* Chapter 3
  + Ethics of phase skipping-impact on equipoise
  + The Discussion section must be at least 5 pages, double-spaced (Master's). It must pertain to the entirety of the thesis.• This discussion should encompass all of the chapters of your thesis and should not be a repetition of the individual chapters. Here you expand on the ideas presented in the manuscripts and show how they contribute to the overall hypotheses for the thesis.

Less giving examples more arguments

Here are various ethical considerations regarding judgment phase 2 skipping

Introduction- This happens with high regularity (prevelance)-table

Read his oxford chapters

**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

**If you are on a IRB what do you do**

What q should u ask for P3 trials that bypassed

When IRBs are deciding whether to approve a phase 3 trial that lacks prior evidence, there may be some ways to mitigate the potential risk/use of resources. The upfront investment of a phase 3 is substantial and the futility bar is often very low to provide a “disaster check”.5 IRBs could require this futility bar to be higher when there is no prior efficacy evidence than a phase 3 trial preceded by a phase 2. Although all phase 3 trials require a DSMB, those without prior evidence should be aware of the lack of prior efficacy of this evidence. Rufibach et al. proposed a method of analyzing a phase 3 after a phase 2 has been skipped that accounts for the fact that overall survival data may not be mature at the time of interim analyses by basing the futility analysis on an intermediate outcome.11 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.12,13

* After bypassing P2 trials, Phase 3 trails can be designed to accommodate the lower level of prior evidence. One such design is adaptive design with early stopping rules, potentially reducing the number of patients exposed to ineffective treatments . 14 Alternatively, phase 3 trials can use pragmatic designs, which use using practical clinical procedures and outcomes that are important to patients and easily interpretable. These trials use less patients and are generally cheaper. 15

FUTURE WORK

Further research should investigate methods of designing a phase 3 trial that account for the lack of prior efficacy evidence such as low futility bars,13 determine how many patients are involved in skipped trajectories or trajectories with earlier phase evidence, and whether certain reasons for skipping may be justified. May be interesting to look if there is more bypassing over time. Citation analyses.

Chapter 3

Other reasons might explain P3 negativity rather than bypassing. These include publication bias, change in outcome duration, time to treatment , not consistant parameters between trials, overestimating early results, time to treatment is earlier in disease progression.1 These non positive results are normal to the natural history of drug development. If it were working perfectly we would see it. So maybe bypass is good.

Why would sponsors bypass?

Different for true bypass and ambiguous bypass-

Ambiguous is more likely to be problematic-especially nonpositive although ppl could claim this is why it should have been brought into P3 first

True bypass reasons-maybe its justified

* + Scientific
    - Need more patients to understand efficacy
      * In order to see efficacy would need to have large sample sizes so why do we need to run it in a P2 first
        + But when we do it in p2 and find nonpos the p3 is more likely to be neg—so this maybe isn’t a good reason
      * May be almost impossible to see a positive result in a P2 so need to do it in P3 anyway
      * In AD, large numbers of patients are needed to see differences in cognitive decline and thus a P3 trial may be needed rather than a P2 trial.16
    - Clinical
      * There is no validated surrogate endpoints for an indication and the clinical endpoints take years to see impact, such as PMS.17
    - Pharmacological
      * like about safety- need long term results to make sure it is safe
  + Profit
    - The current development costs for developing drugs may be unsustainable. A recent analysis of AD clinical trials found that phase 3 trials were more than double as expensive as P3 trials. This indicates that one way of cost-saving in clinical trials would be to find unsuccessful drugs in earlier phase trials, but also that bypassing P2 trials that lead to successful P3 trial

could save up to 10 million per trajectory.18

* + - Have to limit pharma companies leaving neurological drug development
    - “redirecting these investments to new and innovative ways to advance drug development…we may accelerate development of treatments”18
    - Patent stuff
      * Need to go quickly because you are allowed 20 years on patent-need to quickly get it through 1
      * <https://www.sciencedirect.com/science/article/pii/S0896627314009477?via%3Dihub>
  + Repurposing
    - Maybe it is smart, if you know about dose/population and general safety from repurposing what is the point in doing it in p2 first -especially when need lots of patients to figure out efficacy
      * But my results show that maybe this isn’t a good call anyway
    - Riluzole in Huntington’s was not tested in phase ½ in this indication after being approved for ALS
    - B-ionterpheons in SPMS using data from RRMS17
  + Phase 1 trial was extensive
    - There is lots 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. These trials may have been preceded by trials with ample evidence on efficacy in a trial labeled as a phase 1.1
  + Rare patients
    - Going to run out of patients so need to go directly for a definitive answer
      * HD?
      * TPOX for MPOX because during a pandemic the patients are going to disappear- because hopefully the
        + so when risks are potentially low maybe makes sense to let lots of patients take on the risk of a big trial because need a definitive answer as soon as possible.
  + Right to try
    - Get patients access faster-accelerated approval

Can we talk to anyone in pharma to learn more about intention-Ron postuma—at SCT

Need to look at the data closer-is there a clue to why they do it?

When data is finalized- investigate

* Pos P3 trials that bypassed what did they do? What was protective of positivity?
* Look through discussion and intro sections and see what they are referencing
* Neg P3 trials that bypassed do they cite intervention ensemble isssues

Propose new things to investifate

How to derisk when bypass-what is protecting the p3 after skipping

extentiion of my project

o   Future work

o   I have information to pool all p3 trials (first in indication for many indications-interesting for a diff trial

§  Like amandas project with headache, ms, als etc. -more power if not considering bypass subgroups

o   We focused in on the efficacy variable how does eff in P2 translate to P3 but more work should be done to look at safety and dose or others bc for example in Ms a P3 trial may be very positive but not moved to approval because it had immune reactions so not successful??

o   Dose

§  They suggest that P2 trials should be used to optimize dose before progression to P3 to increase the likelihood that the P3 trial is successful.33

§  interesting. what predictions would u make for bypass v nonbypass based on this hypothesis?

§  might expect: greater discussion of dose after trials fail if bypass p2. might expect more dose arms in bypass arm of P3 trial. might expect greater safety events in the highest dose arm for P3 trials that bypass vs. those that do not? maybe add this to ur study!

§  if dose is not explored in p2, does that mean a much bigger p3 trial (since many dose arms)?