass in ten neurological diseases for a decade of phase 3 trials. We defined phase 2 bypass as any case in which researchers initiated a phase 3 trial without positive surrogate or clinical evidence from a phase 2 trial in the same indication.8 Our secondary goals were to present the proportion of phase 3 trials initiated with three types of phase 2 bypass, identify factors associated with phase 2 bypass, and to investigate whether phase 2 bypass affected phase 3 trial outcomes.

Phase 3 Trial Sample

We created our sample of phase 3 trials using a list of search terms on ClinicalTrials.gov for the following neurological diseases: Alzheimer's disease, Parkinson’s disease, amyotrophic lateral sclerosis, Huntington's disease, relapsing multiple sclerosis, progressive multiple sclerosis, headache, epilepsy, traumatic brain injury, and stroke recurrence or recovery. We chose these conditions based on the relatively high volume of clinical trialing in each area. All phase 3 and phase 2 / 3 trials with primary completion dates January 1, 2011- January 1, 2021 were downloaded from ClinicalTrials.gov for screening.

We included trials that: a) tested a drug or biologic; b) had at least one research site in US, Canada, EU, UK, or Australia; and c) involved an intervention that was purportedly disease modifying or that targeted a symptom regarded as a proxy for disease modification typically used as a primary outcome in phase 3 trials. We excluded trials where: a) the primary purpose was diagnostic or screening; or b) trials were preceded by a phase 3 or 4 trial that started >1 year earlier.

We searched for phase 3 trial publications on ClinicalTrials.gov, Google Scholar, MEDLINE and EMBASE. When we were unable to find publications, we used results deposited on ClinicalTrials.gov for our analysis.

Matching Phase 3 Trials to Prior Phase 2 Trials

For every phase 3 trial in our sample, we searched for “matched” phase 2 trials using references in published phase 3 trials, ClinicalTrials.gov, and Drugs@FDA (for drugs that received approval). Phase 2 trials were considered to match a phase 3 trial in our sample if: 1) they investigated the same treatment in the same condition and 2) the phase 2 trial started at least one year earlier than the phase 3 trial. When we could not find any matched phase 2 trials, corresponding authors of phase 3 trial results were queried by email.

Extractions

We extracted the following items from phase 3 trials: a) completion status; b) the outcome on the primary endpoint; c) the proportion of patients who withdrew due to adverse events in each arm; d) the approval status of the experimental treatment in any indication at the time of trial initiation; e) funding (industry or non-industry); and f) phase (2/3 or 3).

We extracted the following items from all matched phase 2 trials: a) whether the primary endpoint was a clinical or a reasonably validated efficacy surrogate endpoint; and b) the outcome on the primary endpoint. Neurologist co-authors (EA and LS) and additional neurologists provided input on whether surrogates were reasonably validated.

Prevalence of Phase 2 Bypass

Our primary outcome was the prevalence of phase 2 bypass across all neurological indications in our sample. We calculated the proportion of phase 3 trials that were launched using three different levels of phase 2 support: 1) preceded by a phase 2 trial that was positive on a primary clinical or validated surrogate endpoint (“non-bypass”); 2) preceded by a phase 2 that provided evidence other than that from primary efficacy result (“ambiguous”). The ambiguous category was split into: a) preceded by a phase 2 trial that was non-positive on clinical or validated surrogate endpoints (“non-positive”); and b) preceded by a phase 2 trial whose primary endpoints only investigated proof of concept, safety, or non-validated surrogate outcomes (“not efficacy-centered”). The final category was: 3) not preceded by a phase 2 trial in the same indication with the same drug (“full bypass”). For our purposes, all trials that were not in the first category were deemed to have bypassed phase 2.

We also tested whether phase 2 bypass was associated with the following characteristics of phase 3 trials: industry funding, the approval status of the experimental treatment in a different indication at the time of trial initiation, or primarily degenerative conditions (Alzheimer’s disease, Parkinson’s disease, amyotrophic lateral sclerosis, Huntington’s disease, and progressive multiple sclerosis). We included two additional post-hoc analyses investigating whether phase 3 sample size or trial duration were greater in phase 3 trials that bypassed phase 2.

Impact of Bypass on Phase 3 Trial Outcomes

As a secondary analysis, we investigated whether phase 2 bypass was associated with three unfavourable outcomes: 1) a diminished proportion of positive phase 3 trial results; 2) an increased proportion of phase 3 trials that are terminated due to safety or futility; and 3) increased risk to patients, using within trial risk ratios (RR) for withdrawal-related adverse events (WdAEs). As a post-hoc sensitivity analysis to further probe the impact of phase 2 bypass, we tested whether phase 2 bypass was associated with phase 3 positivity when we excluded indications with near universal non-positive (<15%) or positive (>85%) results.

Statistical Analysis

We used Fisher-exact tests to investigate whether three phase 3 trial characteristics and two phase 3 trial results were associated with phase 2 bypass. In addition, we compared average phase 3 trial sample sizes and trial durations between trials that bypassed and those that did not using paired t-tests. To compare whether risk of withdrawal due to adverse events was impacted by bypassing, we pooled RRs in a meta-analysis with subgroup contrasts between phase 3 trials that bypassed and those that did not. We used the two-tailed *p-*value of Cochran’s Q for subgroup difference to investigate significance. We did not adjust for multiple hypothesis testing. We determined significance using a nominal significance level of 0.05 for all analyses.

Our protocol was registered at <https://osf.io/crf62/>. See supplement for more methodological details, screening criteria, and protocol deviations. All extractions were performed in duplicate, and disagreements were resolved with input/guidance from JKi.

**Results**

Sample of Index Phase 3 trials

A total of 113 phase 3 trials were included (**Figure 1**). Together, Alzheimer’s disease (n = 30, 27%), and headache (n = 26, 23%) accounted for the majority of the trials. Most trials were funded by industry (n = 94, 83%) and were investigating treatments that were not approved in any indication (n = 92, 81%) at the time of trial initiation (**See Table 1**).

Prevalence of Phase 2 Bypass

Overall, 52 phase 3 trials (46%) were scored as having bypassed positive efficacy results from a phase 2 trial. The most common form of bypass was full bypass (n = 19, 17%). Among disease areas with more than ten trials in our sample, phase 2 bypass was most common in Alzheimer’s disease trials (n = 19, 63%) and least common in trials investigating treatments for relapsing multiple sclerosis (n = 1, 6%) (**see** **Table 2**).

Phase 2 bypass was not significantly associated with industry funding: 77% (n = 40) of trials that bypassed phase 2 were funded by industry compared to 89% (n = 54) of trials that were preceded by phase 2 trials (p = 0.13). Similarly, phase 2 bypass was not significantly associated with the investigational drug’s approval status: 23% (n = 12) of trials that bypassed were approved in different indications compared to 15% (n = 9) of trials that were preceded by phase 2 (p = 0.33) (**Table 3**). Phase 3 trials investigating treatments for primarily degenerative conditions were significantly more likely to bypass phase 2 than trials in nondegenerative conditions: 61% (n = 32) of trials investigating primarily degenerative diseases bypassed phase 2 compared to 33% (n = 20) of trials investigating nondegenerative conditions (p =< 0.005). Mean phase 3 trial sample size and duration were not significantly different between trials that bypassed and those that did not (Sample size-1322 vs 1058 patients respectively, p = 0.12; Duration-1049 vs 931 days respectively, p = 0.63).

Patient Risk and Benefit of Phase 2 Bypassing

Phase 3 trials that bypassed phase 2 were significantly less likely to be positive on their primary outcome than trials that were preceded by positive efficacy evidence from a phase 2 trial (31%, n = 15 vs 57%, n = 34 respectively, p = 0.01). When we excluded indications with near universal positivity (RMS and PMS) or non-positivity (Stroke, TBI, HD, and AD), this effect was not present (61%, n = 11 for phase 2 bypass vs 61%, n = 17 for phase 2 non-bypass, > .99). The frequency of phase 3 trial termination due to safety or futility was non-significantly higher in the group that bypassed phase 2 (29%, n = 15 for phase 2 bypass vs 15%, n = 9 for phase 2 non-bypass, p = 0.11)(**see** **Table 3** and **eTable 1** for indication-specific results). Pooled RRs for withdrawals due to adverse events were not significantly different between trials that bypassed and those that did not (RR = 1.46 vs RR = 1.36 respectively, p = 0.65) (**see** **eFigure 1**).

**Discussion:**

Phase 2 bypass was common (46%) in our sample of phase 3 trials investigating treatments for neurologic conditions. Phase 3 trials for primarily degenerative diseases were more likely than not to bypass phase 2 trials. In contrast, phase 3 trials in relapsing-remitting multiple sclerosis rarely employed phase 2 bypass.

Phase 2 trials play a crucial role in providing a scientific and ethical justification for phase 3 testing. They provide opportunities for sponsors to find dosing or patient populations that maximize the prospect of attaining a positive result in pivotal trials. By probing efficacy, they may also play a key role in increasing the prior probability that a phase 3 trial will produce a positive result. Ethically, phase 2 trials help establish the basis for clinical equipoise in phase 3 trials, and minimize the prospect that patients receive prolonged exposure to a futile drug.

However, sponsors might defend phase 2 bypass in three ways. First, sponsors may prefer to put a drug candidate directly into phase 3 testing to reduce the costs and time needed to obtain regulatory approval. Second, sponsors might argue that phase 2 testing is not necessary for trials testing repurposed drugs. In such circumstances, researchers may be able to use evidence from other indications to establish safety and target engagement. Third, sponsors might defend phase 2 bypass by appealing to scientific feasibility. For example, in research areas where there are no validated surrogate endpoints, sponsors may face difficulty designing phase 2 trials that are smaller and shorter than a phase 3 study, but that are adequately powered to detect efficacy. In such cases, sponsors may opt to use the interim analysis of a phase 3 trial as a substitute for phase 2 trials.

Our findings do not suggest that any of the above explanations predominate. To the argument for cost reduction, we found no relationship between phase 2 bypass and industry sponsorship. Nor was bypass more prevalent with repurposed drugs. Scientific feasibility for indications in our sample is suggested by the fact that, in all indications, there were at least some phase 3 trials that were preceded by positive phase 2 trials. The scientific feasibility of running phase 2 trials in the indication areas we surveyed is also underscored by the fact that phase 2 bypass was not associated with larger sample sizes or greater duration in phase 3 trials.

However, our findings are equivocal as to whether current practices of phase 2 bypass are harmful. On the one hand, our analyses suggest that phase 3 trials launched without positive clinical or validated surrogate evidence from phase 2 trials have more adverse outcomes, as indicated by greater prospect of early termination and significantly greater prospect of negative primary outcomes. However, the patterns we observe may represent the confounding effect of indications in our sample. For example, trials for Alzheimer’s disease accounted for 37% of phase 3 trials that bypassed in our sample. Alzheimer’s disease lacks validated surrogate endpoints for phase 2 trials, and Alzheimer’s disease phase 3 trials in our sample were almost all negative on their primary outcome. When we performed an analysis only within indications where primary outcomes in phase 3 trials were variable, we no longer observed an association between phase 2 bypassing and trial negativity.

Our analyses provide some clues as to where phase 2 trials deliver the greatest value. Firstly, we found that, numerically, phase 3 trials initiated after an ambiguous phase 2 trial were less likely to have a positive result than phase 3 trials that fully bypassed. This trend implies that phase 2 trials that provided information other than primary efficacy evidence, such as dose and population details, may not have increased the probability of phase 3 positivity. Secondly, phase 3 trials started after non-positive results from phase 2 trials were especially likely to be terminated. This may suggest that negative outcomes in phase 2 trials provide especially clear signals that a drug is not worth testing in phase 3 trials.

Limitations

Our study has the following limitations. First, we pooled positivity and termination rates across neurologic diseases with vastly different rates for these outcomes because we were limited by our sample sizes within indications. This introduced a source of confound into our analysis of the impact of phase 2 bypass. Second, some publications for earlier trials did not define their phase. When this happened, we assigned phase based on a set of prespecified rules. Third, positivity is a reductive measure of trial success. Fourth, a planned meta-analysis to measure the impact of phase 2 bypass on efficacy effect sizes could not be completed due to an insufficient sample of trials in different indications. Our ability to assess adverse impacts of phase 2 bypass is limited by the effects of confounds described above.

Conclusion

Our findings suggest that bypassing positive efficacy evidence from phase 2 trials is common in neurologic drug development. However, neither commercial motivation, repurposing approved drugs, or scientific feasibility appears to dominate the reasons for bypass. While logic and studies in other areas suggest that patients and trial outcomes are adversely affected by phase 2 bypass,72 the present analysis does not establish worse outcomes for patients when phase 3 trials are launched absent supporting phase 2 evidence. Given the prevalence of phase 2 bypass and the adverse outcomes of bypass in other disease areas, we urge the development of formal criteria for IRBs, researchers, and patients to decide when phase 2 bypass in neurological drug development is justified.

**Declaration of Interest:** JK received consulting fees from Amylyx Inc. Authors declare no other potential conflicts of interest.

**Data Sharing:** Data will be available on Open Science Framework.

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**Tables and Figures**

**Figure 1: Prisma Flow Diagram for the Phase 3 Trial Sample**

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**Table 1. Characteristics of the Phase 3 Trial Sample**

|  |  |
| --- | --- |
| Indications | Number of phase 3 trials  N=113 (%) |
|
|
| Indication |  |
| Alzheimer's disease | 30 (27) |
| Parkinson's disease | 10 (9) |
| Amyotrophic lateral sclerosis | 5 (4) |
| Huntington's disease | 4 (4) |
| Relapsing Multiple sclerosis | 16 (14) |
| Progressive Multiple sclerosis | 4 (4) |
| Headache | 26 (23) |
| Epilepsy | 7 (6) |
| TBI | 5 (4) |
| Stroke | 6 (5) |
| All | 113 |
| General |  |
| Pharmaceutical funder | 94 (83) |
| Pre-approval status | 92 (81) |
| Positive primary endpoint | 49 (45)\* |
| Terminated for safety or futility | 24 (21) |
| Median sample size (IQR) | 835 (706) |
| Median trial duration in years (IQR) | 2.92 (1.97) |

\*Out of 108 trials with primary results available

**Table 2. Prevalence of Bypassing**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Indications | Overall  (N) | Non-Bypass | Bypass | | |
| **Preceded by Positive Phase 2**  **N (%)** | **Preceded by Ambiguous Phase 2**  **N (%)** | | **Full Bypass**  **N (%)** |
| **Non-Positive** | **Not Efficacy-Centered** |
| Alzheimer's disease | 30 | 11 (37) | 6 (20) | 7 (23) | 6 (20) |
| Parkinson's disease | 10 | 5 (50) | 0 (0) | 4 (40) | 1 (10) |
| Amyotrophic lateral sclerosis | 5 | 3 (60) | 2 (40) | 0 (0) | 0 (0) |
| Huntington's disease | 4 | 1 (25) | 2 (50) | 1 (25) | 0 (0) |
| Relapsing multiple sclerosis | 16 | 15 (94) | 0 (0) | 1 (6) | 0 (0) |
| Progressive multiple sclerosis | 4 | 1 (25) | 1 (25) | 1 (25) | 1 (25) |
| Headache | 26 | 19 (73) | 4 (15) | 0 (0) | 3 (12) |
| Epilepsy | 7 | 2 (29) | 1 (14) | 0 (0) | 4 (57) |
| TBI | 5 | 3 (60) | 0 (0) | 1 (20) | 1 (20) |
| Stroke | 6 | 1 (17) | 1 (17) | 1 (17) | 3 (50) |
| All indications | **113** | **61 (54)** | **17 (15)** | **16 (14)** | **19 (17)** |

**Table 3. Relationship Between Phase 2 Bypass and Phase 3 Trial Characteristics / Results**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Non-Bypass | Bypass | | | P-values  Non-Bypass vs Bypass2 |
| **Preceded by Positive Phase 2**  **N (%)1** | **Preceded by Ambiguous Phase 2**  **N (%)1** | | **Full Bypass**  **N (%)1** |
| **Non-Positive** | **Not Efficacy-Centered** |
| Trial Characteristics |  |  |  |  |  |
| Pharmaceutical Funder | 54/61 (89) | 16/17 (94) | 10/16 (63) | 14/19 (74) | 0.13 |
| Approved | 9/61 (15) | 2/17 (12) | 3/16 (19) | 7/19 (37) | 0.33 |
| Phase 3 Trial Results |  |  |  |  |  |
| Positive on Primary Outcome3 | 34/60 (57) | 4/17 (24) | 3/15 (20) | 8/16 (50) | 0.01 |
| Terminated due to Safety or Futility | 9/61 (15) | 6/17 (35) | 4/16 (25) | 5/19 (26) | 0.11 |

1Percents reflect the number of trials with the given trial characteristic/results out of the number of trials that fell into each supportive evidence category.

2Fisher-exact test between trials in non-bypassed trajectories vs bypassed trajectories (Preceded by Ambiguous Phase 2 and Full Bypass trials)

3Trials were only included in the positivity analysis if they had primary results available (N = 108)

**Supplement**

**Supplemental Methods**

Phase 3 Sample Creation

ClinicalTrials.gov search parameters for phase 3 trials:

1. **Condition or disease (including synonyms built into ClinicalTrials.gov):** Alzheimer disease OR Alzheimer's disease OR Alzheimer Dementias OR Dementia of the Alzheimer's type OR dementia alzheimers OR Dementia of Alzheimers Type OR Alzheimer Type Dementia OR Senile Dementia OR Alzheimer Syndrome OR AD OR Parkinson disease OR Parkinson's disease OR PD OR Parkinson OR Primary Parkinsonism OR Paralysis Agitans OR Shaking palsy OR ALS OR Amyotrophic lateral sclerosis OR Gehrig Disease OR Motor neurone disease OR Charcot disease OR Huntington disease OR Huntington's disease OR Huntington's chorea OR Chronic progressive hereditary chorea OR MS OR Multiple Sclerosis OR MS (Multiple Sclerosis) OR Disseminated sclerosis OR Migraine OR Cephalalgia OR Head pain OR Pain in head OR Cephalgia OR Headache OR Epilepsy OR epileptics OR seizure disorders OR epilepsia OR TBI OR Traumatic Brain Injury OR brain traumas OR Traumatic encephalopathy OR brain injuries traumatic OR traumatic brain damage OR Brain damage OR cerebral damage OR injury brain OR cerebral injury OR Stroke OR Cerebrovascular accident OR cerebral vascular accident OR Apoplexy OR Brain attack OR Brain Vascular Accident OR TIA (Transient Ischemic Attack) OR Transient Ischemic Attack OR intracerebral haemorrhage OR subarachnoid haemorrhage
2. **Study type:** “Interventional Studies (Clinical Trials)”
3. **Status of recruitment:** no restriction (looking for Actual primary completion dates, so likely mostly Completed/Terminated/Active not recruiting but completed- checked filtered results to see)
4. **Phase:** 3
5. **Study start date**: no restriction
6. **Primary completion date**: 01/01/2011-01/01/2021
   1. The end range was chosen to allow one year between primary completion and depositing results as per the Final Rule.73 Our objective was to have at least 100 phase 3 trials but we saturated the sample for a full decade of Phase 3 trials. The target minimal sample size of 100 is selected because, for a primarily descriptive study, it seems likely to deliver a reasonably robust estimate of the prevalence of phase 3 bypass. Assuming 30% trials involve phase 2 bypass, availability of 30 trials involving bypass provides a reasonable starting point for secondary objectives for a first ever exploration of the prevalence of bypass.
   2. Semi-automatic screening (using excel filters) for phase 3 trials:
7. **Primary completion date**: checked that type is “Actual” and not “Anticipated”
   1. Excluded, \*unless\* trial had an “Actual” overall completion date;
8. **Trial design**: excluded if trial was labelled as:
   1. “Non-randomized” in randomization field;
   2. “Single group assignment” in “Model” field;
   3. 1 in “Arms” field;
9. **Trial size:** <30
10. **Trial status:** exclude if the trial recruitment status was:
    1. Withdrawn (i.e. no patients enrolled);
11. **Indication:** excluded if primary purpose is
    1. Diagnostic;
    2. Screening;
    3. Basic Science
12. **Intervention/Indication:** excluded if trial:
    1. Did not include at least one intervention that was classified as a “Drug” or “Biological” “ Dietary supplement” or “Genetic” (“Other” and “combination product” were manually checked); ie exclude procedure or behavioral or device or radiation
    2. Included healthy volunteers;
13. **Trial Location**: exclude if the trial does not have a
    1. US or CAD UK, EU, Australian

Manual Screening for phase 3 trials:

1. **Intervention:** Exclude if the intervention is
   1. surgery/behavioral/device/conditioning of stem cells/procedure/ biosimilar
   2. extension, discontinuation studies, phase 1/2/3
   3. head-to-head (trials pitting two approved SOC interventions against each other) or if there are more than two options for the experimental arm (ake “any anticoagulant”)
   4. treating a secondary condition in patients with included conditions (ie infection in PD patients and immune responses to vaccines in MS patients)
2. **Comparator:** Exclude if the comparator is not placebo or another treatment (as opposed to another dose of same drug (no historical controls))
3. **Indication**-Must investigate treatment for the below conditions exclusively:
   1. Alzheimer's disease
      1. Excluded trials investigating treatments for:
         1. Healthy people with AD mutations
         2. MCI without pathologic characteristics of AD
      2. Included trials investigating treatment for:
         1. Trials investigating MCI with pathologic characteristics of AD (prodromal)
         2. Mild-severe AD (however defined)
   2. Parkinson disease,
   3. Amyotrophic lateral sclerosis,
   4. Huntington's disease,
   5. Relapsing Multiple sclerosis,
      1. Relapsing-remitting MS
      2. Trials investigating treatment for CIS only were excluded
   6. Progressive Multiple sclerosis,
      1. Primary progressive MS and secondary progressive MS
      2. Trials investigating treatment for CIS only were excluded
   7. Headaches,
   8. Epilepsy,
   9. TBI,
   10. Stroke
       1. Must be in patients who have had a stoke looking at recurrence or recovery.
4. **Earlier Phase 3 trial:** Trials were excluded if they were preceded by a phase 3 or 4 trial that had at least a year of progress. We used TrialViewer74 to search ClinicalTrials.gov for all earlier phase 3 trials of our experimental drug-of-interest. In addition, we searched for earlier phase 3 trials in our phase 3 trial publications. We did not check for the status of the previous trial. We used the following rules when determining if earlier phase 3 trials counted as evidence for the trial in our sample (the same rules were used to match phase 3 trials to phase 2 trials):
   1. Earlier trials
      1. did not need to be exclusively in the same indication
      2. could investigate the same intervention in control or experimental arm
      3. could be in any aged population
      4. could not be used if they investigated treatments in preclinical populations
         1. Example: CIS, people with AD mutation
      5. did not need to match in adjuvant status if the phase 3 in our sample was adjuvant or monotherapy. However, earlier trials for phase 3 trials in our sample investigating combination therapies had to be testing the same combination.
      6. could be investigating slight variations in the same drug such as small molecular changes or changes the delivery mechanism.
         1. If it was clear that a phase 3 trial in our sample was investigating a variation in an old drug, we checked for approval of the original drug in the same disease area and excluded the trial in our sample if the earlier drug was already approved in the same indication. This criterion was mostly reliant on phase 3 trial publication citations indicating that the drug was a new variation on an old drug.
   2. RRMS and PPMS were treated separately, and they could not be used as prior evidence for the other. If the trial was only SPMS, earlier trials in RRMS or PMS were considered prior evidence.
5. **Primary Endpoint:** Trials were only included if they had a primary endpoint that was a clinical efficacy endpoint widely used as a measure of disease modification in phase 3 trials.
   1. Trials were excluded if they only had primary safety, tolerability, surrogate primary endpoints, or primary endpoints looking only at a symptom that is not used as a measure of disease modification.
   2. Neurologist collaborators were queried: “Would you consider whether the following is a “widely used measures of disease modification in phase 3 trials for X?”
6. **Phase 3 Portion of Phase 2/3 trials**: Exclude if phase 2/3 did not progress to phase 3
   1. Trials were excluded when they were identified as phase 2 in the publication or in ClinicalTrials.gov records.

Phase 3 results

We searched for Phase 3 trial publications on Google Scholar using NCT ID, Title (top-line & official), varying combinations of drug names, indication, and sponsor & investigator last name. We then searched OVID using MEDLINE and EMBASE using a combination of the search terms: drug names from the experimental arm (any synonym of the drug mentioned in ClinicalTrials.gov) + the indication as listed in ClinicalTrials.gov + “Clinical trial” + “Phase 3”.

We prioritized publications reporting the results of at least one primary outcome with a significance test. If we were unable to find primary publications of results, we used primary ClinicalTrials.gov results. If there are no primary results on ClinicalTrials.gov, we used abstracts that reported primary results. We only used interim results if the trial was terminated. Trials without results were included in the prevalence results but not in the positivity analysis (unless they were terminated at DSMB review-which we classified as nonpositive). We performed our final search on July 8, 2023.

Matching phase 2 trials to phase 3 trials

We searched for phase 2 matches in phase 3 trial publications, Clinicaltrials.gov, FDA approval documents (Drugs@FDA), and author solicitation.

* For a phase 2 trial to be eligible to be a match, it had to have a primary start date that was year or more before the primary start date of the phase 3 study in our sample as indicated by ClinicalTrials.gov (or the recruitment start date in the publication if registration date was unavailable). If the date that the phase 2 trial started is unclear, publication within/before the year that the phase 3 trial started was accepted. Expanded access trials, extension studies, non-prospective trials, and trials without any accessible results were not considered.
* If a phase 2 trial passed these criteria, phase 2 trials also had to match on:
  + Indication
    - To ensure our approach for matching phase 2 and 3 trials was standardized and reproducible, we allowed phase 2 trial in the same broad disease area to count as matches for phase 3 trials in our sample. Our broad disease areas are Alzheimer’s disease, Parkinson’s disease, amyotrophic lateral sclerosis, Huntington’s disease, relapse remitting multiple sclerosis, progressive multiple sclerosis, headache, epilepsy, traumatic brain injury and stroke.
    - Relapsing-remitting MS and primary progressive MS were treated separately, and they could not cite the other as prior evidence. Secondary–progressive MS was included in progressive category but could be matched to either RRMS or PMS.
  + Intervention
    - To determine whether phase 2 trials investigated the same drug or biologic, we used the following rules:
      * A trial that investigated a drug/biologic as a monotherapy could not be used as prior evidence for a trial that was investigating the same drug in combination therapy (and vice-versa). Monotherapy evidence could be used for adjuvant phase 3 trials in our sample because the change may be a result of shifting populations from early line to late line patients. Adjuvant evidence could also be matched to monotherapy phase 3 trials in our sample. Two adjuvant trials with different background drugs were also accepted as matches.
        + Adjuvant trials were identified by the terms “adjuvant” or “add on”
      * Slight variations on drugs were allowed to be matches such as small molecular changes or changes to the delivery mechanism (unless the old variation of the drug preceded to phase 3 trials or approval in which case the trial in our sample was excluded (see exclusion criteria)).
* Phase determination:
  + We used the phase status on ClinicalTrials.gov unless they are identified as a different phase in the publication. The phase of an earlier trial was occasionally undefined and we used the following rules to classify them (although we are aware that not all trials followed these rules, they are useful when we were forced to categorize):
    - P1-The trial was not randomized and there was no efficacy endpoint
    - phase 2—These trials could be randomized or not, could have an efficacy endpoint. In cases where trials were randomized and had a primary endpoint, we decided to call trials phase 2 (rather than phase 3) if they involved <300 patients. When the trial publication said called the trial dose-ranging or proof of concept, we put them in this category.
    - phase 3- The trial was controlled and had a primary efficacy endpoint and involved >300 patients. If we found that an earlier trial fell into this category, we excluded the relevant phase 3 trial in our sample.
  + Sample size was the deciding factor in eight cases. We decided to use FDA guidelines that indicated phase 3 trials averaged more than 300 patients.45 Although this undoubtedly varies by indication, we found on average phase 3 trials in relevant indications were all above 300 and it was therefore safe to use this rule to determine which trials were phase 2:
    - * TBI- avg p3 in our sample was 966
      * Headache- avg p3 in our sample was 1052
      * Stroke- avg p3 in our sample was 1115
      * HD- avg p3 in our sample was 695

Classification

Once we determined that a phase 2 trial was an eligible match, we extracted its positivity status and classified the associated phase 3 trial. If any p3 trial had more than one prior trial, the one closest to preceded in the order they are described above took priority.

* Positivity of phase 2 matches: To determine the positivity of phase 2 matches, we used the definition of positivity provided by the trial publication. We used the following rules when applicable:
  + Sequential testing procedures were followed.
  + Trials that were stopped by DSMBs but were then positive were considered positive.
  + phase 2 futility trials were considered positive if they found that the treatment of interest was not futile.
  + When there were two primary analyses where one was positive and the other was not (inconsistent results), we used the following rules:
    - Co-primaries: When they stated that all primaries had to be positive for the trial to be positive, we called inconsistent results nonpositive. We used this rule when researchers did not change adjust for multiple testing.
    - Multiple primaries: When researchers used multiplicity adjustment or partitioned of the alpha levels, we called inconsistent results positive
      * If they used the term “coprimaries” but adjusted the primary, we treated it as multiple primaries
      * In cases where there were 2 dose groups that were both considered primary analysis groups, we called inconsistent results positive. Therefore we did not require multiplicity adjustments for multiple dose arms.
* Each phase 3 trial was then classified into one of the following groups based on its prior evidence:

1. Preceded by a positive phase 2 trial:

* phase 3 trials were put into this category when they were preceded by one or more:
  + phase 2 trial that was positive on a clinical or a reasonably validated surrogate primary endpoint
    - Surrogate endpoints were considered reasonably validated if they are commonly used as a primary endpoint to evaluate efficacy in phase 2 trials in that indication because of time constraints OR make sense mechanistically and have been validated in a phase 3 trial of a similar drug showing clinical efficacy is associated.
      * The only surrogates that we considered to be reasonably validated were number of gadolinium-enhancing lesions and the proportion of patients with ⩾95% peripheral CD19+ B-cell depletion for multiple sclerosis trials
  + For two phase 2 trials, it was unclear what the primary endpoint was in a trial. We used our best judgement to determine the primary objective of the trial.
  + phase 2/3 are put into this category automatically.

1. Preceded by an ambiguous phase 2 trial:

* Every other phase 3 trial with a matched phase 2 trial that did not fall into the above category was put into one of the following categories:
  + Non-positive: Had a phase 2 trial that was nonpositive on their primary clinical or validated surrogate efficacy endpoint.
  + Not aimed at providing efficacy data: Had a phase 2 trial that had a primary endpoint investigating surrogate endpoints (not validated) or safety/tolerability. In addition, when the matched phase 2 trial had a primary efficacy endpoint but was not designed to evaluate significance between groups, we put the associated phase 3 trial into this category.

1. Full bypass

* phase 3 trials were put into this category when we did not find a matched phase 2 trial.
  + These were confirmed with emails to authors when emails were available.
  + When we found potential phase 2 trials but could not find any publication or results, these trials are put into the true bypass group because we could not determine if they were truly matches without information on the intervention, indication, and date.

Extraction

We extracted the following items from each phase 3 trial in our sample:

1. Termination status
   1. We extracted termination status from registration records or publications as well as whether it was due to futility or safety concerns.
2. Positivity status
   1. We extracted whether each trial was positive on their primary efficacy outcome. To do so, we used the definition of positivity in the statistical analysis section. The same positivity rules as above were used.
   2. If the trial was stopped by DSMB but no results were available, trials were deemed to be non-positive.
3. WdueAE in each arm
   1. We extracted the number of participants who withdrew from the study due to adverse events from ClinicalTrials.gov or consort documents in the publications. Where there was disagreement between these sources, the publication took priority.
   2. The denominator was the number of patients at baseline randomization.
   3. When there were multiple arms, we took the one that was first for hierarchical testing and the comparator arm. If there truly was not one arm with a higher priority, we took the highest dose. If one was added as an amendment, the original was taken.
4. Approval status
   1. We classified each phase 3 trial as pre or post-approval depending on whether the treatment under investigation was approved at the time of trial initiation (primary start date in registration).
      1. Pre-approval = drug was approved after the primary start date or never approved
      2. Post-approval = drug was approved before the primary start date
         1. Approval in other indications or with different delivery mechanisms were allowed. If the trial was looking at a new formulation for an old drug- the first formulation will be used for approval date
         2. If the trial was investigating a combination treatment, they both needed to be approved in that indication for the trial to be considered post-approval
5. Funding (industry vs non-industry).
   1. We extracted whether the trial was funded by a pharmaceutical company or not from publications. If no funder was available, we took the sponsor listed on ClinicalTrials.gov.
   2. When the trial was not funded by a pharmaceutical company but drug was supplied by one, we called the trial non-industry.
6. Trial sample size and duration
   1. These numbers were extracted from ClinicalTrials.gov using the following variables: Actual Enrollment, Study Start Date and Actual Primary Completion Date.

**Supplemental Statistics**

Fisher-exact tests were performed using the “fisher.test” R function.75 Risk ratios for WdAE were pooled used the function “metabin” from the “metafor” R package.76 Paired t-tests were performed in R using “t.test”77

**Protocol deviations**

* We did not look at these variables in relationship with the prevalence of bypassing
  + Phase 2/3 vs phase 2 (these were all preceded)
  + Pediatric vs Adult vs Mixed (almost all were adult)
  + Orphan disease (all were not orphan (except maybe HD))
  + Symptoms (most were excluded)
  + Severity-too difficult to operationalize made it into degenerative
* We changed moral economy analyses to focus on Phase 3 trials rather than phase 2 because they we did not have a representative sample of phase 2 trials (only p2 trials that moved on to phase 3 trials).
* We did not include an analysis of phase 2 bypass and phase 3 trial benefit because there was not enough phase 3 trials reporting the same measure in more than one indication.
* We did not search OVID or PubMed for the matches due to the large sample size.

**Supplemental Results**

**eTable 1: Positivity across indications**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Indications | Positivity Rate of Phase 3 | | | Termination Rate of Phase 3 | | |
| Overall Positivity  Rate  N (%)1 | Type of Supportive Evidence | | Overall Termination Rate  N (%) | Type of Supportive Evidence | |
| Preceded by Phase 2  N (%)2 | Phase 2 Bypass  N (%)2 | Preceded by Phase 2  N (%)2 | Phase 2 Bypass  N (%)2 |
| Alzheimer's disease | 3 (10) | 2 (18) | 1 (6) | 12 (40) | 3 (27) | 9 (47) |
| Parkinson's disease | 2 (22) | 0 (0) | 2 (50) | 2 (20) | 1 (20) | 1 (20) |
| Amyotrophic lateral sclerosis | 1 (25) | 1 (50) | 0 (0) | 1 (20) | 1 (33) | 0 (0) |
| Huntington's disease | 0 (0) | 0 (0) | 0 (0) | 1 (25) | 0 (0) | 1 (33) |
| Relapsing multiple sclerosis | 14 (88) | 14 (93) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Progressive multiple sclerosis | 4 (100) | 1 (100) | 3 (100) | 0 (0) | 0 (0) | 0 (0) |
| Headache | 20 (77) | 15 (79) | 5 (71) | 2 (8) | 2 (11) | 0 (0) |
| Epilepsy | 5 (71) | 1 (50) | 4 (80) | 1 (14) | 0 (0) | 1 (20) |
| TBI | 0 (0) | 0 (0) | 0 (0) | 2 (40) | 2 (67) | 0 (0) |
| Stroke | 0 (0) | 0 (0) | 0 (0) | 3 (50) | 0 (0) | 3 (60) |
| All indications | **49 (45)** | **34 (57)** | **15 (31)** | **24 (21)** | **9 (15)** | **15 (29)** |

1Trials were only included in the positivity analysis if they had primary results available (N=108)

2Percents reflect the proportion of trials that were positive or terminated out of the number of trials that fell into each supportive evidence category (non-bypass vs bypass).

Chart

Description automatically generated**eFigure 1: RRs for WdAE Pooled Subgroup Analyses**

**Chapter 3: Why is phase 2 bypass common?**

**Introduction**

Neurologic conditions include some of the most prevalent, disabling, and terminal diseases of modern life.22 However, drug development in neurology has one of the lowest rates of approval across all areas of medicine.26–28 Pharmaceutical companies have decreased their investment in developing treatments for these diseases.26,27 Further research is needed to evaluate current drug development practices to determine how it can be optimized in order to get new and effective treatments to these patients quickly.

This thesis set out to determine whether, and in which cases, bypassing phase 2 efficacy evidence is common in neurologic drug development. Secondarily, we intended to investigate whether the practice had implications for phase 3 trial results. In the chapter that follows, we review four reasons researchers may bypass phase 2, situate our results within these motivations, and recommend future research to guide researchers, IRBs, and patients.

**Reasons for phase 2 bypass**

Given the high prevalence of phase 2 bypass and its potential to worsen outcomes, further work is needed to define criteria for when phase 2 bypass is scientifically or ethically justified. In the following section, we address four motivations researchers may use when they bypass phase 2 and discuss whether we found each to be compelling within the ethical frameworks outlined in chapter one.

Scientific Motivations

To start, there are scientific and statistical reasons that bypassing phase 2 trials may be appropriate. Firstly, many neurologic conditions lack surrogate endpoints with clear associations with clinical outcomes. Therefore, phase 2 trials in these indications may be less useful than in indications that have outcomes which can provide quick read-outs of efficacy information.9 In these cases, phase 2 trials can use clinical outcomes but these outcomes often need large numbers of patients to detect differences or lengthy trials to see long-term safety/efficacy outcomes.57 For instance, Alzheimer’s clinical trials require a large number of patients to show differences in cognitive decline.57 In our sample, we found that bypassing was more common than not in trials for degenerative diseases, most of which suffer from the challenges described above. However, all conditions in our sample were characterized by trials that both bypassed and did not, suggesting that it is possible to run phase 2 trials focused on collecting efficacy before phase 3 trials, even in areas reliant on clinical outcomes.

Efficiency Motivations

Efficiency in drug development typically centers around the attempt to reduce both the money and time it takes for researchers to get new drugs to patients. Pharmaceutical companies have limited funds to invest in new therapies and must make decisions as to which drugs, populations, and phases of clinical trials to invest in. Therefore, economization is the second motivation pharmaceutical companies may have to bypass phase 2 trials in neurologic drug development. A recent analysis of the costs of clinical trials for Alzheimer’s disease shows that bypassing phase 2 trials in this case would cut costs up to 10 million per drug.78 However, if phase 3 trials are nonpositive after bypassing phase 2, additional costs may ensue if further research is needed to determine whether the drug is a truly ineffective or the intervention ensemble was not optimized. In addition, companies may bypass phase 2 trials in order to decrease the proportion of their 20-year patent life that is taken up by clinical development.27 Though commercial considerations are important to limit divestment in the area78 and to efficiently direct scarce resources, they may not be a compelling reason to bypass phase 2 trials for patients involved in the phase 3 trials. In our sample, we did not find that industry funded trials were more likely to bypass phase 2. MORE

Additionally, researchers should be mindful of moral efficiency in drug development, such as decreasing the number of patients needed to bring a drug to approval. These considerations are especially relevant when researchers are designing clinical trials for rare diseases or indications with rapidly changing prevalence. The third reason researchers may be inclined to bypass phase 2 trials is to use limited available patients to get a definitive answer as to the efficacy of an investigational drug. However, phase 3 trials that bypassed may be diverting limited patients from trials with more efficacy evidence priors, although these alternative trials may not exist. In addition, equipoise would likely be threatened if this was the only reason for bypassing phase 2 trials, as there would be little reason to believe that the experimental drug is better for patients. In our sample, Huntington’s disease trials were preceded by phase 2 trials only 25% of the time (although our sample size was very small (n=4). MORE

Other evidence

Fourthly, researchers may bypass phase 2 trials when they have other reasons to be confident in a drug’s safety and dosing. For example, sponsors aiming to repurpose an already approved drug often have extensive evidence about safe dose ranges, pharmacokinetics, and target engagement. However, some commentators question whether this constitutes a compelling rationale for phase 2 bypass because patients with different conditions can have vastly different reactions to similar drugs.79 Nevertheless, we did not find that phase 3 trials that bypassed were more likely to test drugs that had already been approved in other indications (we did, however, observe that repurposed drugs made up 40% of the trials that “fully bypassed” in our sample).

In addition, researchers designing phase 3 trials may use information from phase 1 trials that provided ample evidence on efficacy rather than run a phase 2 trial.80 Although this thesis was not designed to investigate these instances, publications for phase 3 trials that bypassed often cited phase 1 studies. Overall, our results indicate that clinical equipoise may be threatened when researchers bypass phase 2 trials. However, when the preclinical or phase 1 evidence supporting the trial is extraordinarily strong (e.g. huge effect sizes), experts and IRBs might expect that they can support a phase 3 trial that bypassed phase 2 without compromising an expectation of clinical efficacy against a standard of care.

Other justifications for phase 2 bypass, such as bleak treatment landscapes, may be less compelling. None of motivations described above can fully explain the high prevalence of bypassing in neurologic drug development we observed in our sample. However, together, they may likely explain why this practice is so common.

**Conclusions**

Bypassing a phase 2 trial may be associated with diminished benefit and/or higher risk for patients participating in phase 3 trials. Our paper investigating phase 2 bypass in oncologic drug development found that patients in phase 3 trials that were not supported by phase 2 trials had significantly worse efficacy outcomes.72 In neurologic drug development, we did not find that bypassing phase 2 had an impact on the risk for patients to withdrawal due to adverse events in the experimental arm of phase 3 trials. Overall, phase 3 trials in our sample were significantly less likely to be positive on their primary outcome and nonsignificant more likely to be terminated due to safety concerns or futility. However, our results were inconclusive as to whether bypassing, regardless of reason, was problematic for phase 3 trial results.

When an IRB is reviewing a phase 3 trial that bypassed, they should situate the trial within the reasons we outlined and decide if they believe that it justifies the lower level of evidence. If they decide to approve the trial, there may be some ways to mitigate the potential risk/use of resources. For example, the futility bar in the phase 3 trial can be raised to act like a phase 2. Alternatively, researchers designing phase 3 trials that bypassed could use adaptive designs with early stopping rules, potentially reducing the number of patients exposed to ineffective treatments.81 Phase 2 bypass also has implications for consent documents as patients may have an opinion as to whether they wish to participate in a trial that lacks prior efficacy evidence.

Our findings leave unresolved questions that further research may be able to address. Firstly, researchers could use phase 3 trial citations to evaluate whether the reason for phase 2 bypass is associated with phase 3 trial results. Further, this analysis could be used to evaluate whether phase 3 trials that bypassed and were nonpositive were more likely to blame intervention ensemble issues. Secondly, researchers could estimate the amount of patients, money, and time required to reach approval or stop development in bypassed trajectories compared trajectories that involve both phase 2 and 3 trials. Thirdly, researchers could investigate how investigations of safety and dose, rather than efficacy, set phase 3 trials up for success. For example, in multiple sclerosis, a phase 3 trial may be positive but not moved to approval because of immune reactions. In these cases, it would be more interesting to see whether safety and dose were investigated prior to phase 3 trial initiation than efficacy.

Concluding paragraph.

**Conclusion**

Neurologic drug development suffers from various challenges that collectively make it one of the least productive areas of research, such as lackluster animal models, inadequate surrogate outcomes, and long chronic conditions that make it hard to get timely readouts of the efficacy and safety of experimental drugs. Phase 2 trials in neurology traditionally provide researchers with an opportunity to explore dose and population details in the context of preliminary efficacy and safety outcomes.

This thesis provides the first systematically derived estimate of the prevalence in which phase 3 trials in neurology are initiated without positive efficacy evidence from phase 2 trials. We termed this practice “phase 2 bypass” and provided the first comprehensive discussion of its ethical implications.

Our findings show that phase 2 bypass is common (46%). We observed wide variation in the prevalence of bypassing between indications in our sample. Firstly, clinical trials for degenerative conditions were significantly more likely to bypass than the other indications in our sample and did so more often than they were preceded by phase 2 trials. Secondly, relapsing remitting multiple sclerosis almost never bypassed phase 2. Within trials that bypassed, roughly one third fully bypassed any phase 2 trial, one third preceded to phase 3 after finding a non-positive result on a primary endpoint, and one third were preceded by phase 2 trials that were not tailored to efficacy.

There are various reasons that researchers may bypass phase 2 trials including scientific, efficiency, and prior evidence motivations. These motivations likely play different roles within indications. In addition, these motivations vary in whether they are scientifically or ethically justifiable.

Future work is needed to determine whether phase 2 bypass in specific cases are associated with phase 3 trial protection from negative outcomes. These will allow for guidance for researchers, IRBs, and patients.

Patients with neurologic disorders suffer from especially prolonged, life-destabilizing, and occasionally terminal conditions. Although there is active research in many areas of neurologic drug development, there remain many areas without a standard of care that can significantly change the clinical outcomes of patients. It is the role of researchers to determine how to safely and ethically research new treatments. The results of this thesis disrupt the narrative that phase 3 trials are typically started after a phase 2 trial that was positive on its primary outcome. In addition, we provide ethical lens in which to interpret this practice in the future.

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