**Discussion**

Phase 2 bypass was common (47%) in our sample of phase 3 trials investigating treatments for neurologic conditions. Furthermore, phase 3 trials without positive clinical or validated surrogate evidence from phase 2 trials were significantly less likely to have a positive result and insignificantly more likely to be terminated due to safety concerns or futility analyses.

In our sample, phase 2 bypassing was more common in primarily degenerative conditions. This is likely due to two reasons. The first is these conditions generally lack effective treatments and therefore may be more likely to bypass P2 due to the desire to bring treatments to patients with high therapeutic need compared to conditions with established standards of care. Secondly, these conditions generally lack surrogate endpoints with clear associations with clinical outcomes, thus phase 2 trials are potentially less useful. Alternatively, relapse remitting MS has a good surrogate soutcome (lesions) which likely decreased the need to bypass phase 2 trials.

We did not find that P2 bypassing was associated with industry funding or repurposing treatments in new indication. However, trials in the full bypass group were the most likely to be investigating drugs that were already approval in other indications at the time of initiation. This result indicates that repurposing is likely one motive for researchers to fully P2 bypass, due to the availability of evidence of how the treatment works in other conditions.

Our results indicate that phase 2 bypass may decrease the likelihood that phase 3 trials will have a positive result. However, it should be noted that nonpositive results are common in indications such as Alzheimer’s disease because the disease is not well understood. Therefore, the association between phase 2 bypass and nonpositive results may be the result of confounding factors that both increase the likelihood of P2 bypass and decrease the likelihood of phase 3 positivity. However, because the disease is not well understood, it may be important to first investigate efficacy in phase 2 trials to avoid putting futile treatment into phase 3. Alternatively, in indications such as RMS where bypassing is not common and positive results are common, it is possible that researchers are overproving efficacy in phase 2 trials. MORE

We did not find that bypassing was associated with any difference in the risk of withdrawing due to adverse events when focusing on the efficacy variable.

In addition, our results show that phase 3 results are impacted differently by different types of phase 2 bypassing. We found that, numerically, P3 trials initiated after an ambiguous phase 2 trial were less likely to have a positive result than p3 trials that fully bypassed. In addition, phase 3 trials started after non-positive results from P2 trials were especially likely to be terminated. In these cases that phase 3 trials are initiated after ambiguous phase 2 trials, researchers would likely have more information to optimize dose, schedule, and population details5 than in cases where they fully bypass p2. However, these results indicate that the presence of positive efficacy evidence, not the presence of a P2 generally, may be important to set phase 3 toward positive outcomes. Furthermore, phase 2 trials may be especially useful as a go/no go step to stop investigating futile or unsafe treatments in neurology.

Running a P2 trial is costly however. When phase 3 trials end up being positive after bypassing, they would save an estimated x amount of money and y amount of time to approval. In addition, there is an opportunity cost to not bypassing in these cases-as patients miss out on treatments. These commercial motivations for bypass are clear, however it is unclear if this is truly a cost/time saving measure when phase 3 trials are nonpositive and researchers will not know if it due to ineffective treatments or the lack of optimization of the intervention ensemble. Bypassing P2 trials and the information gained from them may be important to avoid without putting large numbers of patients and money into futile phase 3 trials.

ETHICS paragraph s

‘we had not choice but to bypass’ from ‘yeah, we’re cutting corners.’ u and i aren’t equipped to make that call. but what we can do is point out it has ethical implications and shd not be seen merely as a business or scientific decision. the fact that in some areas, both bypass and nonbypass occurs, suggest that it is in fact possible to run p2 trials.. Our results indicate the need for a more sustained discussion of the appropriateness of phase 2 bypass and perhaps criteria to be used for determining when bypass is justified.

**Limitations**

There are important limitations to our study. Firstly, we pooled positivity and termination rates across neurologic diseases with vastly different base rates for these outcomes. And heterogeneity. MS does not bypass much and is more likely to be positive- is this the bypass or is that a product of MS drug development. We did so because were limited by our sample sizes within indications and did not find these analyses had enough power. Secondly, we included P2/3 trials in our sample and automatically counted these as preceded by positive phase 2 trial. In these cases, we could not often access the phase 2 portions of the trial to confirm this. In some cases, we could not be sure trials moved on to P3 portions as well. Thirdly, we were not always able to find publications or results for phase 2 trials. In these cases, we may have characterized trials as bypass when there was a trial available before a P3 trial. Although it is possible that P3 researchers also could not access these results, they may have been associated with the same company/institution and have had special access. Fourthly, our results are specific to the first phase 3 trials testing an intervention in an indication and are not generalizable to all P3 trials. Finally, some indications may have no clinical or validated surrogate endpoints used in phase 2 trials although no indications failed to have at least one preceded trial. We gave them so much leeway- dose, population, treatment could be diff formulation or diff adjuvant status. Instead, cases of bypass often truly bypassed. It was also unclear what phases in old trials and there may be no way for us to distinguish phase 1b to phase 2. Phase 3 vs phase 2 was also difficult and our rules would have excluded trials in our sample.

**Future research**

We focused on whether positive efficacy evidence was associated with P3 trial success. Future research should focus on investigating how acquiring other types of evidence may set P3 trials up for success. For example, how do phase 2 safety concerns translate to P3 trial safety outcomes if one is initiated.