**Introduction**

Neurologic conditions include some of the most prevalent of modern life, primarily due to demographic transitions and developing global economies.1 One 2016 estimate found that this disease area was the most common cause of DALYs and second most common cause of deaths globally.82 Although increasingly common, many neurologic diseases do not have any effective treatments.3 This dismal treatment landscape shows the need for innovative modifications to the drug development process to get treatments to patients faster and to increase the incentives for companies to invest in their development.

In the following chapter, we first review the drug development landscape for neurologic diseases and one method of designing trial trajectories to reduce the time it takes to get effective treatments to patients - bypassing phase 2 (P2) trials. Next, we will provide an overview of the rationale for running P2 trials before starting P2 trials in neurology. This will be followed by a discussion of how bypassing P2 trials may impact research trajectories and the welfare of trial participants.

1. **Neurologic drug development**

1.1 Challenges

Despite being one of the most disabling disease areas, neurologic drug development has proven more challenging than many other areas of drug development, with some indications lacking any established disease-modifying standard of care (SOC).3 These difficulties start with the basic science, where we understand relatively little about disease pathology. When these theories are brought into preclinical studies, they suffer from a reliance on animal models that vary significantly in their neuronal makeup from humans. Additionally, CNS drug delivery is made more difficult than other targets due to the inability for anything other than small molecules to cross the blood-brain barrier.3–5 Together, these issues mean that new treatment options for CNS disorders are brought into clinical trials with less of an understanding of the treatment and disease than in other indications. Once in clinical trials, development then faces challenges measuring the impact of treatments on the CNS, using endpoints that often lack validation as surrogates for clinical outcomes, measuring the long accumulative nature of the impairments, and determining how the chronic exposure to treatments will impact safety over time.6 Additional challenges include the risk of intervening in an organ system- the brain- where personal identity and decisional capacity originate.3

These factors together create an area of drug development where clinical development has a low chance of leading to an FDA approval (between 6-9%).7–9 One review found that CNS drugs were half as likely to be approved as other indications.9 Hurdles to development have discouraged companies from investing in developing treatments for these diseases7,8 For example… However, several classes of medications are available to treat other neurologic diseases such as relapsing multiple sclerosis and migraine.3 Historically, the probability that a trial in some neurologic disorders will show positive results is low. However, this outcome would have a massive impact on the experience of millions of patients.1 This emphasizes the need for innovation and research on how to bring drugs to approval in this disease area.

1.2 Efforts to accelerate drug development

To reduce the risk of exposing patients to ineffective and/or unsafe treatments, modern drug development systems use a phased approach since the 1960s (1-4), with each phase increasing cost and number of patients enrolled. The goals of each phase vary across disease areas and the phase priorities are occasionally flexible.11 In neurology, phase 1 (P1) trials focus on gathering pharmacokinetic data and safety information for the treatment in humans. Next P2 trials usually aim to collect safety and dose relationships while also gathering preliminary information on the efficacy of the new treatment using surrogate endpoints.11 P2 trials are sometimes separated into 2a (which look mainly at safety, tolerability, and proof of concept),12 and 2b (which test for efficacy). Next, phase 3 (P3) trials aim to determine whether there are sufficient signals that the drug is efficacious to move forward to approval. Finally, phase 4 (P4) trials are typically run post-approval to widen the approved population and/or gather additional safety data.

Although this four-step paradigm has been a mainstay for decades, many drug developers use different approaches. For example, when interventions have shown exceptional promise in P2 trials, some commentators have called for bypassing P3 trials and going directly to approval without this extra layer of evidence gathering.13 Other designs, such as phase 1/2 or 2/3, create seamless transitions from phase to phase, using fewer patients, time, and resources – at least in the ideal.14–19 In neurology, other techniques for accelerating drug development include shortening P2 trials,15 using basket or platform trials,12 historical controls,20 pragmatic P3 trials,21 enrichment designs,22 adaptive trials,23 and futility designs.23,24 For example, recent trials investigating treatments for amyotrophic lateral sclerosis,25 Alzheimer’s disease,26 and Parkinson’s disease27 have used various innovative trial designs to improve drug development efficiency.

1.3 P2 Bypass

The present thesis will focus on a practice less reliant on novel trial methodologies: abridgment of the phased approach to clinical development.” In particular, we will focus on the practice of initiating P3 trials without positive efficacy evidence from a P2 trial investigating the same treatment in the same disease area (“P2 bypass”). In these cases, researchers initiating P3 trials may rely on data from other indications or drugs to infer promise for a particular drug-indication pairing. For example, P3 trial investigators can extrapolate from trials looking at a similar drug in the same indication28 or the same drug but a similar indication.21,29 Alternatively, investigators sometimes run P2 trials that are not primarily aimed at investigating efficacy but rather at investigating safety or pharmacokinetics. Finally, investigators may launch P3 relying on positive signals from secondary or subgroup analyses in an otherwise negative P2 trial.. There are many instances of P3 trials that bypassed P2 trials in neurology.21,30–32 This practice raises the question of how much evidence is sufficient to proceed to P3?”19

A previous study of the present author suggests that in other disease areas, P2 bypass is common and potentially problematic. We found that 47% of P3 cancer trials bypass P2 trials and that the risk/benefit balance for participating patients was significantly diminished compared to P3 trials preceded by positive P2 trials. However, these trends may differ in neurology as the drug development landscape is vastly different. For example, there are significantly fewer clinical trials in neurology than in cancer, and trials typically run longer. The treatments investigated in neurology are often palliative.33 Contrary to oncology, where bypassing may be due to encouraging early safety or efficacy signals, researchers who bypass P2 trials in neurology may be influenced by an absence of biomarkers, low “pipeline density” \*(i.e.), the lack of surrogate endpoints that could be used as a readout of promise in phase 2 trials,3,34 and desperation to find new treatments for a population with little to no options.21,35 Other reasons companies might bypass P2 include market pressures, intense competition between companies, and the vast potential for payoff if successful.30

Bypassing a P2 trial, if the treatment proves effective, would likely reduce the time it takes for a treatment to be approved. However, some reviews highlight the importance of P2 trials in neurology drug development and admonish against bypassing P2 trials.6,29,36 This is because P3 trials that bypass P2 are initiated with a lower amount of evidence available to optimize dose, safety, efficacy, and population details. This may limit the chance that a P3 trial will be successful. Alternatively, other reviews introduce P2 bypass as a viable trajectory to limit drug development time in neurology.37

1. **The purpose of P2 trials in neurology**

To understand potential justifications for bypassing P2 trials, it is first important to understand the role of P2 trials in traditional neurologic drug development. Together with P1 trials, P2 trials make up what some commentators call the “learn zone”38 of drug development, where researchers collect data that has “a significant impact on future trial size, expense, and risk.”11 The information learned from P2 trials helps generate knowledge on the “intervention ensemble”, the package of variables surrounding the treatment that must be researched to make it clinically meaningful.39 In addition, guidance from the FDA states that “sponsors assess P2 results to determine if the preliminary results are sufficiently promising to justify a phase 3 study”37

In this section, we will describe the current literature on three elements typically investigated in P2 trials to inform the design of future trials: dose/schedule, preliminary efficacy, and population. We will then review how P2 findings can be used to shape subsequent trials and make go/no-go decisions.

2.1 Dose and schedule

The first task of a typical P2 trial in neurology is to find a roughly optimal dose and schedule for administering the drug.28,29,40–43 This is a stage where, using many doses, researchers can begin to see a dose relationship in their safety and efficacy endpoints.11 Dose optimization is important to find a high enough dose that treatments are efficacious but low enough to limit toxicity.

Information gained from P2 trials can help ensure that the a safe dose is moved forward to P3 testing. In CNS disorders this is critical because drugs treating these conditions are often taken for prolonged periods such that safety issues might emerge with chronic exposure. As well, CNS drugs can affect the core of who we are and cause adverse psychiatric outcomes, such as suicidal behavior.3,11 Many doses are changed (mostly lowered) after FDA approval due to safety concerns.44,45 One study investigating these post-approval modifications found that dose changes were most common in neurologic drugs.46 These findings show the importance of investigating dose and safety relationships prior to approving a new treatment. P2 trials serve as an opportunity to do so before investing in a P3 trial. In addition, reviews of P3 trials investigating treatments for Alzheimer’s disease,47,48 traumatic brain injury,40,49,50 and stroke23 have postulated that the lack of prior dose optimization may have led to non-positive outcomes.

2.2 Efficacy

The second task of a P2 trial is to begin to evaluate whether the drug has promise for treating a condition. Ideally, these trials would use clinical endpoints so that researchers could determine if the treatment impacts the illness course of patients with the condition. However, in some chronic neurologic diseases, using clinical outcomes to measure efficacy would significantly prolong clinical trial duration or demand large sample sizes, thus defeating the purpose of P2 evaluation.28,29,43,51 In these cases, P2 trials may use endpoints that are surrogates for the clinical outcomes.3,34 For example, a useful endpoint to investigate treatments for patients with RMS is annualized relapse rate, but this endpoint typically takes years to measure. Researchers instead use MRI measures of lesions to evaluate disease progression much quicker. Endpoints such as these can be powerful when validated because of their ability to decrease trial duration or sample size.38 BAD aspects about surrogates-not validatied Surrogate endpoints are especially widespread in Alzheimer’s drug development, where the lack of validated surrogate endpoints to use in P2 trials has led to the initiation of P3 trials without any indication that there is a clinical effect.35 Some commentators argue that reliance on these endpoints may have played a role in recent non-positive P3 trial results for Semagacestat37 and Solanezumab30 in Alzheimer’s disease.

Because of these difficulties, investigating clinical or surrogate efficacy is often not the primary goal of P2 trials in neurology.28 In these cases, trials may rely more on “proof of concept” endpoints. These endpoints simply show that the drug has the desired effect on a target, which sponsors assume will have the desired therapeutic effect. Proof of concept may be a vital minimum level of efficacy to show in early trials.52–54 For example, several P3 trials were initiated for treatments in amyotrophic lateral sclerosis55 and Alzheimer’s disease56 without showing proof of concept before initiation, and were ultimately non-positive.

2.3 Relevant patient populations

Finally, the above variables are all investigated and optimized within a patient population of interest. There can be vast heterogeneity of disease presentation and baseline characteristics between patients with the same condition, such as differences in patients’ line of treatment, subgroup disease classification, genetic status, and disease severity.12,57 Determining which type of patients to optimize the treatment to can take trial and error. Sometimes, sponsors expand patient populations beyond those which have been investigated in P2 trials. However, this practice may jeopardize the generalizability of the supporting evidence for a trial or clinical application. In particular, the prior safety evidence may not indicate how patients with more severe disease will respond.36,41 Nevertheless, broadening the population may be necessary to ensure that patients beyond a restrictive trial population can benefit from a later approval.11 Alternatively, investigators can further restrict a population from a P2 trial using evidence from subgroups. However, extrapolation from subgroup populations to guide the design of P3 can lead to nonpositive results,14,51,54 shown by examples in RRMS,30 PMS,29 and AD.30,51

2.4 Deciding to initiate a P3 trial

Information on these variables (especially efficacy) in P2 trials can help guide “go/no-go” decisions for further testing in order to limit waste in drug development.12,53 For example, P2 trials can be used to weed out drugs that are not likely to be successful early in the development process.29,51 One analysis from 2015 found that P3 CNS drugs were almost 50% less likely to move from the P3 trial to approval than all other indications but that P2 and P1 trials were not more likely to be “unsuccessful”. This indicates that P3 trial initiation in neurology may be ill-informed.58

However, researchers are unclear on the type of efficacy evidence (proof of concept, surrogate, or clinical) to use as an indicator that the intervention should be brought into P3 trials in neurology. Current guidelines in ALS28, PMS29, and AD51,54 suggest that P3 trials can be initiated without apparent clinical efficacy but not without proof of concept, dose information on safety, and a defined population. This step may be an important method of “de-risking” the P3 trial from negative outcomes.54 In these cases, P3 trial designers will learn from other aspects of the P2 trial to optimize the intervention ensemble. Similarly, researchers who run P2 trials that have clinical efficacy endpoints but get a non-positive result will learn from other aspects of the P2 trial to optimize the intervention. However, they have also been given reason to believe that the treatment may not be effective and to stop further investment (a no-go signal). More research is needed to understand how P3 trial success is impacted by the type of evidence available to guide their design.

Transition…

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

In what follows, we will review

that this section addresses the ethical stakes of bypass

better connection to the previous section.

* 1. Efficiency

Trials have not “failed” when researchers find that an experimental treatment does not improve patient outcomes. Rather, these instances can be opportunities to learn more about a disease and treatment target.47,59,60 However, the stage of the development process in which a treatment is abandoned can profoundly impact the cost, time and number of patients involved in the endeavor.

Researchers have proposed that bypassing P2 trials would only be reasonable if there were unlimited resources for researchers to use in clinical trials. This way, there would be no cost to researching ineffective therapies.61 The reality of drug development is far from this ideal as the cost of running a P2 or P3 trial differs significantly. Although reporting on average costs of different phases is sparce,62 one review estimated that the median cost of a P2 trial was $8.6 million and that P3 trials cost $21.4 million.63 In a review of trials investigating treatments for Alzheimer’s disease, the cost/time of a P3 trial was roughly double that of a P2 trial.1

The efficiency of bypassing P2 trials differs depending on the outcome of the P3 trial. For example, suppose researchers bypass a P2 trial and the subsequent P3 trial is positive. In this case, bypassing a P2 trial likely saved money and time compared to running both a P2 and P3 trial. However, in situations in which researchers bypass P2 trials and the following P3 trial is nonpositive, resources may have been a wasted by the sponsor’s failure to first perform a P2 trial (provided it would have been possible to find the non-positive result in P2). In addition, investigators may not know if this result was due to truly ineffective drugs or the lack of evidence on the intervention ensemble. The later would require more testing and add to the cost and time to bring that treatment to approval.

In addition to research costs and time to development, patients are an essential resource to consider. There is no research, to the best of our knowledge, describing the average number of patients in P2 or P3 trials in neurology nor the number of hours that these participants contribute of their time. Still, a P3 trial would likely use greater amounts of both resources. This donation of time, especially for patients who are made vulnerable by their conditions, should be optimized for the greatest possible return on investment.

* 1. Risks and benefits to patient participants

One way to protect participating patients is to consider the concept of clinical equipoise. Freedman argued that two tenets of clinical equipoise must be fulfilled for researchers to justify randomizing patients to receive an experimental treatment rather than providing them with the standard of care out of a trial: 1) disagreement amongst experts on whether the experimental or control treatment will be better for patients and 2) the trial's ability to quell this disagreement.66 Bypassing P2 trials has implications for both

To the first point, when deciding whether to approve a trial, IRBs should discuss whether existing data have given the expert community reason enough to believe that the experimental arm may be better for patients than the standard of care. When reviewing a P3 trial that bypassed P2, IRBs will likely have less available evidence to consider on the intervention ensemble, efficacy, and safety for the new treatment. In this case, the expert community, with access to data (or lack thereof), would likely have reason to question whether the experimental treatment could be better for patients than the standard of care. Thus, equipoise may be more tenuous for a P3 trial designed with little prior evidence.

To the second point, a non-positive P3 trial that bypassed P2 may be less capable of changing expert opinion. This is because the non-positive result could be due to an ineffective treatment or the lack of intervention ensemble optimization. One review of go/no go decisions in CNS development said it well: “from a scientific perspective, its optimal only to 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.”53

In addition, a P3 trial investigating Verubecestat to treat Alzheimer’s disease bypassed P2 and had significantly worse cognitive outcomes and safety profiles in the experimental arm.64

Write a concluding sentence here.

**Conclusion**

Write after confirm structure with JK…

References

1. Dorsey ER, Johnston SC. The Impact of Clinical Trials in Neurology. In: Ravina B, Cummings J, McDermott M, et al. (eds) *Clinical Trials in Neurology: Design, Conduct, Analysis*. Cambridge: Cambridge University Press, pp. 1–7.

2. Feigin VL, Nichols E, Alam T, et al. Global, regional, and national burden of neurological disorders, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology* 2019; 18: 459–480.

3. Gribkoff VK, Kaczmarek LK. The need for new approaches in CNS drug discovery: Why drugs have failed, and what can be done to improve outcomes. *Neuropharmacology* 2017; 120: 11–19.

4. Kimmelman J. Ethics in Clinical Trials Involving the Central Nervous System:: Risk, Benefit, Justice, and Integrity. In: Ravina B, Cummings J, McDermott M, et al. (eds) *Clinical Trials in Neurology: Design, Conduct, Analysis*. Cambridge: Cambridge University Press, pp. 173–186.

5. Pardridge WM. CSF, blood-brain barrier, and brain drug delivery. *Expert Opinion on Drug Delivery* 2016; 13: 963–975.

6. O’Neill GN. Unique Challenges in The Development of Therapies for Neurological Disorders. In: Ravina B, Cummings J, McDermott M, et al. (eds) *Clinical Trials in Neurology: Design, Conduct, Analysis*. Cambridge: Cambridge University Press, pp. 19–27.

7. Miller G. Is Pharma Running Out of Brainy Ideas? *Science* 2010; 329: 502–504.

8. Choi DW, Armitage R, Brady LS, et al. Medicines for the mind: policy-based ‘pull’ incentives for creating breakthrough CNS drugs. *Neuron* 2014; 84: 554–563.

9. Kaitlin K. CNS Drugs Take Longer to Develop and Have Lower Success Rates Than Other Drugs, According to the Tufts Center for the Study of Drug Development. *Tufts University, Tufts Center for the Study of Drug Development;*, https://www.globenewswire.com/news-release/2014/11/04/1187459/0/en/CNS-Drugs-Take-Longer-to-Develop-and-Have-Lower-Success-Rates-Than-Other-Drugs-According-to-the-Tufts-Center-for-the-Study-of-Drug-Development.html (2014, accessed 14 March 2023).

10. Plascencia-Villa G, Perry G. Status and future directions of clinical trials in Alzheimer’s disease. *Int Rev Neurobiol* 2020; 154: 3–50.

11. Poole RM. The Sequence of Clinical Development. In: Ravina B, Cummings J, McDermott M, et al. (eds) *Clinical Trials in Neurology: Design, Conduct, Analysis*. Cambridge: Cambridge University Press, pp. 8–18.

12. Friedman LG, McKeehan N, Hara Y, et al. Value-Generating Exploratory Trials in Neurodegenerative Dementias. *Neurology* 2021; 96: 944–954.

13. Harmon A. New Drugs Stir Debate on Rules of Clinical Trials. *The New York Times*, 19 September 2010, https://www.nytimes.com/2010/09/19/health/research/19trial.html (19 September 2010, accessed 7 March 2023).

14. Cummings J, Aisen PS, DuBois B, et al. Drug development in Alzheimer’s disease: the path to 2025. *Alzheimers Res Ther* 2016; 8: 39.

15. Scott TJ, O’Connor AC, Link AN, et al. Economic analysis of opportunities to accelerate Alzheimer’s disease research and development. *Ann N Y Acad Sci* 2014; 1313: 17–34.

16. Hunsberger S, Zhao Y, Simon R. A Comparison of Phase II Study Strategies. *Clin Cancer Res* 2009; 15: 5950–5955.

17. Thall PF. A review of phase 2-3 clinical trial designs. *Lifetime Data Anal* 2008; 14: 37–53.

18. Coffey CS. Adaptive Design Across Stages of Therapeutic Development. In: Ravina B, Cummings J, McDermott M, et al. (eds) *Clinical Trials in Neurology: Design, Conduct, Analysis*. Cambridge: Cambridge University Press, pp. 91–100.

19. Cummings JL. Optimizing phase II of drug development for disease-modifying compounds. *Alzheimers Dement* 2008; 4: S15-20.

20. Jahanshahi M, Gregg K, Davis G, et al. The Use of External Controls in FDA Regulatory Decision Making. *Ther Innov Regul Sci* 2021; 55: 1019–1035.

21. Schneider LS. Pragmatic Trials and Repurposed Drugs for Alzheimer Disease. *JAMA Neurol* 2020; 77: 162–163.

22. Fournier CN. Considerations for Amyotrophic Lateral Sclerosis (ALS) Clinical Trial Design. *Neurotherapeutics* 2022; 19: 1180–1192.

23. Qureshi AI, Lobanova I, Huang W, et al. Lessons Learned from Phase II and Phase III Trials Investigating Therapeutic Agents for Cerebral Ischemia Associated with Aneurysmal Subarachnoid Hemorrhage. *Neurocrit Care* 2022; 36: 662–681.

24. Yeatts SD. Novel Methodologic Approaches to Phase I, II, and III Trials. *Stroke* 2013; 44: S116–S118.

25. HEALEY ALS Platform Trial, https://clinicaltrials.gov/ct2/show/NCT04297683 (2023, accessed 17 June 2023).

26. Howard R, Zubko O, Bradley R, et al. Minocycline at 2 Different Dosages vs Placebo for Patients With Mild Alzheimer Disease: A Randomized Clinical Trial. *JAMA Neurology* 2020; 77: 164–174.

27. Creanor S, Vickery J, Eyre V, et al. Two-arm randomised futility trials: PD-stat - a futility trial of a potential neuroprotective treatment in people with Parkinson’s disease. *Trials* 2015; 16: P236.

28. van den Berg LH, Sorenson E, Gronseth G, et al. Revised Airlie House consensus guidelines for design and implementation of ALS clinical trials. *Neurology* 2019; 92: e1610–e1623.

29. Ontaneda D, Fox RJ, Chataway J. Clinical trials in progressive multiple sclerosis: lessons learned and future perspectives. *Lancet Neurol* 2015; 14: 208–223.

30. Gold M. Phase II clinical trials of anti–amyloid β antibodies: When is enough, enough? *Alzheimers Dement (N Y)* 2017; 3: 402–409.

31. Egan MF, Kost J, Tariot PN, et al. Randomized Trial of Verubecestat for Mild-to-Moderate Alzheimer’s Disease. *New England Journal of Medicine* 2018; 378: 1691–1703.

32. Budd Haeberlein S, Aisen PS, Barkhof F, et al. Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer’s Disease. *J Prev Alzheimers Dis* 2022; 9: 197–210.

33. Feustel AC, MacPherson A, Fergusson DA, et al. Risks and benefits of unapproved disease-modifying treatments for neurodegenerative disease. *Neurology* 2020; 94: e1–e14.

34. Fox RJ, Chataway J. Advancing Trial Design in Progressive Multiple Sclerosis. *Mult Scler* 2017; 23: 1573–1578.

35. Mullane K, Williams M. Alzheimer’s disease (AD) therapeutics – 1: Repeated clinical failures continue to question the amyloid hypothesis of AD and the current understanding of AD causality. *Biochemical Pharmacology* 2018; 158: 359–375.

36. Mitsumoto H, Brooks BR, Silani V. Clinical trials in amyotrophic lateral sclerosis: why so many negative trials and how can trials be improved? *Lancet Neurol* 2014; 13: 1127–1138.

37. Commissioner O of the. 22 Case Studies Where Phase 2 and Phase 3 Trials Had Divergent Results. *FDA*, https://www.fda.gov/about-fda/reports/22-case-studies-where-phase-2-and-phase-3-trials-had-divergent-results (2019, accessed 11 October 2020).

38. Holloway RG, Siderowf AD. Selecting Outcome Measures. In: Ravina B, Cummings J, McDermott M, et al. (eds) *Clinical Trials in Neurology: Design, Conduct, Analysis*. Cambridge: Cambridge University Press, pp. 69–77.

39. Kimmelman J, London AJ. The Structure of Clinical Translation: Efficiency, Information, and Ethics. *Hastings Center Report* 2015; 45: 27–39.

40. Howard RB, Sayeed I, Stein DG. Suboptimal Dosing Parameters as Possible Factors in the Negative Phase III Clinical Trials of Progesterone for Traumatic Brain Injury. *J Neurotrauma* 2017; 34: 1915–1918.

41. Lammertse D, Tuszynski M, Steeves J, et al. Guidelines for the conduct of clinical trials for spinal cord injury as developed by the ICCP panel: clinical trial design. *Spinal Cord* 2007; 45: 232–242.

42. Stein DG. Lost in translation: understanding the failure of the progesterone/traumatic brain injury Phase III trials. *Future Neurology* 2016; 11: 9–13.

43. Bullock MR, Merchant RE, Choi SC, et al. Outcome measures for clinical trials in neurotrauma. *Neurosurg Focus* 2002; 13: ECP1.

44. Peck CC, Cross JT. “Getting the Dose Right”: Facts, a Blueprint, and Encouragements. *Clinical Pharmacology & Therapeutics* 2007; 82: 12–14.

45. Peck C. Preventing Postmarketing Changes in Recommended Doses and Marketing Withdrawals. In: Venitz J, Sittner W (eds) *Appropriate Dose Selection — How to Optimize Clinical Drug Development*. Berlin, Heidelberg: Springer, 2007, pp. 209–216.

46. Cross J, Lee H, Westelinck A, et al. Postmarketing drug dosage changes of 499 FDA-approved new molecular entities, 1980-1999. *Pharmacoepidemiol Drug Saf* 2002; 11: 439–446.

47. Toyn J. What lessons can be learned from failed Alzheimer’s disease trials? *Expert Review of Clinical Pharmacology* 2015; 8: 267–269.

48. Mehta D, Jackson R, Paul G, et al. Why do trials for Alzheimer’s disease drugs keep failing? A discontinued drug perspective for 2010-2015. *Expert Opinion on Investigational Drugs* 2017; 26: 735–739.

49. Schumacher M, Denier C, Oudinet J-P, et al. Progesterone neuroprotection: The background of clinical trial failure. *J Steroid Biochem Mol Biol* 2016; 160: 53–66.

50. Stein DG. Embracing failure: What the Phase III progesterone studies can teach about TBI clinical trials. *Brain Inj* 2015; 29: 1259–1272.

51. Greenberg BD, Carrillo MC, Ryan JM, et al. Improving Alzheimer’s disease phase II clinical trials. *Alzheimers Dement* 2013; 9: 39–49.

52. Vissers MFJM, Heuberger JAAC, Groeneveld GJ. Targeting for Success: Demonstrating Proof-of-Concept with Mechanistic Early Phase Clinical Pharmacology Studies for Disease-Modification in Neurodegenerative Disorders. *Int J Mol Sci* 2021; 22: 1615.

53. Potter WZ. Optimizing early Go/No Go decisions in CNS drug development. *Expert Rev Clin Pharmacol* 2015; 8: 155–157.

54. Cummings J. Lessons Learned from Alzheimer Disease: Clinical Trials with Negative Outcomes. *Clin Transl Sci* 2018; 11: 147–152.

55. A controlled trial of recombinant methionyl human BDNF in ALS: The BDNF Study Group (Phase III). *Neurology* 1999; 52: 1427–1433.

56. Selkoe DJ. Resolving controversies on the path to Alzheimer’s therapeutics. *Nat Med* 2011; 17: 1060–1065.

57. Feltner DE, Evans KR. Phase II development and the path to personalized medicine in CNS disease. *Essential CNS Drug Development* 2012; 70–91.

58. Kesselheim AS, Hwang TJ, Franklin JM. Two decades of new drug development for central nervous system disorders. *Nature Reviews Drug Discovery* 2015; 14: 815–816.

59. London AJ, Kimmelman J. Why clinical translation cannot succeed without failure. *eLife* 2015; 4: e12844.

60. Knopman DS. Lowering of Amyloid-Beta by β-Secretase Inhibitors - Some Informative Failures. *N Engl J Med* 2019; 380: 1476–1478.

61. Rubinstein LV, Korn EL, Freidlin B, et al. Design issues of randomized phase II trials and a proposal for phase II screening trials. *J Clin Oncol* 2005; 23: 7199–7206.

62. Speich B, von Niederhäusern B, Schur N, et al. Systematic review on costs and resource use of randomized clinical trials shows a lack of transparent and comprehensive data. *J Clin Epidemiol* 2018; 96: 1–11.

63. Martin L, Hutchens M, Hawkins C, et al. How much do clinical trials cost? *Nat Rev Drug Discov* 2017; 16: 381–382.

64. Doggrell SA. Lessons that can be learnt from the failure of verubecestat in Alzheimer’s disease. *Expert Opinion on Pharmacotherapy* 2019; 20: 2095–2099.

65. Moyer H, Bittlinger M, Nelson A, et al. Bypassing phase 2 in cancer drug development erodes the risk/benefit balance in phase 3 trials. *J Clin Epidemiol* 2023; S0895-4356(23)00079–3.

66. Freedman B. Equipoise and the Ethics of Clinical Research. *New England Journal of Medicine* 1987; 317: 141–145.