**Introduction**

Neurologic conditions include some of the most prevalent, disabling, and terminal diseases of modern life.1 However, drug development in neurology has one of the lowest rates of approval across all areas of medicine.2–4 Pharmaceutical companies have decreased their investment in developing treatments for these diseases.2,3 Further research is needed to evaluate current drug development practices to determine how it can be optimized in order to get new and effective treatments to these patients quickly.

This thesis was designed primarily to determine 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. Next, we review the ethical implications for phase 2 bypass as well as offer a series of recommendations to investigators or 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. Before we discuss whether phase 2 bypass is morally acceptable, it is important to understand why researchers may be inclined to follow this trajectory. In the following section, we address four motivations researchers may use when they bypass phase 2.

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 which can provide quick read-outs of efficacy information.5 In these cases, phase 2 trials can use clinical outcomes. However, these outcomes often need large numbers of patients to detect differences or lengthy trials to see long-term safety/efficacy outcomes.6 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.6 In addition, systemic 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 such as oncology.

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, at least some trajectories involved proper phase 2 evaluation for all indications in this study. This suggests that it is possible to run phase 2 trials focused on collecting efficacy before phase 3 trials, even in areas reliant on clinical outcomes. 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 are not the driving force behind the practice of phase 2 bypass.

Economic Considerations

Sponsors and societies have strong motivations to reduce both the money and time it takes to get new drugs to patients. Pharmaceutical companies have limited funds to invest in new therapies and must make decisions as to which drugs, populations, and phases of clinical trials to invest in. Moreover, drugs have a limited patent life (typically 20 years).3 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. Pharmaceutical companies therefore may bypass phase 2 trials in neurologic drug development because it makes economic sense. 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.7 However, if phase 3 trials are nonpositive after bypassing phase 2, additional costs may ensue if further research is needed to determine whether the drug is promising enough to continue developing.

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. We are therefore reluctant to dismiss this motivation as morally irrelevant. Despite the above, our analysis did not find that industry funded trials were more likely to bypass phase 2 than non-industry. This suggests that financial considerations are less likely to be an overriding motivation for phase 2 bypass in neurology.

Strong evidence

Researchers may 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 above, 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.8 Although this thesis was not designed to investigate these instances, publications for phase 3 trials that bypassed often cited phase 1 studies.

To the latter point above, sponsors aiming to repurpose an already approved drug often have extensive evidence about safe dose ranges, pharmacokinetics, and target engagement. However, some commentators question this rationale for phase 2 bypass, because patients with different conditions can have vastly different reactions to similar drugs.9 Nevertheless, we did not find that phase 3 trials that bypassed were more likely to test drugs that had already been approved in other indications (we did, however, observe that repurposed drugs made up 40% of the trials that “fully bypassed” in our sample).

Other Motivations

Researchers may 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.

Additionally, researchers may consider bypassing phase 2 when researchers are designing clinical trials for rare diseases or indications with rapidly changing prevalence. In these cases, it would be understandable to try to use limited available patients to get a definitive answer as to the efficacy of an investigational drug. However, phase 3 trials that bypassed may be diverting limited patients from trials with more efficacy evidence priors, although these alternative trials may not exist. In addition, equipoise would likely be threatened if this was the only reason for bypassing phase 2 trials, as there would be little reason to believe that the experimental drug is better for patients. The only rare disease included in our sample was Huntington’s disease and we found that these phase 3 trials bypassed phase 2 trials 75% of the time (although our sample size was very small (n=4)). MORE

None of motivations described above can fully explain the high prevalence of bypassing in neurologic drug development we observed in our sample. However, together, they may likely explain why this practice is so common.

**Ethical considerations in bypassing phase 2 trials**

Together, these motivations may or may not make it morally acceptable to bypass phase 2 trials. In the following section, we suggest that there are three major 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 (considering clinical equipoise); b) minimization of patient exposure to research burden (using the concept of moral efficiency); c) reducing the 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.10 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 form of phases in drug development help 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. 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. Likely, fewer informed experts would prefer the experimental arm over the comparator in P3 clinical trials. That would undermine clinical equipoise: there would be less division among informed experts. In some cases, this division would be insufficient to be considered to fulfill clinical equipoise. 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 point made by Freedman, a non-positive phase 3 trial that bypassed phase 2 efficacy evidence may be less capable of changing expert opinion. This is because the non-positive result could be due to an ineffective treatment or the lack of intervention ensemble optimization. One review of go/no go decisions in CNS development said it well: “from a scientific perspective, its optimal only to make “Go” decisions when one is clear that results of a study will prove interpretable about the potential of an intervention in the absence of a positive finding.”11

However, bypassing may be morally acceptable under clinical equipoise when the following are true. First, when there are strong grounds for anticipating that an intervention ensemble tested in phase 3 is roughly optimal. This might be accomplished if phase 1 studies establish clear evidence favouring a particular dose, schedule, etc. used for phase 3 trials. Second, an intervention ensemble that has higher prior odds of showing efficacy or other clinical advantage after phase 1 testing might be a candidate for justified phase 2 bypassing. 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. Accordingly, there might be grounds for advancing a precision medicine drug directly from phase 1 to phase 3 trials. The third condition is safety: a trial of an intervention that has not been shown to provide 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 advantage 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, and either of conditions 2 or 3 are met.

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. The following two considerations are helpful to sponsors, researchers, and to consider the concept of phase 2 bypass as a whole.

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 level, it is important for researchers/sponsors to consider what our authors have previously termed as “moral efficiency.”12 This is the notion that research efforts should strive to minimize the loss of human welfare in order for a medical community to arrive at a given state of knowledge regarding the value of a new treatment approach. This donation of time, especially for patients who are made vulnerable by their conditions, should be optimized for the greatest possible return on 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 produces greater moral efficiency, since there is no need to enroll patients in a phase 2 trial. In other circumstances, bypassing 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, 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 evidence on the intervention ensemble. The later would require more testing and add to the number of patients need to bring that treatment to approval.

Prioritization

Thirdly, it is important to ask whether bypassing phase 2 trials is the best way to invest limited time and money in order to get a new drug to approval. Trials have not “failed” when researchers find that an experimental treatment does not improve patient outcomes as non-positive results are normal in the natural history of drug development. Rather, these instances can be opportunities to learn more about a disease and treatment target.13–15 However, the stage of the development process in which a treatment is abandoned can profoundly impact the cost and time involved in the endeavor.

Researchers have proposed that bypassing phase 2 trials would only be reasonable if there were unlimited resources for researchers to use in clinical trials. This way, there would be no cost to researching ineffective therapies.16 The reality of drug development is far from this ideal as the cost of running a phase 2 or phase 3 trial differs significantly. Although reporting is sparse on average costs of different phases,17 one review estimated that the median cost of a phase 2 trial was $8.6 million and that phase 3 trials cost $21.4 million.18 In a review of trials investigating treatments for Alzheimer’s disease, the cost/time of a phase 3 trial was roughly double that of a phase 2 trial.1 Therefore, bypassing phase 2 trials would significantly save money and time to reach drug approval when phase 3 find positive results.

Error tolerance calibrated according to relative costs of type I and type II error. If u get a negative P2 trial, could be a type 2 error. Cost of that greater in low pipeline density. Lots of potential candidates; less loss with a false negative. Few candidates- greater loss. More severe disease- less loss. Less Severe- greater loss. [portfolio] Opportunity cost stuff?

Guidance for IRBs

What are we to make of this? 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.20 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. MORE

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.21

Finally, 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 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.

**Future Studies**

Our findings leave unresolved many questions that further research may be able to 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 comparing 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, researchers could interrogate how investigations of safety and dose, rather than efficacy, set phase 3 trials up for success. For example, in multiple sclerosis, a phase 3 trial may be positive but not moved to approval because of immune reactions. In these cases, it would be more interesting to see whether safety and dose were investigated prior to phase 3 trial initiation than efficacy. In addition, this analysis could be used to evaluate whether phase 3 trials that bypassed and were nonpositive were more likely to blame intervention ensemble issues.

Concluding paragraph.

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