**Equipoise:**

There are a few compelling reasons why researchers may skip a phase 2 trial. Theoretically, if researchers see a massive efficacy signal in a phase 1 dose expansion trial, there might be reason to directly test this treatment in a phase 3 trial. Another reason might be an unusually safe compound in earlier phase trials. For example, the use of statins in oncology are a interesting case of a drug type that is relatively safe and does not tend to have conflicting safety profiles with chemotherapy drugs. One study that added pravastin to sorafenib in advanced hepatocellular carcinoma without previous phase 2 efficacy signals from this indication did not show survival benefit even when they had mechanistic reason to believe it was practical, but also did not impact adverse event and safety outcomes.1 Although there is large use in resources in these cases, there is no undue risk to these patients.

It is obvious from the examples given above that the risks and benefits of skipping early phase trials are unknown, thus complicating the ethical implications. We would expect that there to be better safety profiles for trials that skipped early efficacy evidence but that there may be overall worse efficacy because those without proper efficacy are not being weeded out by earlier trials. This is the hopeful hypothesis that would show that skipping early efficacy trials is not putting patients at great risk but does have implications for consent and waste of resources.

Its not that trials that bypass are in less equipoise this is not possible—see his paper with alex London, it just that they are closer to the null-likely because they did not learn dose information from a p2 so they couldn’t tailor it-just that there is an erosion of risk and benefit- we cannot comment on the state of equipoise overall or if each was justified under the equipoise conditions

that we layed out

When those equipoise critreria are truly true it might be ok:Other reasons that may not be ok under equipoise If P1 showed huge amount of P1 efficacy evidence

If genuially happening like this there would be comparable efficacy

Or exceptionally safe drug

<https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1001010>

look at revisions for cancer bypass

Value

Diminished value in a nonpositive P3 trial, could be the wrong dose! Don’t know if it really is the results we would have seen if we had validated this early on

Consent

The consenting process for clinical trials can be extremely confusing to patients. In an older study by Joffe et. al, 70 % of participants in a survey of understanding after clinical trial participation, participants did not understand the unproven nature of the treatment and 63% did not recognize the potential for incremental risk from participation.2 In cases where there has been no prior direct evidence of efficacy, therapeutic misconception could lead to a break in patient consent.3,4 Without disclosing this lack of evidence to patients, researchers risk gravely damaging patient trust, regardless of the potential lack of additional risk of adverse events.

Instead, there are many examples of skipping that was not precipitated by compelling reasons. This may happen because pharmaceutical companies succumb to market pressures and competition. In immune-oncology for example, competition for space in the market has driven an explosion of clinical trials trying new drugs in many indications. This speed has driven many phase 3 trials to start without phase 2 evidence.5,6 Companies may also have only one a product and are invested in getting it out.

Early efficacy phase skipping may also happen in cases where treatment options for a tumor type are so bad that the treatment landscape is sparse. 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. More recently, a plaque targeting drug for Alzheimer’s patients, Aducanumab, was approved after precarious efficacy and concerning safety data in phase 3 trials. Development for this drug skipped a phase 2 trial, potentially relying on the fact that treatment options are especially bleak for Alzheimer’s patients7 Alternatively, some trials have shown this to be an effective mode of translation. One such trial in HCC-which has only one systemic treatment-based a phase 3 trial off of a phase 2 safety study that looked at efficacy as a secondary outcome and ended up showing survival advantage.8

Researchers have also been increasingly reliant on mechanistic evidence, especially biomarker enriched evidence in the design of phase 3 trials,9

Sometimes researchers rely on evidence from “similar indications” without biomarker evidence, and rather similarities between tumor or histology types.

Probs a difference between neg and skipping

**Efficiency**

Moral

They may not know dose or frequency at all so it is missing in the phase 3- may be less effective (less pos like in our cancer paper) but this may mean that a less the optimal use of the drug becomes soc-optimal is impossible but less than best. x

When those equipoise critreria are truly true it might be ok

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

But do we know if p3 neg with bypass is more patients than p2 then p3 no

But if p2 found neg it is better

More money and patients in the p3 that ins nonpos than non pos in p2

Coordination problems- we have failed to coordinate phase of trials with the evidence available from earlier phases

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

Don’t we gain patient welfare when we get good drugs out to patients faster, which may stand in cancer, but in neurology, where most drugs will not be positive, you are likely exposing more patients in a p3 than if you found it in P2

But these patients that we use in clinical trials are not exchangeable- we are worried about the use of patients in these trials.

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

Opportunity cost-how to pick which trials to run

If you skip

If the phase 3 ends up being pos—less patients were exposed -to a drug that works

IF the phase 3 ends up being neg—more patients were exposed to a drug that doesn’t work

If they do not skip

If the phase 3 ends up being pos—more patients were exposed -to a drug that works

If the phase 2 ends up being very neg—less patients were exposed to a drug that doesn’t work because saw the signal before with less patients

If the phase 2 ends up being neg and phase 3 is done and is also neg—more patients were exposed to a drug that doesn’t work—but had to see enough of a signal to move along

Pipeline science translation medicine Hey ethics, error and initial trials of efficacy (phase 2 trial productivity)

In huntington’s disease P3 trials use 3 times as many patients and double as much time than phase 2 trials.10

Value

Diminished value in a nonpositive P3 trial, could be the wrong dose! Don’t know if it really is the results we would have seen if we had validated this early on