**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 quickly.

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

**Reasons for phase 2 bypass**

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

Scientific Motivations

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

Efficiency in drug development typically centers around the attempt to reduce both the money and time it takes for researchers to get new drugs to patients. Pharmaceutical companies have limited funds to invest in new therapies and must make decisions as to which drugs, populations, and phases of clinical trials to invest in. Therefore, economization is the second motivation pharmaceutical companies may have to bypass phase 2 trials in neurologic drug development. A recent analysis of the costs of clinical trials for Alzheimer’s disease shows that bypassing phase 2 trials in this case would cut costs up to 10 million per drug.4 However, if phase 3 trials are nonpositive after bypassing phase 2, additional costs may ensue if further research is needed to determine whether the drug is a truly ineffective or the intervention ensemble was not optimized. In addition, companies may bypass phase 2 trials in order to decrease the proportion of their 20-year patent life that is taken up by clinical development.5 Though commercial considerations are important to limit divestment in the area4 and to efficiently direct scarce resources, they may not be a compelling reason to bypass phase 2 trials for patients involved in the phase 3 trials. In our sample, we did not find that industry funded trials were more likely to bypass phase 2. MORE

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

Other evidence

Fourthly, researchers may bypass phase 2 trials when they have other reasons to be confident in a drug’s safety and dosing. For example, sponsors aiming to repurpose an already approved drug often have extensive evidence about safe dose ranges, pharmacokinetics, and target engagement. However, some commentators question whether this constitutes a compelling rationale for phase 2 bypass because patients with different conditions can have vastly different reactions to similar drugs.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 may use information from phase 1 trials that provided ample evidence on efficacy rather than run a phase 2 trial.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.

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

**Conclusions**

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

When an IRB is reviewing a phase 3 trial that bypassed, they should situate the trial within the reasons we outlined and decide if they believe that it justifies the lower level of evidence. If they decide to approve the trial, there may be some ways to mitigate the potential risk/use of resources. For example, the futility bar in the phase 3 trial can be raised to act like a phase 2. Alternatively, researchers designing phase 3 trials that bypassed could use adaptive designs with early stopping rules, potentially reducing the number of patients exposed to ineffective treatments.11 Phase 2 bypass also has implications for consent documents as patients may have an opinion as to whether they wish to participate in a trial that lacks prior efficacy evidence.

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

Concluding paragraph.