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

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Abstract

Objective:

Pivotal trials for neurologic drugs in clinical development 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 of phase 2 bypass in neurologic phase 3 drug trials for 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.

Methods:

We used ClinicalTrials.gov to create a sample of phase 3 trials investigating treatments for ten neurologic conditions and that were completed between 2011-2021. To assess the prevalence of phase 2 bypass, we searched for 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, 46% of which were not preceded by a positive phase 2 trial. The prevalence of phase 2 bypass varied across indications, with bypass common in trials for Alzheimer’s disease (63%, 27% of trials in our sample) and rare in trials for relapsing-remitting multiple sclerosis (6%, 14% of trials in our sample). Phase 2 bypass was not more prevalent for industry funded or drug repurposing trials than for non-industry funded trials or trials investigating unapproved drugs. Overall, the phase 3 trials in our sample that bypassed phase 2 trials were significantly less likely to be positive on their primary outcome (31%, n = 15 vs 57%, n = 34 respectively, p = 0.01) and non-significantly more likely to have terminated early

due to safety or futility (29%, n = 15 vs 15%, n = 9 respectively, p = 0.11). These results were likely confounded by varying positivity rates across indications included in our sample. In addition, phase 3 trials started after non-positive results from phase 2 trials were especially likely to be terminated (35%).

Conclusion:

In our sample, 46% of neurologic disease phase 3 trials were launched absent supporting evidence from positive phase 2 trials. Our evaluation of the impact of phase 2 bypass on phase 3 outcomes was inconclusive due to confounding. However, phase 2 trials may provide an important opportunity for investigators to investigate dose, efficacy, and safety. We urge development of criteria defining when phase 2 bypass is ethically and scientifically justified.

Résumé

Objectif :

Les essais pivots pour les médicaments neurologiques en cours de développement clinique sont souvent lancés sans le soutien des essais de phase 2 positifs. Un tel "contournement de la phase 2" peut dégrader les risques/bénéfices des essais de la phase 3. Notre objectif principal était de déterminer la prévalence du contournement de la phase 2 dans les essais de phase 3 de médicaments neurologiques pour la maladie d'Alzheimer, la maladie de Parkinson, la sclérose latérale amyotrophique, la maladie de Huntington, la sclérose en plaques récurrente, la sclérose en plaques progressive, les céphalées, l'épilepsie, les lésions cérébrales traumatiques et la récurrence ou la récupération des accidents vasculaires cérébraux (AVC).

Méthodes :

Nous avons utilisé ClinicalTrials.gov pour créer un échantillon d'essais de phase 3 portant sur des traitements de 10 maladies neurologiques et terminés entre 2011 et 2021. Pour évaluer la prévalence du contournement de la phase 2, nous avons recherché des essais de phase 2 antérieurs portant sur le même couple médicament-indication. Ensuite, nous avons étudié les circonstances dans lesquelles le contournement de la phase 2 était plus fréquent, et si le contournement de la phase 2 était associé à des résultats défavorables de l'essai de phase 3.

Résultats :

Nous avons inclus 113 essais de phase 3, dont 46 % n'avaient pas été précédés d'un essai de phase 2. La prévalence du contournement de la phase 2 variait selon les indications, le contournement étant courant dans les essais sur la maladie d'Alzheimer (63 %, 27 % des essais dans notre échantillon) et rare dans les essais sur la sclérose en plaques récurrente-rémittente (6 %, 14 % des essais dans notre échantillon). Les contournements de phase 2 n'étaient pas plus

fréquents pour les essais financés par l'industrie ou les essais de repositionnement de médicaments que pour les essais non financés par l'industrie ou les essais portant sur des médicaments non approuvés. Dans l'ensemble, les essais de phase 3 de notre échantillon qui ont contourné les essais de phase 2 étaient significativement moins susceptibles d'être positifs sur leur résultat principal (31%, n = 15 contre 57%, n = 34 respectivement, p = 0,01) et non significativement plus susceptibles d'avoir pris fin prématurément pour des raisons de sécurité ou de futilité (29%, n = 15 contre 15%, n = 9 respectivement, p = 0,11). Ces résultats ont probablement été confondus par des taux de positivité variables selon les indications incluses dans notre échantillon. En plus, les essais de phase 3 commencés après des résultats non positifs d'essais de phase 2 étaient particulièrement susceptibles d'être interrompus (35 %).

Conclusion :

Dans notre échantillon, 46% des essais de phase 3 sur les maladies neurologiques ont été lancés sans preuve de soutien provenant d'essais de phase 2 positifs. Notre évaluation de l'impact du contournement de la phase 2 sur les résultats de la phase 3 n'a pas été concluante en raison de facteurs de confusion. Cependant, les essais de phase 2 peuvent constituer une occasion importante pour les chercheurs d'étudier la dose, l'efficacité et la sécurité. Nous recommandons vivement l'élaboration de critères définissant quand le contournement de phase 2 est justifié d'un point de vue éthique et scientifique.

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Contribution of Authors

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

Chapter 2: Conceptualization: HM, RM, EA, LS, JK. 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, from small, phase 1 safety studies through to large and lengthy phase 3 trials. This regimentation plays a key role in limiting the number of patients who are exposed to experimental drugs, as well as the duration of that exposure. Traditionally, 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 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 practice "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 47% 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. 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 endpoints[5,6] and an extremely high degree of unmet therapeutic need in neurological conditions. Despite these

reasons for bypassing, commentaries on amyotrophic lateral sclerosis and multiple sclerosis suggest that phase 2 studies should be required before phase 3 trial initiation.[7,8]

In neurology, phase 2 trials have often been used to optimize dose and schedule[7,9–13] and to map out the safety and tolerability of the treatment regimen under investigation.[7,9,11,13] 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 effect[7,9,11] However, methods to provide proof of concept often rely on surrogate endpoints with little evidence that they are sensitive or reliable.[5,6] Beyond proof of concept, showing signs of clinical efficacy in phase 2 trials is desirable, but often very difficult [7,9,13] 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.[14] Due to the limitations associated with clinical endpoints, guidelines in amyotrophic lateral sclerosis and Alzheimer's disease 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.[9,14]

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.[9] Investigators may also initiate a phase 3 relying on data from same drug but a similar indication,[7] 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.[15,16]

Alternatively, investigators sometimes do run phase 2 trials in the same indication but persevere after obtaining a nonpositive result on their clinical outcomes (or not testing a clinical

outcome at all). This is especially prevalent in Alzheimer's disease drug development. Indeed, phase 3 trials for three major Alzheimer's disease drugs- tarenflurbil[16], solanezumab[17], and atorvastatin[8-] were launched based on phase 2 trials that were nonpositive on their clinical endpoints, relied on post-hoc analyses, or did not have clinical endpoints All drugs produced negative outcomes in their phase 3 testing.

In chapter one, we will review the role of phase 2 trials in neurologic drug development. In chapter two, we 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. In chapter three, we will evaluate contemporary practices to 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.[17] One 2016 estimate found that this disease area was the most common cause of DALYs and second most common cause of deaths globally.[818] Although increasingly common, many neurologic diseases do not have any effective treatments.[5] 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, introduce one method of designing trial trajectories to reduce the time it takes to get effective treatments to patients - bypassing phase 2 trials- and discuss what may be lost when phase 2 trials are not fully utilized.

Neurologic drug development

1.1 Challenges

Neurologic drug development has proven more challenging than for many other indication areas, with some indications lacking any established disease-modifying standard of care (SOC).[5] 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, central nervous system (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.[5,19,20] 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 cumulative nature of the impairments, and determining how the chronic exposure to treatments will impact safety over time.[21] Additional challenges include the risk of intervening in an organ system- the brain- where personal identity and decisional capacity originate.[5]

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%).[22–24] One review found that CNS drugs were half as likely to be approved as other indications.[24] Hurdles to development have discouraged companies from investing in developing treatments for these diseases[22,23] Nevertheless, several classes of medications are available to treat other neurologic diseases such as relapsing multiple sclerosis and migraine.[5] Historically, the probability that a trial in some neurologic disorders will show positive results is low.[22–24] However, this outcome would have a massive impact on the experience of millions of patients.[17] 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.[25] 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.[25] Phase 2 trials are sometimes separated into 2a (which look mainly at safety, tolerability, and proof of concept),[26] and 2b (which test for efficacy). Next, phase 3 trials aim to determine whether there are sufficient signals that the drug is effective enough 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.[27] Other trial 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.[16,28–32] In neurology, other techniques for accelerating drug development include shortening phase 2 trials,[28] using basket or platform trials,[26] historical controls,[33] pragmatic phase 3 trials,[15] enrichment designs,[34] adaptive trials,[35] and futility designs.[35,36] For example, recent trials investigating treatments for amyotrophic lateral sclerosis,[37] Alzheimer's disease,[38] and Parkinson's disease[39] 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 indication[9] or the same drug in a similar indication.[7,15] 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.[15,40–42] 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 salient?[32]

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.[43] 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.[44] 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,[5,6] desperation to find new treatments for a population with little to no options,[15,45] market pressures, intense competition between companies,[13,40] and the vast potential for payoff if successful.[40]

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 commentators highlight the importance of phase 2 trials in neurology drug development and admonish against bypassing phase 2 trials.[7,8,21] 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 reduce the chance that a phase 3 trial will be successful. Alternatively, other commentators introduce phase 2 bypass as a viable trajectory to limit drug development time.[46,47]

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 in 1963.[48] Together with phase 1 trials, phase 2 trials make up what some commentators call the "learn zone"[49] of drug development, where researchers collect data that has "a significant impact on future trial size, expense, and risk."[25] 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.[50] 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"[46] Phase 3 trials are traditionally focused on determining whether a drug has an appropriate risk/benefit ratio to warrant approval.

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.[7,9–13] This is a stage where, using many doses, researchers can begin to see a dose relationship in their safety and efficacy endpoints.[25] 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.[5,25] Many doses are changed (mostly lowered) after FDA approval due to safety concerns.[51,52] One study investigating these post-approval modifications found that dose changes were most common in neurologic drugs.[53] 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,[54,55] traumatic brain injury,[10,56,57] and stroke[35] 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.[7,9,13,14] In these cases, phase 2 trials may use endpoints that are surrogates for the clinical outcomes.[5,6] For example, a useful endpoint to investigate treatments for patients with relapsing-remitting multiple sclerosis is annualized relapse rate, but this endpoint typically takes at least a year 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.[49] 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.[45] Surrogate endpoints are especially widespread in Alzheimer's drug development, where the lack of validated surrogate endpoints in phase 2 trials has led to the initiation of phase 3 trials without any indication that there is a clinical effect.[45] Some commentators argue that reliance on these endpoints may have played a role in recent non-positive phase 3 trial results for Semagacestat[46] and Solanezumab[40] 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.[9] 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.[58–60] For example, several phase 3 trials were initiated for treatments in amyotrophic lateral sclerosis[61] and Alzheimer's disease[62] 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.[26,63] 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.[8,11] Nevertheless, broadening the population may be necessary to ensure that patients beyond a restrictive trial population can benefit from a later approval.[25] 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,[14,16,60] shown by examples in RRMS,[40] PMS,[7] and AD.[14,40]

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.[26,59] For example, phase 2 trials can be used to weed out drugs that are not likely to be successful early in the development process.[7,14] 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.[64]

However, 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 is contended within neurology. Current commentaries in amyotrophic lateral sclerosis[9], progressive multiple sclerosis[7], and Alzheimer's disease [14,60] suggest that phase 3 trials can be initiated without evidence of clinical efficacy provided the following are established: proof of concept, dose information on safety, and a defined population.

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.

Conclusion

In this chapter, we reviewed the reasoning and evidence for preceding phase 3 trials with positive phase 2 trials in neurology. In the chapter that follows, we will investigate how often efficacy evidence is bypassed and whether this decision 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 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 heterogenous populations and slow progression, thus necessitating lengthy clinical trials and large populations.[9,14,21,63] Uncertainties surrounding pathophysiology and the severe limitations of animal models for neurological diseases further add to the challenges of developing effective treatments for neurologic disease.[5,19,20]

The standard approach to drug development begins with phase 1 trials aimed at testing safety and dose. Drugs then advance to preliminary tests of efficacy in phase 2 trials, often using surrogate endpoints. Drugs showing promise in phase 2 are then tested in large, randomized phase 3 trials using clinical endpoints. To reduce the expense and time associated with testing new neurologic drugs in patients, however, sponsors sometimes truncate the clinical development path by skipping preliminary evaluation of a drug's efficacy in phase 2 clinical trials. For example, investigational Alzheimer's disease anti-amyloid monoclonal antibody treatments aducanumab[42] and gantenerumab 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 trials[66] and the absence of validated surrogate endpoints for many neurologic conditions.[5,6]

However, forgoing phase 2 testing is controversial.[7,8,16,21,46] Risk/benefit balance for phase 3 trials may be degraded when they are started without supporting evidence from phase 2 trials. For example, when clinical development programs bypass phase 2, there is less information available for optimizing variables like dose or trial eligibility for the phase 3 trial.[5] In addition, phase 2 trials provide an opportunity to eliminate ineffective drug candidates before they are evaluated in larger phase 3 trials.

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 10 neurological illnesses with phase 3 trials between 2011 and 2021. We defined phase 2 bypass as any case in which researchers initiated a phase 3 trial without positive surrogate or clinical evidence of benefit from a phase 2 trial in the same indication.[8] Our secondary goals were to examine 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 is associated with phase 3 trial outcomes.

Phase 3 Trial Sampling

We created a sample of phase 3 trials using a list of search terms on ClinicalTrials.gov for the following neurological diseases: Alzheimer's disease, Parkinson 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 trials in each area. All phase 3 and phase 2 / 3 trials with primary completion dates January 1, 2011- January 1, 2021 were screened.

We included trials that: a) tested a drug or biologic; b) had at least one research site in the United States, Canada, European Union, United Kingdom, 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. These sites were chosen to limit our sample to trials conducted in places that would be likely to register/publish in the English language, seek approval in the US or Canada, and have robust research regulatory bodies. 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, searches of ClinicalTrials.gov, and the Drugs@FDA database (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. We determined whether primary outcomes were positive using the definition of positivity provided by the trial publication and statistical significance.

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 a positive primary efficacy result ("ambiguous"). The latter category was split into a) preceded by a phase 2 trial that was non-positive on primary clinical or validated surrogate endpoints (non-positive); and b) preceded by a phase 2 trial that only investigated safety or used non-validated surrogate endpoints as their primary endpoint ("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"). 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 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) non-positive phase 3 trial results; 2) phase 3 trials termination due to safety or futility; and 3) increased risk to patients, using within trial risk ratios (RR) for withdrawal-related adverse events (WdAEs).

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-analyses 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 consensus was sought from JK.

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 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%) 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) in 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). Phase 3 trials investigating treatments for primarily degenerative conditions were significantly more likely to bypass phase 2 than 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 ($p<0.01$). 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 (31%, n=15 vs 57%, n=34 respectively, p=0.01). 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 nonpositive (<15%) or positive (>85%) results. 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 P2 bypass vs 61%, n=17 for P2 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 P2 bypass vs. 15%, n=9 for P2 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 trials were fully bypassed in about 17% of the sample. About 30% of phase 3 trials were launched after phase 2 trials that were nonpositive or that were not designed to test efficacy. Phase 3 trials for Alzheimer's disease, Huntington's disease, progressive multiple sclerosis, epilepsy and stroke were more likely than not to bypass phase 2 trials. In contrast, 15 of 16 phase 3 trials in relapsing-remitting multiple sclerosis were preceded by a positive phase 2 trial.

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 will receive prolonged exposure to a futile drug.

However, sponsors might defend phase 2 bypass in four ways. First, sponsors may prefer to put a drug candidate directly into phase 3 testing to reduce the amount of patent time elapsed during clinical development. Second, sponsors might argue that phase 2 testing is not necessary for some medications where safety and dosing information have been established for other therapeutic indications, for example with repurposed medications. In these cases, drug developers might use evidence from other indications to establish safety and dosing. 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 argue that their phase 3 design includes dose ranging, safety assessments, sample size re-estimations, and stopping rules that might obviate the need for phase 2.

Our findings do not suggest that any one explanation predominates. To the argument for reducing clinical development timelines, 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 suggests that phase 3 trials launched without positive clinical or validated surrogate evidence from phase 2 trials have more adverse outcomes, as indicated by the non-significantly 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 (at least at the time when trials in our sample were run), 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 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 increase 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 may have underestimated the prevalence of bypass due to assumptions about the timing of phase 2 trials. We assumed phase 3

studies were supported by phase 2 if the latter was positive and launched at least one year earlier. In some cases, phase 3 trials meeting these criteria might have been launched before any phase 2 trial results were available to phase 3 trial investigators. However, we had no way of knowing when results of phase 2 trials were made available to sponsors, and thus defaulted to criteria that erred on the side of classifying a phase 3 trial as having been supported by a phase 2 trial. Second, 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. The low volume of phase 3 neurologic drug trials available for analysis limited the extent to which this source of confound could be addressed. Third, some publications for earlier trials did not define their phase. When this happened, we assigned phase based on a set of prespecified rules. Fourth, positivity is a reductive measure of whether a phase 2 trial pointed to the promise of a new drug. Some observers might argue that the phase 2 trials in our sample that we categorized as "non-positive" in fact pointed to promise in phase 3 trials, based on secondary outcomes or subgroup analyses. However, our method of classifying phase 2 trials as positive or non-positive is simple, does not require specialized knowledge, and thus could be implemented reproducibly by experts and non-experts alike.

Conclusion

Our findings suggest that launching phase 3 trials without a positive efficacy result from a phase 2 trial is common in neurologic drug development. While logic and studies in other areas suggest that patients and trial outcomes are adversely affected by phase 2 bypass,[43] 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, the association between its

occurrence and unfavorable outcomes, and the observation of unfavorable outcomes in other disease areas,[43] we urge the development of formal criteria for deciding 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

Table 1. Characteristics of the Phase 3 Trial Sample

Trial Characteristics	Number of phase 3 trials N (%)
Indication	
Alzheimer's disease	30 (27)
Headache	26 (23)
Relapsing multiple sclerosis	16 (14)
Parkinson's disease	10 (9)
Epilepsy	7 (6)
Stroke	6 (5)
Amyotrophic lateral sclerosis	5 (4)
Traumatic Brain Injury	5 (4)
Huntington's disease	4 (4)
Progressive Multiple sclerosis	4 (4)
All	113
General	
Pharmaceutical funder	94 (83)
Investigating an approved treatment	21 (19)
Median sample size (IQR)	
Alzheimer's disease	967 (528)
Headache	887 (1125)
Relapsing Multiple sclerosis	982 (417)
Median trial duration in days (IQR)	
Alzheimer's disease	1333 (512)
Headache	465 (205)
Relapsing multiple sclerosis	1370 (374)
Results	
Positive primary endpoint	49 (45)*
Terminated for safety or futility	24 (21)

*Out of 108 trials with primary results available

Table 2. Prevalence of Bypassing

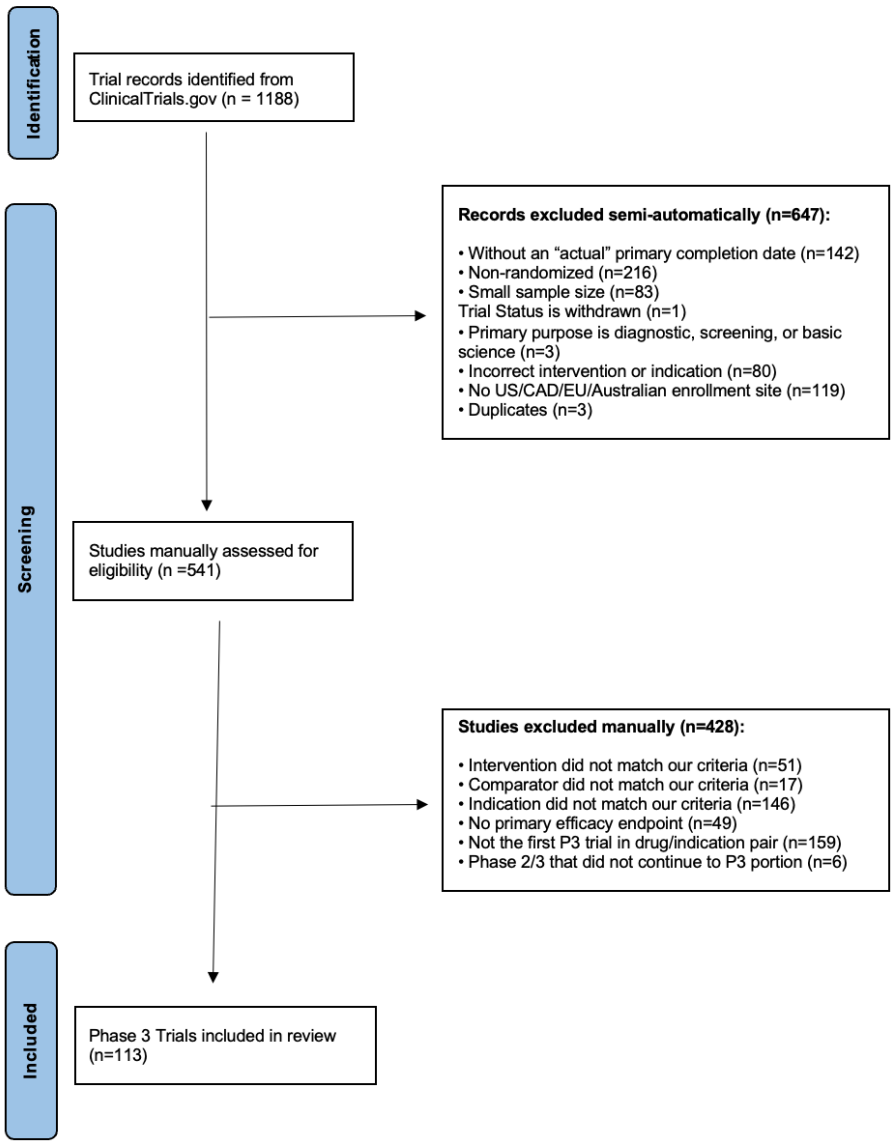
Indications	Overall (N)	Non-Bypass	Bypass		
		Preceded by Positive P2 (N, %)	Preceded by Ambiguous P2 (N, %)		Full Bypass (N, %)
			Non-positive	Not Efficacy-centered	
Alzheimer's disease	30	11 (37)	6 (20)	7 (23)	6 (20)
Parkinson's disease	10	5 (50)	0 (0)	4 (40)	1 (10)
Amyotrophic lateral sclerosis	5	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 Bypass[2]
	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 Company 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 Outcome[3]	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

[1]Percents reflect the number of trials with the given trial characteristic/results out of the number of trials that fell into each supportive evidence category.
[2]Fisher-exact test between trials in non-bypassed trajectories vs bypassed trajectories (Preceded by Ambiguous Phase 2 and Full Bypass trials)
[3]Trials were only included in the positivity analysis if they had primary results available (N = 108)

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



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
    a. The end range was chosen to allow one year between primary completion and depositing results as per the Final Rule.[67] 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.
    b. Semi-automatic screening (using excel filters) for phase 3 trials:
7. **Primary completion date**: checked that type is "Actual" and not "Anticipated"
    a. Excluded, *unless* trial had an "Actual" overall completion date;
8. **Trial design**: excluded if trial was labelled as:
    a. "Non-randomized" in randomization field;
    b. "Single group assignment" in "Model" field;
    c. 1 in "Arms" field;
9. **Trial size:** <30
10. **Trial status:** exclude if the trial recruitment status was:

a. Withdrawn (i.e. no patients enrolled);

11. **Indication:** excluded if primary purpose is
    a. Diagnostic;
    b. Screening;
    c. Basic Science
12. **Intervention/Indication:** excluded if trial:
    a. 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
    b. Included healthy volunteers;
13. **Trial Location**: exclude if the trial does not have a
    a. US or CAD UK, EU, Australian site

Manual Screening for phase 3 trials:

1. **Intervention:** Exclude if the intervention is
    a. surgery/behavioral/device/conditioning of stem cells/procedure/ biosimilar
    b. extension, discontinuation studies, phase 1/2/3
    c. 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")
    d. 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:
    a. Alzheimer's disease
        i. Excluded trials investigating treatments for:
            1. Healthy people with AD mutations
            2. MCI without pathologic characteristics of AD
        ii. Included trials investigating treatment for:
            1. Trials investigating MCI with pathologic characteristics of AD (prodromal)
            2. Mild-severe AD (however defined)
    b. Parkinson disease,
    c. Amyotrophic lateral sclerosis,
    d. Huntington's disease,
    e. Relapsing Multiple sclerosis,
        i. Relapsing-remitting MS
        ii. Trials investigating treatment for CIS only were excluded
    f. Progressive Multiple sclerosis,
        i. Primary progressive MS and secondary progressive MS
        ii. Trials investigating treatment for CIS only were excluded
    g. Headaches,
    h. Epilepsy,
    i. TBI,

j. Stroke

i. 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 TrialViewer[68] 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):

    a. Earlier trials

        i. did not need to be exclusively in the same indication

        ii. could investigate the same intervention in control or experimental arm

        iii. could be in any aged population

        iv. could not be used if they investigated treatments in preclinical populations

            1. Example: CIS, people with AD mutation

        v. 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.

        vi. 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.

   b. 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.
   a. 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.
   b. 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
   a. 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.[46] 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.

2. 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.
3. 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
    a. We extracted termination status from registration records or publications as well as whether it was due to futility or safety concerns.
2. Positivity status
    a. 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.
    b. If the trial was stopped by DSMB but no results were available, trials were deemed to be non-positive.
3. WdueAE in each arm
    a. 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.
    b. The denominator was the number of patients at baseline randomization.
    c. 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
    a. 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).
        i. Pre-approval = drug was approved after the primary start date or never approved
        ii. 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).
    a. 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.
    b. 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

a. 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.[69] Risk ratios for WdAE were pooled used the function "metabin" from the "metafor" R package.[70] Paired t-tests were performed in R using "t.test"[71]

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 phase 2 trials that moved on to phase 3 trials).
- We did not include an analysis of phase 2 bypass and phase 3 trial efficacy 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.

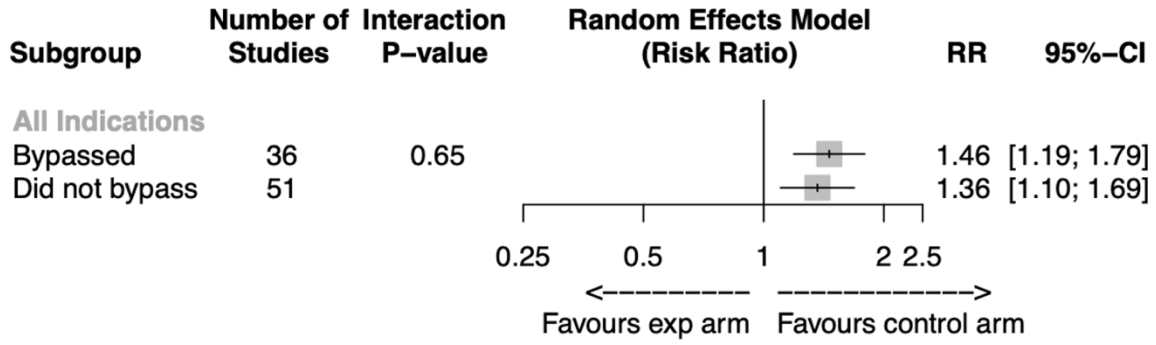
Supplemental Results

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)**

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

eFigure 1: RRs for WdAE Pooled Subgroup Analyses



Chapter 3: Ethical Considerations in Bypassing Phase 2 Trials in Neurology

Introduction

The present thesis reports the frequency with which sponsors bypass phase 2 efficacy evidence in neurologic drug development. Secondarily, we investigated whether the practice had implications for phase 3 trial outcomes. Our results indicated that researchers bypassed phase 2 trials nearly half of the time, and that this practice was significantly more common in the development of drugs for degenerative conditions. In addition, we found that phase 2 bypass may be associated with a lower positivity rate than trials that bypassed. However, this result was ambiguous when we performed sensitivity analysis excluding trials with uniform positivity or negativity.

In the chapter that follows, we first discuss various motivations that may explain our findings that sponsors and researchers bypass phase 2 efficacy data nearly half of the time they initiate phase 3 trials and review the ethical implications for phase 2 bypass. We also offer a series of recommendations to investigators, sponsors, or institutional review boards (IRBs) who might contemplate proposals for phase 3 trials that bypassed phase 2. We close by discussing our recommendations for future research in this area.

Reasons for phase 2 bypass

Our results indicated that researchers initiated phase 3 trials without phase 2 efficacy evidence almost half of the time. To address the question of whether phase 2 bypass is morally appropriate, we begin with an exploration of reasons researchers might offer for following this trajectory.

Statistical Considerations

To start, sponsors have scientific and statistical reasons for bypassing phase 2 trials. Firstly, many neurologic conditions lack surrogate endpoints with clear associations with clinical outcomes. For these indications, phase 2 trials may be less useful than in indications that have outcomes that can provide quick read-outs of efficacy information.[7] In these cases, phase 2 trials can use clinical outcomes. However, these outcomes often need large numbers of patients to detect differences.[60] For instance, Alzheimer's clinical trials require a large number of patients, observed over 1.5-2 years, to show meaningful differences in cognitive decline.[60] Both defeat the purpose of phase 2 testing. In addition, underpowering of phase 2 trials may lead to an abundance of false negatives. Therefore, the value of a phase 2 trial in neurology may be lower than in other disease areas, like oncology, where surrogate endpoints are more validated.

In our sample, we found that bypassing was more common than not in trials for degenerative diseases, many of which suffer from the challenges described above. However, all indications in our study included at least one trajectory involving phase 2 non-bypass. This suggests that it is possible to run phase 2 trials focused on collecting efficacy evidence before phase 3 trials, even in areas lacking validated surrogate endpoints. Moreover, we previously found phase 2 bypass was highly prevalent in cancer drug development. Unlike neurology, cancer drug developers have a host of surrogate outcomes that are considered reasonably validated. Together, this suggests that statistical considerations- while perhaps providing moral grounds for phase 2 bypass- are not the driving force behind the practice of phase 2 bypass.

Strong evidence

Researchers might bypass phase 2 trials when they have other reasons to be confident in a drug's promise. This might be the case where preclinical or phase 1 evidence strongly favours a new drug or where safety and dosing has been well worked out in other disease areas.

To the former point, 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.[72] Although this thesis did not evaluate phase 1 evidence, publications for phase 3 trials that bypassed often cited phase 1 studies.

To the dosing/safety point above, sponsors aiming to repurpose an already approved drug often have extensive evidence about safe dose ranges, pharmacokinetics, and target engagement. This may appear to offer strong grounds for phase 2 bypass. However, some commentators question this, arguing that patients with different conditions can have vastly different responses to similar drugs.[73] For example, pembrolizumab was a highly effective treatment for lung cancer and an ineffective and dangerous treatment for myeloma.[74] Nevertheless, we did not find that phase 3 trials that bypassed were more likely to involve 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).

Other Motivations

Researchers might also proceed to phase 3 before phase 2 trials when they lack effective treatment options to treat the condition of interest. Here, they may be desperate to have a treatment to offer both participating and future patients. Alone, this decision to attempt a "Hail Mary" may risk violating clinical equipoise in the phase 3 trial, as we will discuss below.

Researchers might also consider bypassing phase 2 when they are developing treatments for rare diseases or for indications with rapidly changing prevalence. In these cases, it would be understandable to try to use a limited patient pool to get a definitive answer about the efficacy of an investigational drug. However, phase 3 trials that bypass run the risk of diverting limited patients from phase 3 trials supported by stronger evidence of efficacy. In addition, the rare

disease rationale by itself would not be compelling, since rarity has no bearing on the question of whether a phase 3 trial is in clinical equipoise. The only rare disease included in our sample was Huntington's disease. Here, we found that phase 3 trials bypassed phase 2 trials 75% of the time (although our sample size was very small (n=4)). Similarly, ALS (which has a lower prevalence relative to many other indications in our sample) bypassed phase 2 trials 40% of the time (n=5).

None of motivations described above can by themselves explain the high prevalence of bypassing in neurologic drug development we observed in our sample. However, together, they likely explain why phase 2 bypass occurs so frequently.

Ethical considerations in bypassing phase 2 trials

Together, these motivations may explain why, in practice, sponsors opt to bypass phase 2 trials. But is phase 2 bypass ethical? How should IRBs or regulators approach the assessment of risk/benefit for trials that are not supported by phase 2 evidence?

We suggest that there are three major ethical considerations that ought to govern initiation of phase 3 trials: a) ensuring that patients are not receiving inferior care by participating in the clinical trial ("clinical equipoise"); b) minimization of patient exposure to research burden (using the concept of "moral efficiency"); c) reducing opportunity cost (i.e. squandering research resources on unproductive research).

Clinical Equipoise

One way to protect patients participating in clinical trials from receiving sub-standard care 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.[75] Bypassing phase 2 trials has implications for both.

To the first, clinical equipoise entails that at the outset of a randomized trial, a new treatment should be backed by evidence suggesting the new intervention is likely to be competitive with, and possibly superior to, existing standard of care. By "competitive," we mean that a treatment is anticipated to deliver a combination of efficacy, safety, ease of administration etc. of similar or greater value than a standard of care treatment.

Regimentation in the form of phases in drug development helps to establish grounds for clinical equipoise in two ways. First, initial phases of testing identify the roughly optimal conditions- like dose, schedule, and patient eligibility etc.- for eliciting the therapeutic properties of a new pharmacological agent (this is termed the "intervention ensemble"). Second, early phase trials (primarily phase 2) establish that a pharmacological agent, when applied within an intervention ensemble, shows pharmacological properties that are suggestive of a level of clinical benefit similar to or exceeding standard of care. This is typically accomplished by measuring the impact of an intervention ensemble using surrogate endpoints that provide a rapid readout of pharmacological properties.

Therefore, when IRBs are reviewing a phase 3 trial that bypassed phase 2, they 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. Under such circumstances, 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. We found that phase 3 trials that bypassed were less likely to be positive on their primary outcomes than trials that were proceeded by positive efficacy evidence from phase 2 trials. This suggests, though does not prove, that clinical equipoise may be threatened when researchers bypass phase 2 trials.

To the second condition of clinical equipoise, a non-positive phase 3 trial that bypassed phase 2 efficacy evidence may be less capable of changing expert opinion about the value of a treatment approach. This is because the non-positive result could be due to an ineffective treatment or because the intervention ensemble has not been optimized. For example, on seeing a negative result, advocates of the new treatment approach might not change their view on its efficacy and instead argue that the wrong dose of the drug was used in the phase 3 trial. 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."[59]

However, bypassing may be morally acceptable under clinical equipoise when at least one of the following conditions are met. First, when there are strong grounds for anticipating that an intervention ensemble tested in phase 3 is roughly optimal and that it will be effective. This might be accomplished if phase 1 studies establish clear evidence favouring a particular dose, schedule, etc. used for phase 3 trials, and the intervention ensemble has higher prior odds of showing efficacy or other clinical advantage. For example, drugs that target patient populations with predictive biomarkers have repeatedly been shown to have greater prior odds of attaining a regulatory approval or a positive outcome in phase 3 trials.[76,77] Accordingly, there might be grounds for advancing a precision medicine drug directly from phase 1 to phase 3 trials, provided there is good optimization of dose and biomarkers in phase 1 or other studies. The second

condition is safety: a trial of an intervention that for which there are serious doubts about an efficacy advantage might nevertheless appeal to clinical equipoise if there is a high level of confidence that the intervention is likely to offer a substantial safety or quality of life advantages over a standard of care. In our view, bypassing may be acceptable under clinical equipoise if condition 1 is met with a credible and evidence-based rationale for thinking all the elements of an effective intervention ensemble have been optimized.

These concepts can help IRBs determine whether an individual trial is permissible, not whether a phase 3 trial would be the most appropriate next step for research. Of note, such judgments might be difficult to make in a vacuum. Appeal to safety advantage requires that IRBs have good knowledge of the safety problems with standard of care. Therefore, in appealing to this justification, protocols should provide information about the safety of standard interventions, or the strength of efficacy evidence typically used to support clinical development.

Moral Efficiency

As noted, clinical equipoise is a necessary condition for launching a phase 3 trial and will help exclude some cases where bypassing is inappropriate. When we broaden our scope to think about moral considerations on a trajectory and programmatic level, it is important for researchers/sponsors to consider what our team has previously termed "moral efficiency."[78] This is the notion that research efforts should minimize the loss of human welfare in order for a medical community to arrive at a given state of knowledge about the value of a new treatment approach. The donation of time and welfare, especially for patients who are made vulnerable by their conditions, should be utilized in a manner that maximizes the return on their investment. Thus, research efforts should run the smallest trials possible for informing decisions to abandon or take up a new treatment strategy.

In some circumstances, phase 2 bypass might seem to produce greater moral efficiency, since bypassing phase 2 trials may reduce the number of subjects (and time) needed to advance a drug to approval. In other circumstances, phase 2 bypass could counteract moral efficiency, since running a phase 3 trial rather than a phase 2 will generally expose more patients, for longer periods of time, merely to establish the futility of further clinical development. In addition, investigators may not know if this nonpositive result in the phase 3 trial was due to truly ineffective drugs or the lack of optimization of the intervention ensemble. The later would require more testing and add to the number of patients needed to bring that treatment to approval.

The goal of moral efficiency may support phase 2 bypass where the following conditions are met. First, there is a very high prior on both safety and efficacy, based on preclinical and phase 1 trial results. This might occur where animal models are believed to be good models of human illness (e.g. dogs with hemophilia), or where many lines of strong evidence converge on a claim of efficacy. Note that this would rarely be the case where a phase 2 trial was run, and the result was negative (i.e. "Non-positive" in chapter 2). A second condition is limited pipeline density, such that more promising candidates are not being developed simultaneously and a trial is less likely to divert patients from other more promising trials. Phase 2 bypass contradicts the cause of moral efficiency in cases where there are high failure rates of drugs (thus suggesting flaws in model systems used to validate a drug preclinically), or where there is high pipeline density. Alzheimer's disease and Parkinson's disease, for example, are disease areas where phase 2 bypass seems to run counter to the goal of moral efficiency, since failure rates are extraordinarily high, and there is a large number of drug candidates in development.

Opportunity Cost

It is tempting to dismiss economic considerations as morally irrelevant. However, the reality is more complex. The goal of drug development is to discover new treatments. In our current economy, much of the work of clinical development is undertaken by private, for-profit sponsors. If those sponsors deem the costs of drug development to be prohibitive in a field like neurology, their investment in that area is unlikely to match societal demand. Pharmaceutical companies must use their limited funds to invest in new therapies and must make decisions as to which drugs, populations, and phases of clinical trials to invest in. Moreover, drugs have a limited patent life (typically 20 years).[23] The longer a drug remains in pre-license development, the less time firms have to recoup costs of development and earn a profit on their products. 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.[79] Pharmaceutical companies therefore may bypass phase 2 trials in neurologic drug development because it makes economic sense.

The final moral consideration we will focus on is the opportunity cost associated with false negatives in phase 3 trials. In many areas of neurology, the number of drug candidates in development is limited. Because of economic pressures, drug candidates are typically given one shot at producing a positive phase 3 trial before it is abandoned from further development. Imagine a neurologic drug has activity but fails to demonstrate promise in phase 3 because it was applied at an inappropriate dose, or in an inappropriate patient population. The abandonment of that drug entails opportunity cost for society.

Insofar as phase 2 bypass increases the chances that phase 3 trials will employ new drugs within suboptimal intervention ensembles, it may increase the probability that society incurs large opportunity costs because otherwise promising drugs are not given a proper chance to

demonstrate their promise. Opportunity costs due to phase 2 bypass will tend to be greater under the following conditions. First, if there are a small number of similar drugs in the pipeline, abandonment of an otherwise effective drug may be very costly to society. Second, opportunity costs will be greater where clinical demand is greater. Abandoning an otherwise effective Huntington's disease drug is a much graver error than abandoning an otherwise effective drug for a similarly prevalent but milder neurological disease. Third, opportunity cost will be greater under circumstances where it is more certain a drug will be abandoned if it fails. Commitment or plans from sponsors to plow past negative results into redevelopment of a drug candidate may mitigate the risk of opportunity cost. Finally, concerns about opportunity cost are going to be greater in realms where failure rates are high. In contrast, where drug development efforts are characterized by high rates of success, loss of a candidate due to a false negative phase 3 result will quickly be neutralized by success for a different drug.

Before closing this section, it is important to anticipate one criticism of our opportunity cost argument. Some patients might argue that, since phase 2 trials add more time to drug development, phase 2 bypass reduces opportunity cost for patients with a disorder. This reflects that if a drug is truly effective, it will advance to license faster (and reach patients sooner) via a trajectory that bypasses phase 2. While such reasoning is sound, the reasons we reject this argument should be clear from the following. First, for a drug to be effective, it must be employed within a roughly optimized intervention ensemble. If phase 2 trials reduce the prospect that a drug will show efficacy in phase 3 because the intervention ensemble is not optimized, then opportunity costs for patients is even greater. Second, it is important to understand bypass from the "10,000 foot" view. In failure prone areas of drug development- like Alzheimer's disease or Parkinson's disease- truncating each trajectory using phase 2 bypass seems likely to

actually slow progress towards an effective treatment, resulting in substantially greater opportunity costs for patients.

Guidance for IRBs and Other Stakeholders

IRBs are likely to continue to receive proposals for phase 3 trials that involve phase 2 bypass. How should they respond? All major policies on human protections require that investigators and sponsors conduct a comprehensive survey supporting evidence for a clinical trial, and provide adequate justification based on prior evidence. However, that phase 2 bypassing occurs with regular frequency suggests that independent oversight structures, including drug regulators, IRBs, and grant review panels are often willing to initiate phase 3 trials that are not directly supported by discrete trials designed primarily to support them, and in some cases support phase 3 trials despite evidence admonishing against their conduct.

Our study 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.[43] 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. However, 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. Although we think our findings are subject to limitations elaborated in the previous chapter, we offer the following suggestions.

First, reviewers should situate the trial within the reasons we outlined and determine whether the trial fulfills clinical equipoise. In addition, efficiency, both moral and economic, should be considered to ensure that limited resources are well utilized. If reviewers decide to approve the trial, there are ways sponsors can mitigate the risks and potential misallocation of

resources. For example, all such studies should have independent data monitoring. In addition, researchers designing phase 3 trials that bypassed could use adaptive or seamless designs with early stopping rules, potentially reducing the number of patients exposed to ineffective treatments.[47]

Second, phase 2 bypass 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. Overall, we found that a patient may benefit less from a trial that bypassed compared to one that did not, while they appear to be at the same risk for withdrawal due to adverse event. IRBs may be inclined to require a statement be included in consent documents stating that there has not been a positive investigation of efficacy prior to the trial at hand, and that prospect of direct benefit and clinical impact is more speculative where trials involve phase 2 bypass.

Last, considerations of moral efficiency and opportunity cost are helpful for sponsors and researchers to consider the concept of bypassing phase 2 trials generally and are likely to be beyond either the remit or capacity of IRBs. Specifically, there is nothing in human protections policies that explicitly instructs IRBs to consider these factors. Moreover, it seems that IRBs are unlikely to be effective at incorporating such considerations into their judgment. However, healthcare policy-makers, drug regulators and research sponsors are in a position to consider opportunity costs and moral efficiency. Consider drug regulators. If FDA were charged with minimizing opportunity cost for drug development, it would apply the above considerations to sponsors who petitioned the agency to conduct a phase 3 trial based on phase 2 bypass. FDA might apply more stringent criteria to authorize bypass where pipeline density was low (note- FDA would be in a privileged position to assess pipeline density). However, this would require

that FDA view its task less as regulating individual drugs, and more as a steward of the broader drug development enterprise in different clinical arenas.

Future Studies

Our findings leave unresolved many questions that further research might address. Firstly, researchers could do a similar analysis as above but include more years and/or more neurological conditions. These changes would provide more power to analyses investigating the impact of phase 2 bypass on phase 3 trial results.

Secondly, researchers could use phase 3 trial citations to evaluate whether the reason for phase 2 bypass is associated with phase 3 trial results. For example, the study could compare the results of phase 3 trials that bypassed phase 2 primarily due to the availability of other evidence to cases where bypassing was likely due to statistical limitations. The results of this study would substantially add to our ability to make recommendations for IRBs as to when phase 2 bypass may be morally acceptable.

A third future study should 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. These studies could use modeling to estimate moral efficiency and determine whether overall there are financial and time savings associated with phase 2 bypass. These results would provide further guidance as to whether phase 2 bypass is a wise prioritization of resources.

Fourthly, it would be interesting to investigate whether trial monitoring rules differ for phase 3 trials that bypassed vs those that did not bypass. It is possible that there are checks already in place when phase 3 trials bypass phase 2 trials.

Finally, researchers could interrogate how investigations of intervention ensemble components, like safety and dose, set phase 3 trials up for positive results. In the above study, we labeled phase 3 as having bypassed where they were preceded by a negative phase 2 trial. However, that negative phase 2 trial may have contained key information for adjusting intervention ensembles used in phase 3 trials. Subsequent study of phase 2 trials might investigate how phase 2 trials (positive or negative) are used to adjust intervention ensembles in phase 3, and whether such adjustments lead to more favorable outcomes in the latter. For example, in multiple sclerosis, a phase 3 trial may be positive but not moved to approval because of concerns about rare but severe side effects.

Conclusion

Neurologic conditions include some of the most prevalent, disabling, and terminal diseases of modern life.[18] In addition, 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. Therefore, pharmaceutical companies have decreased their investment in developing treatments for these diseases.[22,23]

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 before performing phase 3 trials. 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 a comprehensive discussion of its ethical implications.

Our findings show that phase 2 bypass is generally common (46%). However, the prevalence of bypassing between indications in our sample was widely varied. 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. Alternately, trials investigating treatments for relapsing multiple sclerosis almost never bypassed phase 2. Thirdly, 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.

Researchers may bypass phase 2 trials because of innate statistical limitations of phase 2 trials or the availability of other types of evidence. Individually, these motivations did not explain the high prevalence of phase 2 bypass that we observed in our study. Rather than focus on the reasons researchers bypass phase 2 trials, we suggest that IRBs and sponsors consider three ethical concepts, clinical equipoise, moral efficiency, and opportunity cost when determining whether to initiate a phase 3 trial that bypassed phase 2. Future work is needed to determine whether phase 2 bypass in specific cases are associated with phase 3 trial protection from negative outcomes.

Patients with neurologic disorders suffer from especially prolonged, life-destabilizing, and occasionally terminal conditions. Although there is ample research in neurologic drug development, the field has one of the lowest rates of approval across all areas of medicine.[22–24] 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, trials that did so in our sample had a lower likelihood of being positive on their primary outcome. Future research is needed to understand whether bypassing phase 2 trials might play a role in the low likelihood for positive results in neurologic phase 3 trials.

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