**Introduction**

Literature review—why this is an important problem

We set out to determine whether, and in which cases, bypassing phase 2 efficacy evidence is common in neurologic drug development. In the chapter that follows, we will situate our results within potential justifications of phase 2 bypass as well review of what our results regarding the impact of phase 2 bypass on phase 3 trial outcomes suggest for IRBs and future research.

**Ethics**

Equipoise

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 a) there is no supporting evidence from phase 2, *and* b) the preclinical or phase 1 evidence supporting the trial is not extraordinarily strong (e.g. huge effect sizes), 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 fulfil clinical equipoise. In our sample, we observed an erosion of benefit in trials that bypassed that may risk whether the phase 3 trials are in equipoise.

Efficiency

When we develop drugs we have to put many into to get a few effective safe drugs

Look at it through patient welfare and the number of patients that we put in.Exchange rate of patient welfare to get an amount of evidence

Areas with worse exchange rate—amyloid cascade-dozens of clinical trials that target this mechanism all negative low yield also vitamin D

Ways that we can do research that have a higher yield- contribute to lowering the amount of patient welfare needed Particular duty to the patients that we are putting into the enterprise-different than what we owe future patients inequity of health cost and benefit to patient

Most drugs fail so we are taking more time and patients to kill drugs by bypassing P2.

And diverting patients from trials with more efficacy evidence priors

Nonpositive-not necessarily a bad thing

* 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, other reasons might explain P3 negativity rather than bypassing. These include publication bias, change in outcome duration, not consistent parameters between trials, overestimating early results, time to treatment is earlier in disease progression.8 These non-positive results are normal to the natural history of drug development. If it were working perfectly, we would see it. In an ideal world, phase 3 trials would not all be positive. In fact, if we run phase 2 trials, find a positive result, and then find positive results in a subsequent phase 3 trial, we may be overproving efficacy. We don’t want phase 2 trials to be that predictive of phase 3 trials otherwise equipoise may be disturbed for the patients included in the phase 3 trial. Our results indicated that this may be the case for RMS trials.

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

We found that bypassing positive efficacy evidence from phase 2 trials happened with high regularity. Though there are cases in which bypassing phase 2 trials may be justifiable, work in other disease areas suggests phase 2 bypass adversely affects outcomes for patients.1 Given the 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 and scientifically justified. In the following section, we will address four motivations researchers may use when they bypass phase 2 and discuss whether we found it to be driving our results and 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. There is no validated surrogate endpoints for an indication and the clinical endpoints take years to see impact, such as PMS.2 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. 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, In Alzheimer’s drug development, a large number of patients are needed to see differences in cognitive decline. This implies that it would be hard for researchers to see a positive result using a phase 2 trial. Thus, the decision to run a P3 trial rather than a P2 trial may be smart.3 In our sample, we found that bypassing was more common than not in trials for degenerative diseases, most of which suffer from both 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.

Monetary

A second reason sponsors might bypass phase 2 is cost savings. 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 number of years clinical development uses of the 20 year patent life on new drugs.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 as the patient

Other evidence

A third reason for phase 2 trial bypass is confidence in the safety and dosing for a drug. Sponsors aiming to repurpose an already approved drug often have extensive evidence about safe dose ranges, pharmacokinetics, and target engagement. For example, after Riluzole was approved for ALS, it was brought into testing for Huntington’s disease in a phase 3 trial directly. However, some commentators question whether this constitutes a compelling rationale for phase 2 bypass because different indications 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, 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. For example, what is usually defined as phase 2 could be performed in a phase 1 trial. 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 project was not designed to investigate this, phase 3 trials that bypassed often cited phase 1 studies. In these cases, experts and IRBs might expect that they can support a P3 trial that bypassed P2 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.

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. It is obvious from the examples given above that the risks and benefits of bypassing early phase trials are unknown, thus complicating the ethical implications. Our results were inconclusive as to whether bypassing, regardless of reason, was problematic for phase 3 trial results.

**Conclusions**

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

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?

Neurology is very scary, and we need to find ways to get new drugs to patients. Concluding paragraph