**Introduction**

Neurologic conditions include some of the most prevalent, disabling, and terminal diseases of modern life.4 However, drug development in neurology has one of the lowest rates of approval across all areas of medicine.1–3 Pharmaceutical companies have decreased their investment in developing treatments for these diseases.1,2 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.

This thesis set out to determine whether, and in which cases, bypassing phase 2 efficacy evidence is common in neurologic drug development and whether the practice had implications for phase 3 trial results. In the chapter that follows, we review two relevant ethical concepts introduced in previous chapters, situate potential justifications for phase 2 bypass within these concepts, and recommend future research to guide researchers, IRBs, and patients.

**Ethical Considerations**

Efficiency

Efficiency in drug development typically refers to the motivation to reduce both the money and time it takes for researchers to get new drugs to patients. Pharmaceutical companies have limited funds to invest in new therapies and must make decisions as to which drugs, phases trials, and populations to invest in. In addition to cost, when we develop drugs, we exchange patient welfare and time for a given amount of evidence. There may be ways to conduct research that lower the amount of money, time, and patient welfare needed to bring a drug to approval. We remain unclear as to whether bypassing phase 2 before running phase 3 trials offers these benefits, although it does not seem promising as a tactic to reduce the amount of patient welfare it takes to approve a new drug.

Risk and Benefit

Bypassing a phase 2 trial may be associated with diminished benefit and/or higher risk for patients participating in phase 3 trials. Our paper investigating phase 2 bypass in oncologic drug development found that patients in phase 3 trials that were not supported by phase 2 trials had significantly worse efficacy outcomes.65 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.

These results indicate that clinical equipoise may be threatened when researchers bypass phase 2 trials. Clinical equipoise reflects a view of what experts would believe, were they able to access the totality of relevant evidence and were they exercising competent evidentiary judgment.9 If we were to conduct a phase 3 trial, and informed experts see that there is no supporting evidence from phase 2, 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. In our sample, the erosion of benefit in trials that bypassed may risk whether the phase 3 trials are in equipoise.

**When may phase 2 bypass be justifiable?**

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

Scientific

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

Ethical

Monetary

A second reason sponsors might bypass phase 2 is to reduce costs. Bypassing phase 2 trials offers pharmaceutical companies one-way to economize in a clinical development area characterized by poor surrogate endpoints. By determining efficient areas of drug development to direct our resources, we can attempt to get drugs to patients and limit divestment in the area.4 A recent analysis of Alzheimer’s clinical trials found that bypassing phase 2 trials in this case would cut costs up to 10 million per drug.4 However, if phase 3 trials are nonpositive after bypassing phase 2, additional costs may ensue from further research into determining whether it is a truly ineffective treatment or an issue with optimization of the intervention ensemble. Finally, companies may bypass phase 2 trials in order to decrease the proportion of their 20 year patent life taken up by clinical development.5 Though commercial considerations undoubtedly influenced some instances of phase 2 bypass in our sample, we did not find that industry funded trials were more likely to bypass phase 2. This may not be an especially compelling reason to patients involved in the phase 3 trials.

Other evidence

Thirdly, researchers may bypass phase 2 trials when they have other reasons to be confident in a drug’s safety and dosing. For example, sponsors aiming to repurpose an already approved drug often have extensive evidence about safe dose ranges, pharmacokinetics, and target engagement. However, some commentators question whether this constitutes a compelling rationale for phase 2 bypass because patients with different can have vastly different reactions to similar drugs.6 Nevertheless, we did not find that phase 3 trials that bypassed were more likely to test drugs that had already been approved in other indications (we did, however, observe that repurposed drugs made up 40% of the trials that “fully bypassed” in our sample).

In addition, researchers designing phase 3 trials could use information from phase 1 trials that are especially extensive. There is a lot of variation in how different phases are defined. Therefore trials that bypassed phase 2 trials may have been preceded by trials with ample evidence on efficacy in a trial labeled as a phase 1.7 Although this thesis was not designed to investigate these instances, publications for phase 3 trials that bypassed often cited phase 1 studies. When the preclinical or phase 1 evidence supporting the trial is extraordinarily strong (e.g. huge effect sizes), experts and IRBs might expect that they can support a phase 3 trial that bypassed phase 2 without compromising an expectation of clinical efficacy against a standard of care.

Rare Patients

Fourthly, some indications have very few patients. In cases where researchers may run out of patients to put into clinical trials, they may as well go directly for a definitive answer. In areas of medicine outside of neurology, such as infectious disease medicine in pandemics, it is possible that the number of patients will diminish quickly as incidence decreases in waves. In these cases, it can be debated if we should let large numbers of patients take on the risk of a big trial for the sake of future patients. Our sample did not focus on answering this question. However, in Huntington’s disease, a rare neurodegenerative disease, bypassing phase 2 was more common than not. In huntington’s disease P3 trials use 3 times as many patients and double as much time than phase 2 trials.10However, this may put equipoise into question as this is putting a large number of patients into high risk phase 3 trials for the sake of future patients. You may be able to argue that in the case of these indications, these trials are not diverting patients from alternative trials that could be based off of more efficacy data, but this would only be the case if participation in the trials does not add burden to these patients.

It is important to note that the amount that these reasons play apart in the motivation to bypass differ by type of bypass. We found that fully bypassing phase 2 trials was the most common form of bypass. We hypothesized that phase 3 trials would be protected by ambiguous phase 2 trials rather than fully bypass because there would be other evidence to help design the phase 3 trial. However, the most problematic type of bypass was nonpositive trials. In these cases, phase 3 trials were the most likely to be terminated and relatively quite unlikely to be positive. Phase 2 trials may thus be especially useful for making decisions whether to initiate phase 3 trials.

We may also be diverting patients from trials with more efficacy evidence priors.

None of these reasons can fully explain the high prevalence of bypassing in neurologic drug development. However, together, they may likely explain why this practice occurs. Our results were inconclusive as to whether bypassing, regardless of reason, was problematic for phase 3 trial results.

**Conclusions**

review of what our results regarding the impact of phase 2 bypass on phase 3 trial outcomes suggest for IRBs and future research.

When researchers designing phase 3 trials are deciding to bypass, or an IRB is reviewing a trial that bypassed, they should situate the trial within the reasons we outlined and decide if they believe that it justifies the lower level of evidence and are compelled by the benefits of bypassing phase 2. If they decide to approve the trial, there may be some ways to mitigate the potential risk/use of resources. For example, the futility bar in the phase 3 trial can be used less as a low line to cross as a “disaster check”,10 and more as a high bar to stay in the place of the phase 2. In addition, DSMBs should potentially be made aware of the lack of prior efficacy evidence for phase 3 trials that bypassed phase 2. Alternatively, phase 3 trials that bypassed could use adaptive designs with early stopping rules, potentially reducing the number of patients exposed to ineffective treatments.11 In these cases, researchers could use intermediate outcomes to account for the fact that clinical outcome data may not be available at interim analysis.12 In these cases, Phase 3 researchers might also simultaneously start both a phase 2 trial and a phase 3 trial with an adaptive design to guide the phase 3’s use of resources.13,14

We found that overall, phase 3 trials were more likely to be positive when they were preceded by positive efficacy evidence from a phase 2 trial. However, non-positive results are normal in the natural history of drug development. If researchers always run phase 2 trials, find a positive result, and then find positive results in a subsequent phase 3 trials, they may be overproving efficacy because the phase 2 trial is too predictive of phase 3 trial results. Our results indicate that this may be the case for relapsing multiple sclerosis trials. Nonpositive results in phase 3 trials may be the result of many other factors including publication bias, change in outcome duration, inconsistent parameters between trials, or a change in time before treatment.8

Phase 2 bypass may also have 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.

Future research should tease apart reasons for phase 2 bypass that may be justifiable and do not set the phase 3 trial up to be nonpositive. In addition, researchers should determine how many patients, money, and time are involved in bypassed trajectories or trajectories with phase 2 followed by phase 3 trials. In addition, researchers should investigate how investigations of safety and dose translate to 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. Dose is especially interesting because you might expect that after bypassing phase 2 trials, phase 3 trials may have more dose arms, greater safety events in higher does arms. We did not find that phase 3 trials were on average bigger after bypassing phase 2 trials Finally, a citation analysis of phase 3 trials that bypassed would be interesting. For example, when phase 3 trials that bypassed were nonpositive, did researchers cite intervention ensemble issues, such as dose more often?

Concluding paragraph

In addition to cost, when we develop drugs, we exchange patient welfare and time for a given amount of evidence. There may be ways to conduct research that lower the amount of money, time, and patient welfare needed to bring a drug to approval. We remain unclear as to whether bypassing phase 2 before running phase 3 trials offers these benefits, although it does not seem promising as a tactic to reduce the amount of patient welfare it takes to approve a new drug.