Thesis topic-P3 go/no go decisions

Chapter 1-Review of guidance for how p2 studies should be designed in neurology in order to best guide the go/no go decisions for p3 studies

Chapter 2-What are the different types of evidence that guide go/no decisions for p3 studies and how does this impact risk/benefit to patient participants

Chapter 3- What are the ethical implications of P2 trial bypass before P3 studies

Neuro-Masters ideas <https://www.mcgill.ca/gps/files/gps/initial_thesis_submission_checklist.pdf>

* A current, comprehensive review of the literature consisting in a total of approximately 10 pages, double-spaced for Master’s students

Thesis topic-Neurological phase skipping

Minocycline

References

Essential CNS Drug Development

Hop, Skip, and Jump: Do We Need Phase II Cardiovascular Clinical Trials?

Pragmatic Trials and Repurposed Drugs for Alzheimer Disease

Revised Airlie House consensus guidelines for design and implementation of ALS clinical trials

Alzheimer’s disease (AD) therapeutics – 1: Repeated clinical failures continue to question the amyloid hypothesis of AD and the current understanding of AD causality

Phase II clinical trials of anti–amyloid β antibodies: When is enough, enough?

**Advancing trial design in progressive multiple sclerosis**

**Clinical trials in progressive multiple sclerosis: lessons learned and future perspectives**

Outcome measures for clinical trials in neurotrauma

Suboptimal Dosing Parameters as Possible Factors in the Negative Phase III Clinical Trials of Progesterone for Traumatic Brain Injury

**Clinical trials in amyotrophic lateral sclerosis: why so many negative trials and how can trials be improved?**

Drug development in Alzheimer’s disease: the path to 2025

Lost in translation: understanding the failure of the progesterone/traumatic brain injury Phase III trials

Resolving controversies on the path to Alzheimer's therapeutics

The Need for New Approaches in CNS Drug Discovery: Why Drugs Have Failed, and What Can Be Done to Improve Outcomes

Economic analysis of opportunities to accelerate Alzheimer’s disease research and development

Improving Alzheimer’s disease phase II clinical trials

Guidelines for the conduct of clinical trials for spinal cord injury as developed by the ICCP panel: clinical trial design

Why do we need phase 2 trials in neurology—what do they tell us

What are different types of for prior evidence used for go/no go decisions before phase 3 trials in neurology?

Cost and Timing

* Significant differences between the cost characterizations with the existing and the recommended infrastructure were found in four aspects of the development environment: the durations of Phases II and III, the transition probability from Phase II to approval, and the ratio of Phase II failures to the total failures in Phases II and III combined.
* Shortening Phases II and III could by itself reduce the expected cost of a new drug by 18%. Reducing the risk of failure in clinical trials and shifting failures from Phase III to Phase II could reduce the expected cost of a new drug by 55%. Specifically, in comparison to the baseline capitalized cost estimate of $5,693 million to develop one new disease-modifying drug, shortening Phases II and III by 2.5 and 11.5 months, respectively, reduces the expected cost to $4,667 million, while increasing the probability of transitioning from Phase II to approval from 11% to 24%, andw
* Reducing the overall risk of failure has a relatively larger impact on expected cost compared with shifting failures from Phase III to Phase II. Again, compared to the baseline estimate of $5,693 million, if the probability of transitioning from Phase II to approval is increased from 11% to 24%, while the ratio of Phase II failures to the total failures in Phases II and III holds constant at 60%, the expected cost is reduced to $2,768 million. This represents a 51% cost reduction that is spread over all stages of development. If, instead, the probability of transitioning from Phase II to approval is held constant at 11%, while the ratio of Phase II failures to the total failures in Phases II and III is increased from 60% to 77%, the expected cost falls by only 10%, with all of the reduction concentrated in Phase III (a 32% reduction in the capitalized cost incurred in Phase III for each new drug approved).
* Thus, identifying in phase II, or preferably phase I, drugs that are likely to fail could have a dramatic impact on the costs associated with developing new drugs

“Ideal”

* Phase 2b/ab -positive
  + General guidelines
    - Phase 2 trial assess optimal dosing, expand pharmacokinetics, determine whether a therapy has the desired biological effect, monitor safety and tolerability, and whether a potential therapy reaches and affects its intended target.39,40 Clinical efficacy is not the main goal of phase 2 studies.39,41,42
    - \*Investigators should carefully review phase 2 trial results and choose a primary endpoint that is clinically meaningful and adequately powered for phase 3.
    - Investigators may move from phase 2 to phase 3 with at least adequate information on safety and tolerability, and should move forward if there is safety and tolerability in combination with (1) information regarding pharmacodynamically optimal dose, (2) evidence of target engagement, and/or (3) evidence of clinical efficacy.
    - Investigators may assess biological effect and/or preliminary efficacy*,* even using novel methods (e.g., predictive algorithms or exploratory biomarkers), to support a decision to move a therapy to phase 3 trials.
    - The model of phase 2 (proof of concept) to phase 3 (clinically definitive) trials is embedded in the practice of clinical trials. Phase 2 trials are done to establish toxic effects, identify drug doses that seem effective and well tolerated, and provide proof of concept before proceeding to the longer and more expensive phase 3 trials
    - In summary, appropriately targeted phase 2 trials have the potential to identify the treatments most likely to succeed in phase 3 and those with little chance of success.
    - Phase 3 studies in progressive multiple sclerosis should be done after phase 2 trials have provided a clear proof of concept.
    - For phase 3 studies, mandatory completion of phase 2 studies in the appropriate target group
    - Consider phase 2 studies before pivotal investigations
  + Variables that are important to move forward
    - Pharmacodynamically optimal dose/schedule
      * If there are two p2 with different results with different doses/schedule-suggest that there should be another phase 2 to reconcile- progesterone in TBI
      * Should be established before moving into the phase 3
      * Both phase 2s used too low of a dose anyway
      * Advocating for additional phase 2 trial when there is this hasn’t been optimized
      * All clinical studies based on preclinical drug evaluation should be required to perform preliminary optimization studies of dose and duration of treatment in Phase II testing. The optimization should be based on allometric scaling techniques that are now available to clinicians and researchers [10,16,29];
      * Phase 2 trials can provide important guidance for refinements in the treatment regimen and outcome measurement for subsequent Phase 2 and Phase 3 trials. A Phase 2 study provides further opportunity to further refine the optimal dose, timing, and treatment regimen (eg, concomitant interventions, drug infusion or cellular transplant location, and other potential confounding variables) for the more definitive Phase 3 trial
    - Proof of concept -dose dependent relationaship between drug and pharmocodynamics
      * Evidence of target engagement
      * Usually from a biomarker
      * many surrogate endpoints in AD—two examples below in yellow
      * A common misperception is that biomarkers need regulatory approval to be used in progressive MS phase 2 trials. Most progressive MS phase 3 trials had no phase 2 trials demonstrating efficacy, which highlights how regulators do not require any evidence of efficacy from phase 2 trials. Similarly, T2 and gadolinium-enhancing lesions are typical primary outcomes for most RRMS phase 2 trials, yet they have never received formal regulatory approval for this purpose. The regulatory focus in phase 2 trials is on safety; proof-of-concept efficacy (i.e. using a biomarker) generally is not a regulatory concern in phase 2 trials.
      * The choice of phase 2 outcome is key to any trial’s design, and the lack of consensus regarding a reliable, sensitive, dynamic biomarker for progressive MS is a challenge. Brain atrophy is the current standard, but therapeutic lag and pseudo-atrophy from anti-inflammatory effects of some therapies can confound measures of brain atrophy. Delaying the baseline or re-baselining the measurements or MRI scans can help to reduce this confounding, but can decrease study power by shortening the interval of outcome assessment, and adds to the complexity of the study.
      * Tramiprosate (Alzhemed) was a putative anti–Aβ-aggregation compound, but this mechanism was not proven in its phase 2 trials, and the agent failed phase 3 without evidence that it had efficiently entered the CNS and engaged the Aβ target robustly
      * designed to identify whether a therapeutic effect is likely to be present
      * (i.e., that the target has been engaged in the CNS)
      * require biomarkers.
    - Evidence of clinical efficacy
      * How is “clinical” defined in these contexts
      * This is what is mainly missing from examples that I am finding
      * Even though most Phase 2 trials declare a primary clinical end point and outcome threshold, they should also evaluate a number of different clinical endpoints (secondary outcomes) to guide the selection of the most definitive Phase 3 primary outcome.
      * Ideally, phase II trials would demonstrate that clinical end points are affected, although the difficulties in assessing clinical effects in small phase II trials with short durations are acknowledged, and larger longer trials have obvious drawbacks (see later in the text). Decisions to move on to phase III should at a minimum be based on safety and valid biomarker considerations that are consistent with mechanism of action in phase II, although this only partially de-risks promotion to phase III. It is possible to be misled by positive results from a single phase II trial with a small restricted participant cohort, as this effect might be lost in a larger more heterogeneous multisite phase III trial, particularly if the phase II subgroup is identified post hoc. Perceived clinical efficacy from phase IIa trials may be illusory if based on nonsignificant trends. Thus, single phase II AD trials may be too small and underpowered to allow for clear decision making based on clinical efficacy measures alone, again suggesting that the rigor of biomarker-based proof of mechanism is critical. Larger clinical effects in phase IIa proof-of-concept studies or multiple phase II studies could provide compelling evidence if achieved, as effect size generally decreases as the study populations become more heterogeneous in phase III. Although the use of futility analyses for clinical efficacy data in phase II is of interest, this approach has not yet been demonstrated to improve decision making for phase III
      * Achieving a predetermined clinical end point is desirable in phase II, but in MCI and early AD, this is difficult because there are no firmly established end points
      * Most progressive MS phase 3 trials had no phase 2 trials demonstrating efficacy, which highlights how regulators do not require any evidence of efficacy from phase 2 trials.
    - Side effects mapped
      * Has never been a problem for neuroprotective drugs-all safe even in phase 3 trials without earlier phase 2
      * gather more evidence of the intervention's safety
      * Safety is different in CnS because it impacts personality and behavior
      * Sometimes the side effects hit later or could have been given for longer or higher doses-lots of citations here
    - Population
      * As the patient population under investigation is expanded to include a more heterogeneous group of subjects, appropriate sizing of the trial and consideration of stratification strategies become critically important (cf Steeves *et al*[1](https://www.nature.com/articles/3102010#ref-CR1)). For this reason, it is best to design a Phase 3 protocol based closely on the design features of previous, smaller Phase 2 studies that allow a relevant power analysis to be made.
      * Depending on the strength of the clinical benefit provided by the therapeutic intervention, and careful analysis of existing data, a Phase 3 trial might also be expanded to include subjects with injuries in a broader interval of time-after-injury (eg, the study of an acute intervention might be expanded to include subacute injury subjects). Such broadening of inclusion criteria at the stage of Phase 3 investigation should be supported by preclinical data, indicating efficacy at corresponding intervention time frames, and preceded by examination in a separate Phase 2 study, where dose–response relationships could be adjusted to the specific pharmacokinetics or pharmacodynamics of the new, expanded patient population
      * The target must be active and relevant with respect to therapeutic manipulation in the phase of the disease being studied. As a corollary, given the mechanism of action of a particular compound, consideration should be given to determining whether the posited pharmacology is relevant at the stage of disease being studied. The target population should be identified as clearly as possible with these considerations in mind.
      * Larger clinical effects in phase IIa proof-of-concept studies or multiple phase II studies could provide compelling evidence if achieved, as5 effect size generally decreases as the study populations become more heterogeneous in phase III.

Bypass

* The Alzheimer’s disease literature is replete with phase 3 or pivotal trials that were undertaken without prior demonstration of proof of concept, efficacy evidence, or despite prior negative phase 2 efficacy studies. Examples include γ-secretase inhibitors and modulators, β-secretase inhibitors, amyloid-β antibodies,3, and some small molecules such as methylene blue4 and edonerpic.5For each, either no prior phase 2 efficacy trial was done or a phase 2 trial that did not show efficacy preceded the phase 3 trials.
* Reasons for Bypass
  + AD -Hailmary
    - four of the Aβ-targeted clinical candidates collectively failed 93 times before being discontinued [[134]](https://www.sciencedirect.com/science/article/pii/S000629521830409X#b0670), a number that reflects a clinical culture in AD research that is highly invested in a Hail Mary pass-type approach, a term from American football that describes an effort made in desperation with a small chance of success.
  + Commercial concerns
    - Revenue forecasts if the drugs end up being approved
    - Risk of development spread our among different companies that are independently invested
  + Academic industrial complex
    - Researchers paid by industry in industry-funded trials
  + Intense competition
* Types of Bypass
  + No trials in same drug/same indication-Use of inferential data
    - Same indication/different but similar drug
      * Investigators may assess biological effect and/or preliminary efficacy, even using novel methods (e.g., predictive algorithms or exploratory biomarkers), to support a decision to move a therapy to phase 3 trials
    - Different but Similar indication/same drug
      * Paradigm trial in cardiovascular
        + Used data from preserved ejection fraction heart failure group not heart failure with reduced ejection fraction—phase 3 was positive
        + Claims this saved 3 years development time
      * Minocycline trial
        + Relied on preclinical and indirect evidence for its effects on amyloid-β, reducing τ phosphorylation and aggregates, decreasing microglial activity in patients with traumatic brain injury, other anti-inflammatory effects, and previous studies in Huntington disease, amyotrophic lateral sclerosis, multiple sclerosis, and schizophrenia that overall did not show significant clinical effects—Phase 3 was nonpositive
      * Patient population differed from phase 2 study[45](https://www.sciencedirect.com/science/article/pii/S1474442214701292?casa_token=95kNStRGpFgAAAAA:yuGR0tTC_e4DFBjJRPJlVBU1ioDPKsQ0H1bzJl1zPg8r5N_SQqmYrBiGnW37AF_olfnDBLSa7Yg#bib45)
      * Development of a repurposed agent for use in the AD field could begin with a Phase 2 proof-of-concept and dosing study for AD, thus avoiding the time and expense of preclinical development and Phase 1.
        + Suggest that we use repurpose by putting into p2 first
  + “Flawed” trials in same drug/same indication
    - Too small
      * Need for different phase 2 study[23](https://www.sciencedirect.com/science/article/pii/S1474442214701292?casa_token=95kNStRGpFgAAAAA:yuGR0tTC_e4DFBjJRPJlVBU1ioDPKsQ0H1bzJl1zPg8r5N_SQqmYrBiGnW37AF_olfnDBLSa7Yg#bib23), [25](https://www.sciencedirect.com/science/article/pii/S1474442214701292?casa_token=95kNStRGpFgAAAAA:yuGR0tTC_e4DFBjJRPJlVBU1ioDPKsQ0H1bzJl1zPg8r5N_SQqmYrBiGnW37AF_olfnDBLSa7Yg#bib25)
      * Phase 2a same drug/same indication
        + Thus, to advance a compound into Phase IIb/Phase III trials typically requires that it show a proof of concept, an efficacy signal, in Phase IIa trials
    - Need more to reconcile
      * If there are two p2 with different results with different doses/schedule-suggest that there should be another phase 2 to reconcile- progesterone in TBI
    - Bad outcomes
      * Better outcomes and more rationally designed and longer
      * Bad biomarkers
  + Nonpositive on primary Phase 2b/ab same drug/same indication
    - For [tarenflurbil](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/tarenflurbil), Phase III trials were initiated even though it had been noted by one of the clinicians responsible for running the trials that “at the end of phase 2 we really had no idea if there was a signal or not” [[132]](https://www.sciencedirect.com/science/article/pii/S000629521830409X#b0660).
    - Bapineuzumab
      * Phase 2 was initially for safety then modified primary to efficacy
        + Nonpositive but ran exploratory analysis one of which trended toward significant (p-0.056)
        + Posthoc subgroup analyses based on apoe were significant
        + Multiple testing problems
      * Another Phase 2
        + Positive on primary but not on clinical endpoints
    - Solanezumab
      * Phase ½
        + Suggested target engagement but not able to signal clinical measures
      * Phase 2
        + Dose proportionate response for plasma AB concentation
        + No effects on markers of neurodegeneration
        + Significant on one primary biomarker analysis but not clinical endpoints
    - Alzhemed
      * Tramiprosate (Alzhemed) was reported to inhibit Ab fibril formation and to protect against Ab toxicity in in vitro assays [22]. It reportedly also prevented amyloid accumulation in animal models [23]. A phase II study (n 5 50, 12 weeks treatment) sponsored by Neurochem, Inc. (currently Bellus Health, Inc.) was designed to establish safety and seek evidence of central nervous system (CNS) exposure [24]. This study detected a nonsignificant dose-responsive reduction in CSF Ab42, suggesting that the compound was getting into the CNS in sufficient quantities to have an effect on Ab deposition. On the basis of these data, and given the paucity of disease-modifying agents in development for AD at the time, two large phase III studies were launched in North America and Europe [25]
    - Atorvastatin
      * A trial with 67 participants with mild-to-moderate AD treated for 12 months produced a positive signal on each of the clinical outcomes and cholesterol level, indicating efficacious dosing in the bloodstream, but not on antioxidant biomarkers [46]. These results were used to justify a phase II study that enrolled 600 participants, and which failed to detect any efficacy. Post hoc analyses suggested that those with less cognitive impairment, cholesterol of .200 mg/dL, and who were APOE 34 carriers were more likely to improve [47]. This analysis led to the decision to proceed to a phase III trial that failed
    - Subgroup analyses-might not be bypass
      * however, the decision to proceed to a large phase 3 trial (n=612) for MBP8298 (a [synthetic peptide](https://www.sciencedirect.com/topics/medicine-and-dentistry/synthetic-peptide) similar to myelin basic protein) seems questionable based on a post-hoc, HLA-stratified subgroup of 20 patients.[46](https://www.sciencedirect.com/science/article/pii/S1474442214702649#bib46) Likewise, with the beta interferons, no phase 2 trial was done with a pure cohort of only patients with SPMS, and the decision to move to phase 3 was based largely on extrapolation from the successful RRMS experience.
      * There is a risk of wasting both time and money if this decision is based on secondary analysis and subgroup findings when the primary endpoint is not met in Phase 2. Rigorous adherence to pre-specified outcomes and avoidance of over-interpreting subgroup data, as well as greater understanding of the test agent in Phase 2 and appropriate primary endpoint selection, are crucial and will help preserve resources for agents with a higher likelihood of success.
      * Bap and sol
      * Subgroup, post hoc, or other types of secondary analyses are important, but they are also potentially misleading when not subsequently tested prospectively. An inadequate understanding of the limitations of such exploratory analyses is a primary reason for the failure of phase III trials. Such analyses are known to be fraught with risks in terms of generalization to the original patient population, overestimation of effect size, and biased selection of factors for analyses
      * It is possible to be misled by positive results from a single phase II trial with a small restricted participant cohort, as this effect might be lost in a larger more heterogeneous multisite phase III trial, particularly if the phase II subgroup is identified post hoc.

Type of Phase 3 to account for bypass conditions

* Phase 3 with early stopping “Adaptive design”
  + David-“In the ARDS Network we have often dispensed with phase II and replaced it by a futility stopping rule after 50 patients were accrued. We have done this in several of our ALS trials as well.  Recently I analyzed a 9 patient trial using historical controls, in order to justify funding a large phase III trial.”
  + FIRST trial
    - Launched off of 33 patients without phase 2 but stopped after 450 patients randomized because of excess harm and futility
    - Argues that this saved patients—but don’t know if the phase 2 would have found that—weak arguments
* Pragmatic Phase 3
  + pragmatic trials are designed to be straightforward and externally valid by using practical clinical procedures and outcomes that are important to patients and easily interpretable
  + no biomarker evidence-not overcomplicated with mechanistic undertakings
  + cheap/less patients
* Normal Phase 3
* Out of scope
  + Phase 2/3
    - Talks about it as a viable option
    - <https://link.springer.com/content/pdf/10.1007/s10985-007-9049-x.pdf>
    - Traditionally, individual study phases are completed before moving to the next phase of the study. However, as has been the case in immunotherapy development, combined Phase 1/2 clinical trials may speed development; that is, instead of conducting a Phase 1 trial for toxicity and a separate Phase 2 trial for efficacy, it may be appropriate to integrate these two phases into one study of individuals with AD. Study sponsors can consider an adaptive Phase 2/3 study design, whereby accumulating trial data are used to guide modification of one or more specified aspects of the study design, for example reducing the number of dose arms, or extending or shortening the length of the trial without undermining its validity and integrity. Use of such an adaptive trial design places greater emphasis on Phase 2 learnings as guides to pharmaceutical decision-making (for example, whether to continue development of an investigational drug). While AD drug development could be reduced by months or even years using an adaptive design, there is some skepticism about its value with concern of erroneous trial modifications as a result of the “noise” with our current cognitive measures as well as with non-validated biomarkers. An intensive study of novel study designs will be required to understand their appropriate role within the AD trial setting and potential for drug development acceleration.
* In addition, the phase labels have begun to lose their meaning. Phase 2 trials will focus on safety, phase 1 trials will expand into efficacy.

Lit review number 2

<file:///Users/hannahmoyer/Downloads/Mehta%20ExpOpinInvestDrug17.pdf>

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<https://content.iospress.com/articles/journal-of-huntingtons-disease/jhd170245>

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**Introduction to bypassing in neurology**

Neurological conditions include some of the most prevalent conditions in North America. These conditions are defined as …involving the nervous system and include conditions like AD, PD, stroke, migraine, epilepsy, and many more. In the past 10 to 20 years there has been a shift in the population of North America such that more people are living longer and are susceptible to neurological disorders that are associated with degeneration with age. These conditions pose a huge risk to patients and healthcare systems and include some the least understood or treatable conditions. Neurological drug development also carries exacerbated risks because they involve the brain and could impact all of its associated personality and emotion making features. In addition, these trials are riskier because less is known preclinically due to difficulties understanding the brain and animal models that vary significantly in their neuronal makeup.1 This creates a unique drug development environment that requires special attention.

For neurological disorders, the success rate is lower than other indications at 8%.1 This has been said to be due to difficulties measuring the impact of treatments on the CNS, endpoints that lack validation, and the long accumulative nature of the conditions.1 However, although the probability that a trial in some neurological disorders will find a successful drug historically is very low, if it is positive, it would have huge impact on the population1. This calls of empirical analyses of different drug development trajectories to find the best ways to develop novel neurological drugs within the constraints of limited resources, such as money or patients.

Generally, drug development follows a phased approach (1-4), each with a different goal in mind. Briefly, P1 trials focus on gathering pharmacological and safety information for the treatment in humans. P2 trials usually aim to collect preliminary information on the efficacy of the new treatment while continuing to collect safety information and dose relationships. Then, P3 trials are aimed at determining whether there is enough safety and efficacy signals to move forward to approval. Finally, P4 trials are typically run post-approval to widen the approved population. These goals can vary across disease areas, but typically follow this order.2

However, there are calls for new creative ways of modifying the drug development process to get these drugs to patients faster. For example, when P2 trials have shown exceptional promise, people have called for bypassing P3 trials and going directly to approval without this extra layer of evidence gathering.3 Other designs, such as phase ½ or 2/3, are used to create seamless transitions from phase to phase, using less patients, time, and resources (ideally).1–5 Although interesting, these methods of shortening the drug development process have been widely discussed elsewhere. This paper will focus on a method less widely characterized and understood. This is what we call P2 Bypass which we have defined for our purposes as cases when P3 trials are initiated without positive evidence from a P2 trial. In what follows…

**What is the purpose of P2 Trials and what do we lose from bypassing it?**

To understand whether is appropriate to bypass P2 trials, it is first important to understand the role of P2 trials in traditional neurological drug development. Together with P1 trials, P2 trials make up the “learn zone”1 of drug development, where you can collect data that has “a significant impact on future trial size, expense, and risk.”2 Therefore, bypassing P2 trials, and the information gained from them, may impact the future of the trajectory in P3 trials and post-approval.

One review notes that P3 trials should not be initiated without proof of concept, dose information, and the population defined.11

**Dose/schedule**

The first task of a typical P2 trial in neurology is to find the optimal dose and schedule.8–13 This is a stage where, using many doses, you can begin to see a dose relationship in the efficacy and safety endpoints.2 For example, using a P2 trial to determine the dose helps to ensure that that a safe and effective dose is moved forward to P3 testing. One review investigating nonpositive P3 trials in TBI argues that the equivocal dose optimization results from preceding P2 trials may have contributed to the P3 result. They suggest that a new P2 should have been done to reconcile results if they are inconsistent before progression to P3 to increase the likelihood that the P3 trial is successful.10 In addition, P2 trials tell us more about how the dose of the drug impacts the safety and tolerability.8,9,11,13 This can be especially important in CNS disorders because drugs treating these conditions can effect personality or suicidal behavior.2,17 Data show that many doses are changed (mostly lowered) after FDA approval due to safety concerns. This practice is most common in neurological drugs. Although it is not clear the role that P2 data had in these cases, it is clear that any consideration/checks of dose are important.21

**Efficacy**

The second task of a P2 trial is to begin to evaluate whether the drug has the desired impact on the condition. Ideally, these trials would use clinical endpoints so that researchers could determine if the treatment has an impact on the livelihood of patients with the condition. In some chronic neurological disease however, relying on clinical effects would prolong the duration of clinical trials significantly.8,9,13,14 In these cases, phase 2 trials may investigate endpoints that they believe are surrogates for the clinical outcomes or use “proof of concept” or “pharmacodynamic biomarker” endpoints that simply show that the drug is having the desired biological effect which they assume will have the desired therapeutic effect.8,9,11,15 Although it is difficult to collect clinical information in some neurological clinical trials, surrogate endpoints often are not approved for use as outcomes, with little evidence that they are sensitive or reliable 15,17 though powerful when validated.1 However, guidelines in ALS and AD research suggests that P3 trials can be initiated after seeing safety and tolerability information and dose and proof of concept, but without clear clinical efficacy.8,14

Bypassing P2 efficacy results may impact the success of a P3 trial. If a clinical or validated endpoint is not possible, proof of concept endpoints can be an important step to provide evidence that the treatment is at least working how it is hypothesized to. For example, there are cases in ALS1 and AD22 where P3 trials were nonpositive after they did not show proof of concept that the treatment was entering the CNS and engaging with the appropriate target. There is likely a difference between instances when a P2 trial is run but was nonpositive compared to instances where no P2 trial is run in the same indication/drug. In the former, researchers likely learn from other aspects of the P2 trial along the variables described above. However, a nonpositive result could be used to decide to cease development of that treatment option in that indication because it is unlikely to be positive in the P3 trial. Several reports have investigated the relationship between the presence of P2 efficacy evidence and P3 trial outcomes in cancer clinical trials and found that bypassing was associated with nonpositive P3 outcomes.23–25 Our paper in oncologic drug development found that those trials that are not supported by P2 trials have significantly worse survival outcomes.

**Population**

The final goal of P2 trials is to determine the patient population to test the treatment in. The above variables are all investigated and optimized within a patient population of interest.

Finally, determining whether the treatment works in the patient population of interest is an important piece of information. For example, expanding patient populations beyond that which has been investigated jeopardizes the applicability the existing evidence.11,26 This however may be necessary to ensure that more patients can benefit from the approval that could come from the P3 trial.2 In clinical trials for treatments for spinal cord injuries for example, guidelines suggest that when attempting to move a treatment into a broader, more heterogeneous population, researchers should do so an additional P2 trial instead of a large P3.11 When not preplanned, extrapolation from subgroup population analyses for the design of p3 can lead to nonpositive results4, shown by examples in RRMS20 and AD.14

Conclusion

For example, guidelines in ALS and MS suggest that P2 studies should be required before P3 trial initiation and others in ALS and AD suggest that P3 trials can be initiated without clear clinical efficacy.8,14 Some papers have discussed the flaws of the re-purposing drugs in P3 trials without first investigating it in the new indication in a P2 trial.4,18

**Bypassing-why would it happen and how might bypassing impact the research trajectory?**

Regardless of the value of knowledge gained by this stage of the drug development timeline, P3 trials are often started without direct, P2 trial evidence. In these cases, P3 trials can rely on data from other indications or drugs to infer information for their trial. For example, P3 trial investigators can extrapolate from trials looking at a similar drug in the same indication8 or the same drug but a similar indication9. Alternatively, investigators sometimes do run P2 trials but persevere after obtaining a nonpositive result on their clinical outcomes (or don’t have one). We will use all of these cases to mean P2 bypass. It is also possible that some of these variables were investigated in P1 trials although this is not the primary purpose of these trials.

Our own unpublished study suggests that 48% of P3 cancer trials are launched absent positive P2 evidence. However, the drug development landscape is vastly different in neurology. For example, there are significantly fewer and longer clinical trials in neurology than in cancer, and the benefit gained is often marginal and palliative.16 Contrary to oncology, where bypassing may be due to encouraging early safety or efficacy signals, bypassing P2 trials in neurology may be influenced by the lack of surrogate endpoints15,17 and companies that are desperate to find treatment options for a population with little to no treatment options and attempt a “hail mary”.18,19 Other reasons companies might initiate a P3 trial without affirmative P2 evidence include the academic industrial complex, market pressures or intense competition between companies, and the huge potential for payoff if successful.20 This approach (if the treatment is successful) would likely speed up the time it takes for the treatment to be approved. However, the amount of evidence available to shape the P3 trial to have the best chance of being successful is lower.

Even if care is taken to set up an analysis to stop futile trials, the cost of running a phase 2 and phase 3 differ significantly. Although it is hard to estimate average costs of different phase trials because reporting of such is weak27, one paper estimated that phase 2 trials median cost was $8.6 million and phase 3 trials cost $21.4 million.28 From an economic point of view, costly phase 3 trials that show no efficacy, running a phase 2 trial to look at direct benefit is clearly a better route. In addition, Wong et al. found that only 32.7% of phase 2 trials in oncology move on to phase 3 trials, which underlines the high rate of attrition that makes skipping this stage questionable.29The decision to run a P2 trial before a P3 trial has implications in both cost of drug development and patient burden. or instance, one simulation in AD showed an estimated 55% decrease in the cost of development when drugs are found to be unsuccessful in P2 trials rather than P3 trials,5 because the P2 can be used to weed out drugs that are not likely to be successful earlier in the development process.9,14 Although it is unclear if running a P2 trial followed by a P3 trial changes the time/cost/patient burden compared to trajectories that bypass, a simulation of timelines in pancreatic cancer predicts that P3 drug trials that are ended with futility analyses have longer development times and use more patients when they bypass P2 compared to not bypassing P2.6

An additional important factor to consider is how might bypassing a P2 trial impact the risks and benefits of afforded to patients who participate in these P3 trials compared to patients participating in P3 trials that had P2 trials? The potential benefit for company and future patients cannot be exchanged for the decline in welfare for the patients involved. Rubenstien et al. has proposed that skipping phase 2 trials would only be reasonable if the number of drugs starting the pipeline were limited and there were unlimited resources for researchers to use in clinical trials. This way, screening out ineffective drugs would be unnecessary and there was no cost to researching ineffective therapies.30 Unfortunately, this is not the case in the real world. In the case of rare diseases, the limited number of patients means the diversion of patients from trials that may be more informed by efficacy data. 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. In many cases, this is not true. For example, 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 patients31

Participating in clinical trials is not without its costs for patients.32 There is no evidence to the best of our knowledge describing the average number of patients in phase 2 or 3 trials or the number of hours they contribute of their time, but phase 3 trial will likely have a higher patient load. A few studies have investigated the amount of time different treatments require of patient in clinical care33–35 and one of which found that 10% of living days were involved with seeking care. This amount of time has not been estimated for participation in clinical trials, but it is sure to be higher due to exposure to research methods and assessment.7 Although the cases of finding out a drug is not efficacious in phase 3 trials is not uninformative, in the case where these phase 3 trials skipped earlier efficacy trials the burden of patients is much higher and could have been mitigated to a smaller number of people

The decision to move into a P3 trials and expose large numbers of patients to a new drug should be backed by the greatest chance for success because of limited resources.1

What we don’t know

How my C2 helps us understand

Focus on the efficacy variable-how does bypassing positive clinical evidence this impact p3 trial success?

We don’t allow proof of concept-only looking at clinical-or validated surrogate vs nothing

References

Automatic citation updates are disabled. To see the bibliography, click Refresh in the Zotero tab.

* 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.36 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

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.37 In cases where there has been no prior direct evidence of efficacy, therapeutic misconception could lead to a break in patient consent.38,39 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.

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

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.40,41 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 patients31 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.42

Researchers have also been increasingly reliant on mechanistic evidence, especially biomarker enriched evidence in the design of phase 3 trials,43

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)

**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”.40 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.44 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.45,46

* 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 . 47 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. 18

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