**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 situate potential justifications for phase 2 bypass within ethical concepts previously described and recommend future research to guide researchers, IRBs, and patients.

**Reasons for phase 2 bypass**

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

Scientific

To start, there are a few scientific and statistical reasons that bypassing phase 2 trials may be appropriate. Firstly many neurologic conditions lack surrogate endpoints with clear associations with clinical outcomes. Therefore, phase 2 trials in these indications may be less useful than in indications that have outcomes which can provide quick read-outs of efficacy information.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.

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, populations and phases of clinical trials to invest in.

The 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.

In addition to cost, when we develop drugs, we exchange patient welfare and time for a given amount of evidence. Therefore, it is important to research how to design research trajectories to limit the number of patients it takes to get a drug approved. Efficiency can be especially important when patients are limited. The third reason researchers may be inclined to bypass phase 2 trials in order to find a definitive answer in a phase 3 trial when they are investigating treatments for rare diseases or indications with rapidly changing prevalence. For example, in infectious diseases it is possible that the number of patients will diminish quickly due to the cyclical nature of infection waves. In the case of these indications, 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 may be threatened as there is limited evidence that shows that they experimental drug is better than soc or placebo. In our sample, Huntington’s disease trials were preceded by phase 2 trials only 25% of the time.

Other evidence

The fourth reason researchers may bypass phase 2 trials is 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).

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.

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. Overall, our results indicate that clinical equipoise may be threatened when researchers bypass phase 2 trials.

However, when the preclinical or phase 1 evidence supporting the trial is extraordinarily strong (e.g. huge effect sizes), experts and IRBs might expect that they can support a phase 3 trial that bypassed phase 2 without compromising an expectation of clinical efficacy against a standard of care.

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

**Conclusions**

When an IRB is reviewing a phase 3 trial that bypassed, they should situate the trial within the reasons we outlined and decide if they believe that it justifies the lower level of evidence 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 raised to act like a phase 2. In addition, DSMBs should 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 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