*The structure of Clinical Translation: Efficiency, Information, and Ethics*

Lit Review 3: indication specific

READ INDICATION CHAPTERS IN TEXTBOOK

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6041887/>

* AD
  + Status and future directions of clinical trials in AD
    - <https://www.sciencedirect.com/science/article/pii/S0074774220300532?via%3Dihub>

# Do Headache something

# There are a few methods for adapting the drug development trajectory after bypassing P2 that may decrease the risk to the trajectory and patients. There could be rules that P2 trials could only be bypassed after many mechanistic or safety signals. Alternatively, P3 trials initiated after bypassing could have low futility bars to limit the number of patients exposed in the P3 trial, imitating a P2 trial.15

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.