**Introduction**

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.

Despite being one of the most disabling disease areas in modern life, neurological drug development is delayed compared with other disease areas, with some indications lacking any established SOC that improves clinical outcomes. The difficulties in the development area starts with the basic science, where we understand relatively little about disease pathology. When these theories are brought into preclinical studies, they additionally suffer from a reliance on animal models that vary significantly in their neuronal makeup from humans and with difficulties ensuring that the drug is transported across the blood brain barrier.1,2 Together, these issues mean that new treatment options CNS disorders are brought into clinical trials with less of an understanding of the treatment and disease than in other indications, already a risky investment because little is known on how humans will react. Once in clinical trials, development also suffers from issues measuring the impact of treatments on the CNS, using endpoints that lack validation and are not associated with clinical outcomes, and the long accumulative nature of the conditions that need years to be measured.3 In addition, there are additional risks because modifying brain chemistry can impact personality and emotion.2

These factors together create an area of drug development where investment into the field is relatively risky due to high financial risks and relatively low success rates (between 6-9%).4–6 In fact, one review found that CNS drugs were half as likely to be approved as other indications.6 Over time, R&D expenditures have increased in all fields, but there has not been an associated increase in approvals in neurologic drug development. This has resulted in diminished investment in neurological drug development4,5 and lower numbers of applications for funding by the NIH for neuroscience research.7 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 population.8

Generally, drug development follows a phased approach (1-4), each with a different goal in mind and an increasing cost and number of patients involved. Briefly, P1 trials focus on gathering pharmacological data, safety information, and the maximum tolerated dose 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.9 Phase 2 trials are sometimes separated into Phase 2a to look at safety, tolerability and proof of concept10 and 2b to look at efficacy. Next, 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 and the phase priorities are occasionally flexible, but typically follow this order..9

There are calls for new creative ways of modifying the drug development process to get these drugs to patients faster and to increase the incentives for companies to invest in their development without putting large numbers of patients and money into futile trials.5 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.12 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).13–18 In neurology, other techniques for speeding up drug development include shortening P2 trials14 using basket or platform trials10, historical controls19, pragmatic phase 3 trials20, and futility designs.21 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 that we call P2 Bypass, defined for our purposes as the practice of initiating P3 trials without positive evidence from a P2 trial. Regardless of the value of knowledge gained by this stage of the drug development timeline, there are many documented instances of P3 trials that bypassed P2.20,22–24 In these cases, the P3 trials may 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 indication25 or the same drug but a similar indication20,26. 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.13,20 It is also possible that some variables typically reserved for P2 trials re investigated in P1 trials. Alternatively, investigators sometimes do run P2 trials but persevere after obtaining a nonpositive result on their clinical outcomes. We will use all these cases to mean P2 bypass.

Our own unpublished study suggests that 47% of P3 cancer trials bypassed P2 trials. 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.27 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 endpoints2,28 and desperation to find treatment options for a population with little to no treatment options and attempt a “hail mary”.20,29 Other reasons companies might bypass P2 evidence include the academic industrial complex, market pressures or intense competition between companies, and the huge potential for payoff if successful.22 This approach (if the treatment is successful) would likely speed up the time it takes for the treatment to be approved. However, the lower amount of evidence available to shape the P3 trial may lower its chance of being successful. Some reviews explicitly note the importance of P2 trials in neurology drug development and suggest against bypassing P2 trials.1–3

In what follows, we will present the current literature on the important variables typically explored in P2 trials in neurology along with how the data can be used to make go/no decisions for P3 trial. This will be followed with a discussion of how bypassing P2 trials may impact the research trajectory and enterprise.

**The purpose of P2 trials in neurology**

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”30 of drug development, where you can collect data that has “a significant impact on future trial size, expense, and risk.”9 The FDA has said that “sponsors assess phase 2 results to determine if the preliminary results are sufficiently promising to justify a phase 3 study”31 and P2 trials in AD have been called a “necessary step in drug development”.18 Therefore, bypassing P2 trials, and the information gained from them, may impact the future of the trajectory in P3 trials and post-approval. In what follows, we will discuss three variables that are typically investigated in P2 trials and how the lack of this information may impact future trials.

Dose/schedule and associated safety

The first task of a typical P2 trial in neurology is to find the optimal dose and schedule.25,26,32–35 This is a stage where, using many doses (under the maximum tolerated dose found in P1), researchers can begin to see a dose relationship in the safety and efficacy endpoints.9 In regards to safety, using a P2 trial can help ensure that a safe dose is moved forward to P3 testing. 25,26,28,33,35 This can be especially important in CNS disorders because drugs treating these conditions can effect personality or suicidal behavior.2,9 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.36 In addition, dose optimization is used to find efficacious dose relationships. 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.32

Efficacy

The second task of a P2 trial is to begin to evaluate whether the drug has the desired impact on the condition beyond dose relationships. Ideally, these trials would use clinical endpoints so that researchers can 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.25,26,35,37 In these cases, phase 2 trials may use endpoints that they believe are surrogates for the clinical outcomes. These surrogate endpoints often have little evidence that they are sensitive or reliable 2,28 though they are powerful when validated because of their ability to decrease trial time.30 This is especially prevalent in AD development, where the lack of validated surrogate biomarkers to use in P2 trials lead to the initiation of P3 trials without any indication that there is a clinical relationship.29 Reliance on these endpoints may play a role in causing P3 trials to be nonpositive, as was the case with Semagacestat31 and Solanezumab22

Due to these difficulties, investigating clinical efficacy is often not the main goal of P2 trials in neurology25. In this case, trials may rely more on “proof of concept” endpoints which can be an important step to provide evidence that the treatment is at least working how it is hypothesized to. These endpoints simply show that the drug is having the desired biological effect which they assume will have the desired therapeutic effect.25,26,28,33 This can be a vital minimum level of efficacy to show in early trials.38,39 For example, there are cases in ALS40 and AD41 where proof of concept that the treatment was entering the CNS and engaging with the appropriate target was not shown before P3 initiation and the trials were ultimately nonpositive.

Bypassing P2 affirmative efficacy results may impact the success of a 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.42–44 Our paper in oncologic drug development found that those trials that are not supported by P2 trials have significantly worse survival outcomes. It is unclear where to draw the line for how much efficacy (proof of concept or clinical) should be required before P3 trial initiation in neurology. In addition, there is likely a difference between instances when a P2 trial is run but was nonpositive on its primary endpoint 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 on variables like dose and population. On the other hand, a nonpositive result could be used to decide to cease development of that treatment option because they have been given reason to believe that it may not be efficacious (a no-go signal).

Relevant patient populations

Finally, determining whether the treatment works in the patient population of interest is an important piece of information. The above variables are all investigated and optimized within a patient population of interest. There can be huge amounts of heterogeneity between patients of the same condition, determined by line of treatment, subgroup disease classification, genetic status, severity, and countless other variables that can impact the outcome of a patient.10,45 Determining which type of patients to which to optimize the treatment to can take trial and error. Sometimes, sponsors expand patient populations beyond that which has been investigated in P2 trials, which may jeopardize the applicability the existing evidence, in particular the prior safety evidence, 33,46 although this may be necessary to ensure that more patients can benefit from the approval than a restrictive population.9 Alternatively, they can further restrict a population from a P2 using evidence from subgroups. However, when these are not preplanned, extrapolation from subgroup population analyses for the design of p3 can lead to nonpositive results13,37, shown by examples in RRMS22, PMS26, and AD.22,37 In clinical trials for treatments for spinal cord injuries however, guidelines suggest that instead of using a large P3 trial to attempt to move a treatment into a broader, more heterogeneous population, researchers should do so an additional P2 trial in the population of interest. 33

Information on the variables above can guide “go/no-go” decisions for further testing to limit waste in drug development.10,38 P2 trials can be used to weed out drugs that are not likely to be successful earlier in the development process.26,37For drugs that are found not to be safe, or to have efficacy (however it is defined) in the population of interest, they are an important step to stop further investment. For drugs that they find to be successful, per a predefined threshold, they can be used as supportive evidence to design the next trials. It is unclear how much evidence is needed to make these decisions. For example, guidelines in ALS25, PMS26, and AD37 suggest that P3 trials can be initiated without clear clinical efficacy and but not without proof of concept, dose information on safety, and the population defined.

**Impact of bypassing P2 trials on the research trajectory**

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 and patient welfare.3 One analysis from 2015 found that Phase 3 CNS drugs were almost 50% more likely to move from P3 trial to approval than all other indications, but that P2 and P1 trials were not more likely to be unsuccessful. This indicates that neurology may not be the problem and rather that the initiation of P3 trials may be ill informed.11 In what follows, I will review how the decision to bypass P2 and go directly to P3 may impact cost, number of patients involved, and risk and benefits for patients involved in the P3 trial.

Efficiency

Rubenstein et al. has proposed that bypassing 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.52 Unfortunately, this is not the case in the real world.

The cost of running a phase 2 or phase 3 trial differs significantly. Although it is hard to estimate average costs of different phase trials because reporting of such is weak,50 one paper estimated that phase 2 trials median cost was $8.6 million and phase 3 trials cost $21.4 million.51 Therefore, finding an ineffective drug in a P3 trial that they could have found with a P2 trial could at least double the cost of development in AD. In addition to cost, the length of time it takes to find a result should also be considered. In the case that you find a nonpositive result in P3 after bypassing, it can be unclear if this is due to ineffective drugs or the lack of evidence used to shape the P3 trial, potentially requiring more testing and adding to the cost and time to development. However, this practice would save money and time in the case that the P3 trial is positive after bypassing a P2 trial compared to the case where a P2 is run and then followed by a P3 trial.

In addition to research cost and time to development, patients are an important resource to consider because participating in clinical trials is not without its costs for patients.53 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 use greater amounts of both resources. A few studies have investigated the amount of time different treatments require of patient in clinical care54–56 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 This donation of patient time, especially patients who are made vulnerable by their conditions, should be respected, and optimized to have the greatest possible return on investment.

Risks and benefits to patient participants

In addition to designing efficient research trajectories, it is important to consider how 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 a pharmaceutical company and future patients cannot be exchanged for the decline in welfare for the patients involved. One way to conceptualize protecting risk and benefit for patients in trials is to consider the concept of clinical equipoise.1

There are two tenets of clinical equipoise as described by Freedman. These are disagreement amongst experts and the ability of the the trial to quell the disagreement. Bypassing has implications for both. To the first point, we believe that P3 trial approval decisions should include a discussion as to whether prior data has given us reason enough to believe that the experimental arm will be better for patients than the standard of care to enroll a large number of patients. A trial that does not have affirmative evidence available prior to its initiation may be associated with higher risk and diminished benefit (because of this lower level of evidence). In this case, the expert community, with access to data (or lack thereof), would likely have little reason to believe that the experimental treatment is going to be better for patients than the SOC and thus equipoise may be threatened for a large P3 trial.

To the second point, a P3 trial that bypassed that is nonpositive may have less of an ability to change expert opinion because it could have been a dose issue that we could have found in a P2. One review of go/no go decisions in CNS development said it well: “from a scientific perspective, it optimal to only make “Go” decisions when one is clear that results of a study will prove interpretable about the potential of an intervention in the absence of a positive finding.”38

**Conclusion**

It is clear that…

It should be noted that neurological disorders are not a monolith. While nearly all AD drugs have failed57, other neurological disease such as MS and migraine have several classes of drugs that make clinical differences. There is one approved drug in ALS, however the difference may be marginal. Stroke and TBI similarly have one successful drug2 There may be difference in the rate of bypass in these areas because speed may have a different amount of influence on drug development in areas with established standards of care.

There are a few methods for adapting the drug development trajectory and bypass that may decrease the risk to the trajectory and patients. There could be rules that P2 trials could only be bypassed after much mechanistic or safety signals. Alternatively, P3 trials that are initiated after bypassing could have low futility bars to limit the number of patients exposed in the P3 trial, imitating a P2 trial.14

What my C2 helps us understand?-more for the introduction of manuscript (C2)

The dismal neurologic drug development landscape calls empirical analyses of different drug development trajectories to find the optimal ways to develop novel neurological drugs within the constraints of limited resources, such as money or patients. One such trajectory, bypassing P2 trials, is a possible method for speeding up development to get drugs to patients faster.

Although some have discussed the presence of bypassing in neurology, it is unclear how common this is. One report calls is “rare”10 and others say x. It is also unclear how bypassing positive clinical evidence impacts p3 trial success and “how much information is sufficient to proceed to phase 3 without excessive risk of failure?”18

Using three categories to describe the amount of information available before each P3 trial, we will find if they impact positivity and termination rates. The first category is “preceded” where each trial was preceded by a P2 trial that was positive on a positive clinical or validated surrogate endpoint. The second category is “ambiguous”, where each P3 trial was preceeded by a P2 trial that likely provided evidence other than efficacy. This category includes two subgroups: “Non-positive” where P3 trials preceded by P2 trials that were non positive on clinical or validiated surrogate endpoints and “Unvalidated endpoint” where P3 trials were preceded by P2 trials that may have investigated proof of concept endpoints or only investigated safety. The final category is “True bypass” where all P3 trials were not preceded by a P2 trial in the same indication with the same drug.

By looking at the positivity and termination rates of P3 trials in each of these categories, we will learn about how each level of evidence prepares the P3 trial for success. Maybe we need long trials looking at “medically meaningful” results such as clinical or validated surrogate measures.2 Alternatively, proof of concept P2 trials this may be enough to start a P3 trial off of without sacrificing efficacy18 These results will help guide the decision making as to whether bypassing P2 trials is appropriate.

Secondary analyses will evaluate whether bypassing is more prevalent in indications that are more desperate for treatment like AD vs MS and migraine?

Future research

How much of bypass group are made up from modifications of existing approved drugs?

Citation analysis

References

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

Lit Review 3: indication specific

READ INDICATION CHAPTERS IN TEXTBOOK

* AD
  + Why do trials for Alzheimer’s disease drugs keep failing? A discontinued drug perspective for 2010-2015
    - <file:///Users/hannahmoyer/Downloads/Mehta%20ExpOpinInvestDrug17.pdf>

# Improving and Accelerating Drug Development for Nervous System Disorders

* + - <https://www.sciencedirect.com/science/article/pii/S0896627314009052>
  + The costs of developing treatments for Alzheimer's disease: A retrospective exploration
    - <https://pubmed.ncbi.nlm.nih.gov/34581499/>
  + A call for better reporting of trials using surrogate primary endpoints
    - <https://pubmed.ncbi.nlm.nih.gov/35910671/>

# Cognitive Go/No-Go decision-making criteria in Alzheimer's disease drug development

* + - <https://pubmed.ncbi.nlm.nih.gov/33486115/>

# Clinical Trials in Alzheimer’s Disease: A Hurdle in the Path of Remedy

# <https://www.hindawi.com/journals/ijad/2020/5380346/>

# Lessons Learned from Alzheimer Disease: Clinical Trials with Negative Outcomes

# <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5866992/>

# Lessons that can be learnt from the failure of verubecestat in Alzheimer’s disease

# <https://www.tandfonline.com/doi/full/10.1080/14656566.2019.1654998?casa_token=uJigJo75aDsAAAAA%3A2BAWszFVVjbwQ_-LjaKfD9iEeXc6p55SSDPwDjVdTBAtzDxmjGYlKPCwRgUsq22sgzU0SkmOcA9N>

# Alzheimer’s disease: many failed trials, so where do we go from here?

# <https://jim.bmj.com/content/68/6/1135.abstract>

# What lessons can be learned from failed Alzheimer’s disease trials?

# <https://www.tandfonline.com/doi/full/10.1586/17512433.2015.1034690>

* + Status and future directions of clinical trials in AD
    - https://www.sciencedirect.com/science/article/pii/S0074774220300532?via%3Dihub
* HD
  + Fifteen Years of Clinical Trials in Huntington’s Disease: A Very Low Clinical Drug Development Success Rate
    - <https://content.iospress.com/articles/journal-of-huntingtons-disease/jhd170245>
* Stroke
  + Lessons Learned from Phase II and Phase III Trials Investigating Therapeutic Agents for Cerebral Ischemia Associated with Aneurysmal Subarachnoid Hemorrhage
    - <https://pubmed.ncbi.nlm.nih.gov/34940927/>
  + Why Most Acute Stroke Studies Are Positive in Animals but Not in Patients: A Systematic Comparison of Preclinical, Early Phase, and Phase 3 Clinical Trials of Neuroprotective Agents
    - <https://pubmed.ncbi.nlm.nih.gov/31714631/>
  + Magnesium in clinical stroke
    - <https://www.jstor.org/stable/10.20851/j.ctt1t3055m.19>
  + Trends in Acute Ischemic Stroke Trials Through the 20th Century
    - https://www.ahajournals.org/doi/10.1161/01.str.32.6.1349
* TBI

# Embracing failure: What the Phase III progesterone studies can teach about TBI clinical trials

* + - <https://pubmed.ncbi.nlm.nih.gov/26274493/>

# Progesterone neuroprotection: The background of clinical trial failure

# <https://www.sciencedirect.com/science/article/pii/S0960076015301357?casa_token=I0wKYzjR6GgAAAAA:ZAsV3Yew8H56qqZWZR8R7nESP6eNo41J9Epbm2XHRWNg--U5xRd2CC2BB8Y_uWOwkSshcmKuyA>

# MS

# MS Review

# <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3351877/>

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

# https://pubmed.ncbi.nlm.nih.gov/25772899/

# Do Headache

Lit Review 1

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, as 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.