**Introduction**

Neurological conditions include some of the most prevalent conditions of modern life, mostly due to demographic transitions and developing global economies.1 In fact, one 2016 estimate found that this disease area was the most common cause of DALYs and second most common cause of deaths globally.2 Despite being one of the most disabling disease areas, neurological drug development has proven more challenging than other disease areas, with some indications lacking any established, disease modifying standard of care (SOC).3 The difficulties in the development area start 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 have trouble ensuring that the drug is transported across the blood-brain barrier.3,4 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 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.5 There are additional risks because modifying brain chemistry can impact personality and emotion.3

These factors together create an area of drug development where investment in the field is relatively risky and has a low chance of success (between 6-9%).6–8 One review found that CNS drugs were half as likely to be approved as other indications.8 Over time, R&D expenditures have increased in all areas, but there has not been an associated increase in approvals in neurologic drug development.This has resulted in diminished investment in neurological drug development6,7 and lower numbers of applications for funding by the NIH for neuroscience research.9 However, although the probability that a trial in some neurological disorders will find a successful drug historically is very low, positive results would have a massive impact on the population.1 This emphasizes the need for innovation and research on how to bring drugs to approval in this disease area.

Generally, drug development follows a phased approach (1-4), each with a different goal 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 safety and dose relationships while also gathering preliminary information on the efficacy of the new treatment using surrogate endpoints.10 Phase 2 trials are sometimes separated into Phase 2a (which look mainly at safety, tolerability, and proof of concept)11 and 2b (which test for efficacy). Next, P3 trials aim to determine whether there are 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.10

There are calls for new and 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.7 For example, when interventions ahve shown exceptional promise in P2 trials have shown exceptional promise, some commentators called for bypassing P3 trials and going directly to approval without this extra layer of evidence gathering.12 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).13–18 In neurology, other techniques for speeding up drug development include shortening P2 trials,14 using basket or platform trials,11 historical controls,19 pragmatic phase 3 trials,20 and futility designs.21

The present thesis will focus on a method less widely characterized and understood, which we call “P2 bypass.” defined for our purposes as the practice of initiating P3 trials without positive evidence from a P2 trial. This might occur when drug developers skip phase 2, or…… [describe]. 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 in neurology.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 indication.20,26 It is also possible that some variables typically reserved for P2 trials were studied in P1 trials. Alternatively, investigators sometimes run P2 trials but persevere after obtaining a nonpositive result on their clinical outcomes. We will use all these cases to mean P2 bypass.

A previous study, completed by the present author, suggests that 47% of P3 cancer trials bypass 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 for neurikogy trials(?) 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 an absence of biomarkers, low “pipeline density,” the lack of surrogate endpoints3,28 and desperation to find treatment options for a population with little to no treatment options, a practice termed “hail Mary”.20,29 Other reasons companies might bypass P2 evidence include the “academic industrial complex,” market pressures, intense competition between companies, or the vast potential for payoff if successful.22 Bypassing P2, if a treatment proves effective, would likely speed up the time it takes for the treatment to be approved. However, some reviews explicitly note the importance of P2 trials in neurology drug development and admonish against bypassing P2 trials.5,26,30 The lower amount of evidence available to shape the P3 trial after bypassing may limit its chance of being successful.

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

**The purpose of P2 trials in neurology**

To understand whether it 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 what some commentators call the “learn zone”31 of drug development, where you can collect data that has “a significant impact on future trial size, expense, and risk.”10 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”32 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 drug development trajectory. In what follows, we will discuss three variables typically investigated in P2 trials and how the lack of each may impact future trials.

Dose and schedule

The first task of a typical P2 trial in neurology is to find the optimal dose and schedule for administering the drug.25,26,33–36 This is a stage where, using many doses (under the maximum tolerated dose found in P1 trials), researchers can begin to see a dose relationship in the safety and efficacy endpoints.10 Firstly, the information collected from a P2 trial can help ensure that a safe dose is moved forward to P3 testing. This can be critical in CNS disorders 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. Drugs can affect personality… or Also, CNS drugs often? Sometimes… cause adverse psychiatric outcomes, such as suicidal behavior.3,10 Data show that many doses are changed (mostly lowered) after FDA approval due to safety concerns. Dose changes practice that was most common in neurological drugs.37 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. Secondly, 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 P2 trials may have contributed to the P3 result. They suggest that P2 trials should be used to optimize dose before progression to P3 to increase the likelihood that the P3 trial is successful.33

Efficacy

In addition to the relationship between dose and safety?, the second task of a P2 trial is to begin to evaluate whether the drug has the desired impact on the condition. Ideally, these trials would use clinical endpoints so that researchers can determine if the treatment impacts the livelihood of patients with the condition. However, in some chronic neurological diseases, relying on clinical effects would significantly prolong clinical trial duration.25,26,36,38 For example... 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 predictors of clinical outcomes, 3,28 though they can be powerful when validated because of their ability to decrease trial duration.31 This is especially prevalent in AD development, where the lack of validated surrogate biomarkers to use in P2 trials may lead to the initiation of P3 trials without any indication that there is a clinical relationship.29 Reliance on these endpoints may hurt the chance of positive results in P3 trials, as was the case with Semagacestat32 and Solanezumab.22

Because of these difficulties, investigating clinical efficacy is often not the primary goal of P2 trials in neurology.25 In these cases, trials may rely more on “proof of concept” endpoints. These can be an important step to provide evidence that the treatment is at least working how it is hypothesized. These endpoints simply show that the drug has the desired effect on a target, which sponsors assume will have the desired therapeutic effect, and can be a vital minimum level of efficacy to show in early trials.39,40 For example, there have been several P3 trials initiated for treatments in ALS41 and AD42 that did not show proof of concept before initiation that were ultimately non-positive. It is unclear which type of efficacy evidence (proof of concept, surrogate, or clinical) should be collected before P3 trial initiation in neurology.

Relevant patient populations

Finally, the above variables are all investigated and optimized within a patient population of interest. There can be vast heterogeneity between patients of the same condition, determined by the line of treatment, subgroup disease classification, genetic status, severity, and countless other variables that can impact a patient's outcome.11,43 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. This may jeopardize the generalizability of the supporting evidence for a trial or clinical application. In particular the prior safety evidence.30,34 However, this may be necessary to ensure that more patients can benefit from the approval than a restrictive population.10 Alternatively, they can further restrict a population from a P2 trial using evidence from subgroups. However, when these are not preplanned, extrapolation from subgroup population analyses in P2 trials to guide the design of P3 can lead to nonpositive results,13,38 shown by examples in RRMS,22 PMS,26 and AD.22,38

Together, this information can help generate knowledge on the “intervention ensemble”, the package of variables surrounding the treatment that must be researched to make it clinically meaningful.44 STOPPED…Information on the variables above can also guide “go/no-go” decisions for further testing to limit waste in drug development.11,40 P2 trials can be used to weed out drugs that are not likely to be successful earlier in the development process.26,38 For treatments 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 subsequent trials.

In addition, sometimes P3 trials are initiated after finding a nonpositive result on a primary efficacy endpoint in a P2 trial. In these case, P3 trial designers will likely learn from other aspects of the P2 trial such as information to help optimize the dose and population. On the other hand, a non-positive result could have been used to decide to cease the development of that treatment option because they have been given reason to believe that it may not be efficacious (a no-go signal).

It is unclear how much evidence is needed to make these decisions. One analysis from 2015 found that Phase 3 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.45 Current guidelines in ALS25, PMS26, and AD38 suggest that P3 trials can be initiated without apparent clinical efficacy but not without proof of concept, dose information on safety, and the population defined.

Transition…

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

The decision to move into a P3 trial and expose large numbers of patients to a new drug should be backed by the greatest chance for success because of limited resources and to protect patient welfare.5 In what follows, I will review how the decision to bypass P2 may impact efficiency in drug development, both in cost to develop a new drug and the number of patients involved, and the risks and benefits for patients involved in the P3 trial.

Efficiency

Finding out that a treatment does not work is not a “failure”, but rather a powerful tool to learn more about a disease and treatment target.46 However, in cases where these phase 3 trials skipped earlier efficacy trials, the cost, time and number of patients may have been limited if the treatment was found to not work in a P2 trial. Rubenstein et al. have proposed that bypassing P2 trials would only be reasonable if the number of drugs starting the pipeline was 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.47 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 the average costs of different phase trials because reporting of such is weak,48 one paper estimated that the median cost of a P2 trial was $8.6 million and that P3 trials cost $21.4 million.49 Using a similar estimate for AD development, finding an ineffective drug in a P3 trial that they could have found with a P2 trial could double the cost of development and the time it takes to find this result.1 Suppose there is a nonpositive result in P3 after bypassing. In that case, 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 develop a new drug. However, this practice would save money and time if the P3 trial is positive after bypassing a P2 trial compared to the case where a P2 is run and followed by a P3 trial.

In addition to research costs and time to development, patients are an essential resource to consider because participating in clinical trials is not without its costs and burdens for patients.50 There is no evidence to the best of our knowledge describing the average number of patients in P2 or P3 trials in neurology nor the number of hours they contribute of their time. Still, a P3 trial will likely use greater amounts of both resources. A few studies have investigated the amount of time different treatments require of patients in clinical care.51–53 One found that 10% of living days involved seeking care for cancer patients.53 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. This donation of patient time, especially for patients who are made vulnerable by their conditions, should be optimized to have the greatest possible return on investment.

Risks and benefits to patient participants

In addition to designing efficient research trajectories, it is essential to consider how bypassing a P2 trial impacts the risks and benefits afforded to patients who participate in these P3 trials compared to patients participating in P3 trials based on 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 as described by Freedman. There are two tenets of clinical equipoise that he argued must be fulfilled to justify randomizing patients in a clinical trial rather than providing them with standard of care. These are 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.54 Bypassing P2 trials has implications for both.

To the first point, P3 trial approval decisions should include a discussion as to whether the existing data has given us reason enough to believe that it is possible that the experimental arm will be better for patients than the standard of care. A trial that does not have affirmative evidence available before 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 could be better for patients than the SOC. Thus, equipoise may be threatened for a P3 trial designed to enroll a large number of patients with little prior evidence. Our paper in oncologic drug development found that those trials that were not supported by P2 trials had significantly worse survival outcomes.

To the second point, a non-positive P3 trial that bypassed may have a lower capability to change expert opinion. This because the non-positive result could have been due to a dose or population issue that could have been found in a P2. One review of go/no go decisions in CNS development said it well: “from a scientific perspective, it 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.”40

**Conclusion**

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It should be noted that neurological disorders are not a monolith. While nearly all AD drugs have failed,55 other neurological diseases such as MS and migraine have several classes of medications that make clinical differences. Stroke and TBI for example have one successful treatment.3 There may be a 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 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.14

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

The dismal neurologic drug development landscape calls for empirical analyses of different development trajectories to find the optimal way 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 still being determined how common this is. One report calls it “rare”11, 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 preceded by a P2 trial that likely provided evidence other than efficacy. This category includes two subgroups: “Non-positive,” where P3 trials were preceded by P2 trials that were non-positive on clinical or validated 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 category, we will learn 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.3 Alternatively, proof of concept P2 trials may be enough to start a P3 trial without sacrificing efficacy.18 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 more desperate for treatment like AD vs. MS and migraine.

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. 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.

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

7. 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.

8. 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).

9. Hall DA, Ramos AR, Gelfand JM, et al. The state of clinical research in neurology. *Neurology* 2018; 90: e1347–e1354.

10. 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.

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

12. 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).

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

14. 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.

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

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

17. 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.

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

19. 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.

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

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

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

23. 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.

24. 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.

25. 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.

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

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

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

29. 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.

30. 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.

31. 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.

32. 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).

33. 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.

34. 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.

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

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

37. 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.

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

39. 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.

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

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

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

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

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

45. 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.

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

47. 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.

48. 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.

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

50. Nipp RD, Lee H, Gorton E, et al. Addressing the Financial Burden of Cancer Clinical Trial Participation: Longitudinal Effects of an Equity Intervention. *Oncologist* 2019; 24: 1048–1055.

51. Munro AJ, Sebag-Montefiore D. Opportunity cost--a neglected aspect of cancer treatment. *Br J Cancer* 1992; 65: 309–310.

52. Henry DH, Viswanathan HN, Elkin EP, et al. Symptoms and treatment burden associated with cancer treatment: results from a cross-sectional national survey in the U.S. *Support Care Cancer* 2008; 16: 791–801.

53. Bange EM, Doucette A, Gabriel PE, et al. Opportunity Costs of Receiving Palliative Chemotherapy for Metastatic Pancreatic Ductal Adenocarcinoma. *JCO Oncology Practice*. Epub ahead of print 4 March 2020. DOI: 10.1200/JOP.19.00328.

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

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