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Economics to the Rescue: Balancing Innovation and Access to High-Cost Therapies

Habilitation Thesis

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Abstract

This habilitation thesis explores the intersection of health economics, regulatory policy, and innovation, focusing on the real-world challenges posed by high-cost, potentially transformative medical therapies. As global healthcare systems grapple with aging populations, increasing complexity of care, and the rising costs of pharmaceuticals—particularly those with uncertain clinical effectiveness—this work applies economic frameworks to inform equitable, sustainable, and evidence-based access strategies.

The thesis comprises five core studies, each contributing to a nuanced understanding of market dynamics and policy design for novel therapies. First, it presents a theoretical foundation for alternative payment models (APMs) for pharmaceuticals, demonstrating that while uniform pricing can be efficient under ideal conditions, market failures—such as payer fragmentation, asymmetric beliefs, agency problems, and treatment adherence issues—can justify the use of value-based pricing and performance-based agreements.

Second, the thesis includes an economic evaluation of single-dose, high-cost gene therapies under a fixed budget constraint. Using a case study of congestive heart failure, it demonstrates how deferred payment models (DPMs) can improve clinical outcomes and access by enabling earlier treatment, without increasing overall costs. A Markov model shows that DPMs can significantly reduce mortality and hospital admissions, especially when upfront payments are minimized, while preserving manufacturer revenue and operating within fixed budgets.

Third, the work addresses population-wide therapies for Alzheimer's disease (AD), applying a microsimulation model based on U.S. Health and Retirement Study data. It reveals substantial misalignment between the timing of therapeutic costs and the accrual of benefits across public and private payers. The analysis finds that conventional reimbursement discourages early treatment in commercially insured patients nearing Medicare eligibility. Simulations show that installment-based or pay-for-performance payment models can mitigate this misalignment and support more equitable access.

Fourth, the thesis investigates how non-binding U.S. FDA guidance influences clinical trialist behavior. Drawing on a regression discontinuity in time analysis of AD trials, it demonstrates that FDA draft guidances significantly altered the selection of primary endpoints,

particularly the adoption of the CDR-SB composite measure. These findings underscore the substantial influence of regulatory soft law on evidence generation and, indirectly, on pricing and reimbursement decisions.

Fifth, a systematic review of endpoint selection trends in AD clinical trials complements this analysis by highlighting evolving methodological preferences among trialists. This research shows how trial design is shaped by both scientific and policy-driven forces and raises implications for health technology assessment and payer evaluations.

Collectively, this body of work offers a coherent framework for understanding and addressing the access challenges posed by high-cost therapies. By integrating economic theory, empirical modeling, and policy analysis, it contributes to the design of reimbursement models that can promote both innovation and equitable access. The insights of the presented work support policymakers, payers, and other stakeholders in crafting efficient and fair solutions in an era of rapidly advancing but expensive therapeutic options and serve as foundation for ongoing scholarship in the field.

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1 Introduction

Healthcare systems worldwide are facing growing challenges to financial sustainability due to aging populations, increasingly complex care delivery models, and the rising costs of new therapies. These trends, alongside macroeconomic and geopolitical factors, are intensifying pressure to do more with fewer resources. Yet, the introduction of novel therapies—often for previously incurable diseases—offers a unique opportunity to improve the quality of life for millions, from rare conditions like Duchenne muscular dystrophy to widespread diseases such as Alzheimer's, which affect a growing share of the population.

Drug discovery has never followed a linear path, and the rewards for innovators have varied widely—from just $1 for the patents leading to insulin's discovery to over $100 billion for drugs like Lipitor. This variation stems from multiple factors, including some innovators' willingness to forgo financial rewards in favor of rapid access to their discoveries, the commercial and reimbursement environment that shapes access to therapies (insulin, for instance, remains highly priced in the U.S. despite its inventors' original intent), and the effectiveness and cost-effectiveness of therapies as assessed by robust health economic models. Health technology assessment (HTA) employs various methods to estimate the value of innovative technologies, often using measures like quality-adjusted life years (QALYs) to quantify the incremental benefit of new therapies over standard treatments.

Despite the best efforts of payers (whether commercial insurers, public health plans, or insurance funds) and manufacturers, who produce extensive evidence on the cost-effectiveness of their therapies, access to innovative treatments remains a challenge in both developed and low- and middle-income countries. Hundreds of millions of people still lack access to potentially life-saving treatments, from essential medicines to advanced cancer immunotherapies.

In developed countries, where healthcare budgets tend to represent a growing fraction of the economy as populations get older and need more care, this is particularly frustrating to many people dealing with barriers such as prior authorization, indication (label) restrictions, step therapy mandates and other hurdles introduced by healthcare payers. While these measures aim to ensure the appropriate use of therapies and manage spending, they often create significant hurdles for patients who

could benefit from these treatments, delaying or restricting access to necessary care.

Simple solutions do not exist, but economics may offer tools to address some of the most pressing challenges related to emerging medical therapies. Many of them are very expensive on a unit basis (some reach millions of dollars for just one injection, e.g. in the case of gene therapies that sometimes cost $1 million or more per treatment) and many carry significant uncertainty about their real-world effectiveness (e.g. due to short clinical trial duration or the discrepancy between clinical trial inclusion criteria and the drug's real-world patient population). Such uncertainty and high unit costs seem to contribute to risks in access for several reasons:

- Even if such therapies are deemed cost-effective, their rapid adoption by healthcare systems may result in budget-breaking expenses. This issue, related to the inability of healthcare budgets to deal with rapid changes to spending, has been documented in healthcare systems around the world and resulted in slower uptake of new treatments for conditions such as Hepatitis C and diabetes or weight-loss therapies (Chhatwal et al. 2015; van der Gronde, Uyl-de Groot, and Pieters 2017).
- Clinical trials often test interventions on highly specific patient populations, with real-world use of the same intervention often resulting in different levels of effectiveness than expected (Bartlett et al. 2019). Follow-on expansions of original indications may also result in uncertainty about the cost-effectiveness of therapies across the different patient populations. Initial price negotiations may result in prices that are too high (or too low) given the expanded label, affecting manufacturer behavior.
- Adherence to therapies is often not perfect and factors outside of control of payers and regulators affect the clinical outcomes and subsequently, the cost-effectiveness of high-cost therapies over time. This may vary due to cost-sharing and other factors that contribute to patient-level decision-making, which, too, affects access and sustainability (Rohatgi et al. 2021).
- Trialist behavior is profit maximizing and given both scientific and regulatory uncertainty, strives to optimize decision-making resulting in both drug approval and positive reimbursement determination by healthcare payers. Regulatory guidances, even if non-binding (Emerson 2023), contribute to the selection of primary

endpoints used in clinical trials, which, in turn, affects the way that payers and health technology assessment agencies evaluate the drug's cost-effectiveness and pricing.

Many other factors, which result in worse-than-optimal access to innovative, high-cost medications have been described in literature (Barrios et al. 2023; Gronde, Groot, and Pieters 2017; Sharpe, Barry, and Kefalas 2021) and literature has also described challenges associated with the implementation of innovative payment models (Neumann et al. 2011; O'Connor and Neumann 2006; Vogler et al. 2017).

In this habilitation thesis, I summarize our findings related to innovative payment mechanisms for high-cost pharmaceuticals, including those that respond to uncertainty, disagreement about value, and patient behavior, and discuss how economics can help policy makers navigate thorny issues related to innovative, high-cost therapies in the real-world. I complement this by work related to trialist behavior and the interaction between regulatory guidance and the choice of clinical endpoints.

First, we sought to understand the theoretical foundation for innovative payment models, which offer the promise of addressing existing market failures resulting in suboptimal access, even if drugs are priced cost-effectively. Second, we analyzed how different types of therapeutics may be affected by issues related to real-world uncertainty, high cost and payer fragmentation, with a particular focus on the United States. I include our work on two specific cases, one focusing on a single-dose gene therapy in congestive heart failure (similar to those currently priced at millions of dollars per dose) and one focusing on a population-wide indication, Alzheimer's disease, and emerging biologic therapies in this area. Third, we sought to understand clinical trialist behavior considering regulatory guidances, and on a related note, assessed clinical trial choices with respect to clinical endpoints used to evaluate efficacy of disease-modifying therapies in Alzheimer's disease.

Some of the research questions answered by this work are:

1) What conditions justify the use of alternative payment models for pharmaceuticals?
2) How do current reimbursement and payment mechanism affect access to novel, high-cost therapies, in areas ranging from single-shot gene therapy to chronic treatment of a wide indication?
3) How do regulatory guidances affect the behavior of clinical trialists?

4) What primary endpoints are used in clinical trials of Alzheimer's disease and how does that contribute to our understanding of the value of these therapies?

To answer these and other questions, a range of methods were used, ranging from economic modeling and optimization to Markov models, microsimulation modeling, regression analysis and systematic reviews.

This habilitation thesis provides a commentary on the selected articles, with links to my other works published, and highlights how our findings contribute to broader health economics and policy literature. Given the policy relevance of this research, I also explore how these insights can inform decision-making and enhance population welfare, particularly in the face of the resource constraints that healthcare systems must navigate. By examining how healthcare policies can optimize the allocation of limited resources while maintaining equitable access to care, this thesis underscores the importance of evidence-based strategies in improving health outcomes.

2 The Economics of Alternative Payment Models for Pharmaceuticals

Pharmaceutical pricing has long been a hot issue in health policy. Early research shows that setting drug prices based simply on the number of units sold is problematic compared to pricing them according to the benefits they provide (Goldman et al. 2008). To address this, new payment methods—often called performance-based or outcome-based agreements—have emerged. In these models, the price paid for a drug depends on its clinical effectiveness – how well it works in the real world (Carlson, Chen, and Garrison 2017).

These new models are appealing for several reasons. Payers often have to deal with uncertainty about a drug's future clinical and economic outcomes (Drummond 2015; D. P. Goldman et al. 2018), drugs can also perform differently depending on the condition they treat given the fact that many of them are approved for several indications (Carlson et al. 2017), and there are additional challenges in selecting the most appropriate patients and avoiding wasteful spending (Conrad 2015; Laffont and Martimort 2009). In Europe, alternative payment contracts are explicitly used either to get the most out of health investments (Economist Intelligence Unit 2020) or to keep drug spending under control (Vogler et al. 2017).

Despite hundreds (and possibly more) of these contracts in use around the world, there is little evidence that they deliver net benefits for healthcare systems—especially when the costs of setting them up are taken into account (Mannion and Davies 2008; Neumann et al. 2011). While pricing drugs based on the clinical and economic value they provide seems logical, its application in practice has not become widespread and price determinations are often made at a single point in time based on clinical trial results which suffer from well-documented imperfections (Blonde et al. 2018; Simon et al. 2022; Wilson and Booth 2024).

Value-based or indication-based pricing based on real-world evidence suffers from other challenges, too. European countries continue to deal with challenges related to negotiation frameworks, outcomes and data generation; administrative and implementation hurdles, and limiting laws and regulation (Bohm et al. 2022). In the US., the main hurdles are largely legal and regulatory, though they apply mostly to

some types of novel pricing schemes (Neumann et al. 2011; Sachs, Bagley, and Lakdawalla 2018).

To date, just a few studies have analyzed the economic impacts of value-based pricing. For example, research by Chandra and Garthwaite (2017) suggests that pricing drugs differently for various uses might increase profits for manufacturers rather than lower them. Other researchers (Garber, Jones, and Romer 2006) caution that higher profits for drug developers could lead to excessive spending on some innovation, which might be inefficient. Another study (Pauly 2017a) points out that these pricing models often fail to account for the fact that different patients may value the same health improvement differently.

Our work builds on these ideas by examining when pricing drugs based on their value makes the system more efficient. We start by creating a simple model of how payers (typically insurance companies or government healthcare plans) and drug manufacturers interact in an ideal market. Then, we apply our findings to real-world examples and discuss the challenges of putting these pricing agreements into practice. Ultimately, we argue that while efficient markets may not require value-based pricing, market imperfections can make such pricing schemes beneficial. In cases where the market works well, a single uniform price can be effective, but when failures occur, value-based pricing may offer a valuable corrective tool.

2.1 Theoretical Background

Most pharmaceuticals are uniformly priced despite differences in effectiveness (we refer to uniform pricing as a lack of price variation occurring between most individual payers and drug manufacturers for the majority of products they trade with). While some argue that the variability of clinical effectiveness necessitates more advanced payment models such as indication-based pricing (Preckler and Espín 2022), our theoretical work shows that uniform pricing can yield efficient outcomes on its own.

However, market imperfections—such as incomplete information and misaligned beliefs—may necessitate alternative, value-based pricing structures. In our work (Hlávka et al. 2021), we present a simplified model of efficient interactions among manufacturers, payers, and beneficiaries, where uniform pricing performs well despite variable treatment effects. Using this framework, we then identify specific market

failures that undermine uniform pricing and propose a typology of alternative payment models to address them.

2.2 Contribution of Hlávka et al. (2021)

We posit that treatments are more likely to be covered for patients who benefit more from them, and that insurers can charge higher premiums when providing greater gross surplus (pre-premium surplus) to beneficiaries. These assumptions are valid when insurers possess market power, or when competitive insurers negotiate with powerful drug manufacturers (Lakdawalla and Sood 2013). For simplicity, we assume total premium revenue equals total gross consumer surplus. This assumption, as we will demonstrate, results in a first-best outcome even with a uniform drug price.

In this framework, a patent-protected drug manufacturer with theoretically negligible manufacturing costs negotiates with third-party payers over a uniform drug price and the set of beneficiary groups eligible for the therapy. Beneficiaries $i = 1, \ldots, I$ are classified by type, each with a baseline health status H_i and a treatment benefit expressed as $\Delta_i + \varepsilon_i$, where Δ_i represents the average benefit and ε_i is a normally distributed error with mean zero and variance δ_i^2. Each beneficiary group accrues a gross consumer surplus $G_i(\Delta_i, \delta_i^2)$—increasing in benefit and decreasing in uncertainty—and the model assumes that total premium revenue equals the total consumer surplus, thereby achieving a first-best outcome.

Under Nash bargaining with weights α for the payer and $1 - \alpha$ for the manufacturer, the equilibrium price-utilization agreement solves.

$$\max_{P,i^*} \left[P\sum_{i=1}^{i^*} n(i)\right]^{\alpha} \left[\sum_{i=1}^{i^*} n(i) G_i\left(\Delta_i, \sigma_i^2\right) - P\sum_{i=1}^{i^*} n(i)\right]^{1-\alpha}$$

Our calculation finds that first-best efficiency can be reached because the payer allows access for every type of beneficiary whose gross surplus exceeds the zero marginal cost to manufacture the drug.

The equilibrium price is given by the manufacturer's share of the total surplus, or:

$$P = \frac{\alpha\left(\sum_{i=1}^{i^*} CS_i\left(\Delta_i, \sigma_i^2\right)\right)}{\sum_{i=1}^{i^*} n(i)}$$

This equilibrium allocation ensures that the joint surplus is optimally shared between payers and the manufacturer, rendering variable pricing unnecessary in an efficient market. However, if a binding price ceiling is imposed or if insurance is incomplete due to factors such as deductibles, the model predicts inefficiencies—either overutilization of the drug by low-value groups or underutilization among wealth-constrained patients—that cannot be corrected solely by adjusting pricing strategies.

We presume that manufacturers can bargain with payers rather than setting a single monopoly price. This seems realistic, since manufacturers routinely bargain with public and private payers over prices (Lakdawalla 2018). Both manufacturers and payers have good reason to prefer this approach, since price bargaining leads to more joint surplus for both compared to simple monopoly pricing. Indeed, price bargaining with or without variable pricing strategies produces greater efficiency than simple monopoly pricing.

It is, however, not obvious that bargaining will always make consumers better off. While price-bargaining increases the total amount of gross consumer surplus, insurers with market power may extract these gains in the form of higher premiums. Governments may wish to return some surplus to consumers via taxes on firms and transfers to consumers. We leave the analysis of optimal redistribution policy to future work.

We conclude that in the absence of market failures, there is no need for variable pricing strategies (or alternative payment models), even when the effectiveness of the drug varies.

2.3 Market Failures in the Real World

Each of the failures we identified creates an opportunity for welfare improvements from novel payment strategies. For this discussion, it is convenient to differentiate between "observable heterogeneity" and "unobservable heterogeneity."

- "Observable heterogeneity" means that the benefit of the therapy varies in ways that the payer can readily predict, or that $\Delta_i \neq \Delta_j$ for at least one pair (i, j).
- "Unobservable heterogeneity" means that the benefit of the therapy varies in ways that the payer cannot predict, or that $\sigma_i^2 > 0$ for some value(s) of i.

Above, we showed that observable and unobservable heterogeneity on their own do not justify departures from uniform pricing rules. However, when they intersect with alternative market failures, which we enumerate below, uniform pricing may result in inefficiency.

2.3.1 Uncertainty of patient distribution

Uncertain patient distribution (observable heterogeneity) prevents payers from accurately estimating the number of each patient type receiving treatment, hindering accurate aggregate consumer surplus estimation. This prevents achieving the first-best outcome with a uniform price. However, variable (outcomes-based) pricing, or $P_i = \alpha(CS_i)$, where prices are tied to consumer value, can achieve the first-best without requiring unbiased patient distribution estimates. This yields positive payer surplus for treating patients for whom $CS_i \geq 0$.

This value-based pricing solution requires detailed information on both health outcome and patient valuation variations, which may be impractical. This is especially problematic when those with the greatest health benefits place the lowest value on health improvement (e.g., socioeconomically disadvantaged patients), as documented before (Pauly 2017b). In such cases, health outcomes and consumer surplus may negatively covary, making outcome-based pricing a poor substitute for consumer-surplus-based pricing. For example, intensive diabetes treatments or cardiovascular treatments often disproportionately benefit the poor. Thus, this solution is most effective when patients value health improvements relatively uniformly, and observable health outcome variations accurately reflect consumer surplus variations.

2.3.2 Asymmetric beliefs

"Asymmetric beliefs" occur when payers and manufacturers have different expectations about treatment value (consumer surplus), either due to differing information or uncertainty about treatment effects or patient types. While efficient markets assume aligned expectations, this is not always the case.

The first-best can still be achieved if payment is based on *realized* consumer surplus, not expected, effectively addressing the information asymmetry. This outcome-based payment, determined post-treatment, preserves efficiency even with differing beliefs. For example, if manufacturers believe a treatment is worth x and payers y, the price

could be tied to the *realized* consumer surplus, which may fall between or outside x and y. Hence, any value-based contract should allow for price to reflect the realized consumer surplus (and not be arbitrarily pegged to either x or y) so that the identity $P_i = \alpha CS_i$ holds.

However, the same caveats about varying patient valuations apply. If patients value health differently, especially negatively correlated with treatment effects, identifying contracts linked to consumer surplus may be impossible. The mechanism works best with homogeneous patient valuations.

A special case arises when payers and manufacturers disagree on which therapy yields the highest expected consumer surplus. For instance, if payers prefer an older drug and manufacturers prefer a newer one, single-drug pricing will not resolve this. Outcome-based contracts solve pricing disagreements (Blumenthal, Goldman, and Jena 2017), but not always therapy selection disagreements. Efficiency may be unattainable with competing, controversial treatments (Goldman and Philipson 2007). Thus, value-based pricing is limited where treatment selection is controversial. However, if there is agreement on benefits across treatment stages (e.g., first-line, second-line), reimbursement could vary based on stage-specific consumer surplus.

2.3.3 Payer agency imperfection

"Imperfect agency" arises when payers don't perfectly represent beneficiaries' interests. For example, if a payer covers a therapy with long-term benefits but beneficiaries' coverage is short-term, the payer may only internalize a fraction of those benefits. While more complex than asymmetric beliefs, solutions may exist.

Consider a therapy with long-term benefits where surplus is shared across current and future payers. Theoretically, cost-sharing (each payer pays a proportional share) could achieve the first-best if all agree on treatment benefits. If the total surplus is positive, some payer must perceive positive surplus, and the total willing to pay must equal the total surplus. Payers with negative surplus shares could theoretically be compensated by those with positive shares.

However, practical difficulties remain. Asymmetric beliefs about benefits pose problems, as multiple payers must share similar beliefs with each other *and* the manufacturer. Furthermore, enforcing future payers' responsibility for current treatments is challenging, as they have incentives to renege. Regulatory requirements might be necessary, as

treatment is typically irreversible. Solutions like installment payments across payers have been proposed, but legal and other obstacles (e.g. challenges to inter-payer contracts) complicate this (Phares et al. 2024).

Payer agency issues also exist in single-payer systems. Single-payer decisions don't guarantee perfect internalization of consumer values. They might tie value-based pricing to cost-effectiveness or other methods, which can lack transparency or fail to align with societal value (Jommi et al. 2020). These challenges require a robust and accurate health technology assessment regime, rather than a single solution. Currently, work is underway to explore more suitable methods for value determination, including the Generalized Risk-Adjusted Cost-Effectiveness (GRACE) Approach (Lakdawalla and Phelps 2021). We explore GRACE in ongoing work at the time of this writing.

2.3.4 Provider agency imperfection

Another agency problem involves providers. Efficiency requires that payers, providers, and patient interests align perfectly. While earlier, we noted misalignment between payers and patients, misalignment between physicians and patients is also common (Conrad 2015). Providers may value patient well-being (Chen and Lakdawalla 2019) but also seek profits, which can conflict with patient utility. This conflict can lead to the overuse of profitable therapies and the underuse of less financially rewarding ones, such as preventive treatments.

Here, financial incentives diverge from consumer surplus. One solution is to link provider reimbursement to patient outcomes or total cost rather than profits. This approach, which often involves pricing treatment as a package, has led to payment models like bundled payments, capitation, and shared savings programs designed to mitigate provider incentive issues. A substantial literature examines these models' pros and cons. For example, bundled payment puts providers "at risk for efficient care" during an episode (Conrad 2015). However, such models face challenges, including diagnostic and treatment uncertainties that create performance risks—especially for smaller providers unable to diversify risk—as well as difficulties in defining bundles, establishing acceptable risk-sharing methods, and preventing suboptimal care for sicker patients (Hussey, Ridgely, and Rosenthal 2011).

2.3.5 Patient behavior and treatment adherence

Our model assumes that treatments involve only financial costs. In reality, patients must also invest time and effort—such as adhering to prescriptions and making lifestyle changes. If they do not, the actual benefit Δ_i may be lower than expected. Because payers and manufacturers cannot observe this non-compliance in advance, it creates information asymmetry and differing estimates of consumer surplus (i.e., $CS_i^p \neq CS_i^d \neq CS_i$). The ideal outcome is reached when $P_i = \alpha(CS_i)$, based on the realized surplus, which can be implemented via a value-based contract conditioned on adherence—a model that faces similar challenges as noted above.

2.4 Implications

In our work, we find that the rise of high-cost therapies may be intensifying market failures in healthcare. In response, both public and private payers have debated and sometimes implemented value-based pricing for pharmaceuticals (Carlson et al. 2017; Kesselheim, Avorn, and Sarpatwari 2016). Prior research highlights the need for variable pricing to match variable benefits (Bach 2014) and notes potential cost-savings in single-payer systems like the NHS (Claxton et al. 2008).

However, our analysis shows that variable treatment effects alone do not justify variable pricing over uniform pricing. Efficiency gains from variable pricing occur only when compounded by other market failures—such as uncertainty in patient distribution, asymmetric beliefs about efficacy, agency problems between providers and payers, and issues with patient adherence. Without these failures, payers and manufacturers could efficiently negotiate uniform pricing and formulary rules, even with variable treatment effects, and more efficient pricing strategies do not necessarily lower consumer costs (Chandra and Garthwaite 2017).

Different market failures affect treatments in distinct ways. Therapies for heterogeneous populations risk underutilization when payers limit coverage (e.g., via step-therapy and prior authorization), as seen with gene therapies, Alzheimer's treatments, and off-label uses. Asymmetric beliefs hurt therapies with uncertain long-term efficacy (e.g., emerging cell and gene therapies, hypercholesterolemia drugs). Provider and payer imperfections impact treatments with benefits that

accrue over time (e.g., cures for viral infections, Alzheimer's treatments in older patients), while adherence issues persist in therapies requiring long-term compliance or involving high patient cost-sharing (e.g., insulin, chronic therapies).

Moreover, while our model does not quantify transaction costs, these—and regulatory constraints (such as Medicare's average sales price, Medicaid best price, anti-kickback laws, the 340B program, and off-label promotion rules in the United States) (Pearson et al. 2017; Sachs et al. 2018)—can impede value-based pricing. In ex-US settings, similar issues (including equity concerns (Garner, Rintoul, and Hill 2018)) may affect alternative payment models, and challenges in collecting data on benefits and costs further complicate implementation.

A systematic review conducted by Preckler and Espín (2022) finds that the evidence on the impact of indication-based pricing (as a commonly referenced alternative payment model that may address heterogeneous treatment effects) remains limited, underscoring the need to assess its real-world effects. Establishing an effective pricing and reimbursement model for multi-indication medicines should be prioritized, although this depends on strong political commitment and robust real-world data (RWD) collection systems which are currently lacking in many developed countries.

Other work (Levaggi and Levaggi 2024) adds that indication-based pricing requires that patients are properly stratified—meaning the industry must provide objective evidence of differential drug effectiveness across groups—which can increase costs and delay listing (Jobjörnsson et al. 2016). When only aggregate statistical or surrogate endpoint data are available (Toumi et al. 2017), manufacturers and payers may disagree on a drug's value, with manufacturers often seeking higher prices than regulators find acceptable. In such cases, (performance-based agreements) PBAs can help regulators grant quicker access to new medicines, share preliminary data, and reduce poor coverage decisions. The complexity and burden of evaluating effectiveness in clinical trials further justify alternative (value-based) payment models from the industry's perspective. They are particularly relevant for oncological drugs due to heterogeneous patient responses and sometimes the absence of comparators (Bach 2014; Mailankody and Prasad 2015; Shu and Rizvi 2016). Additionally, while some types of alternative payment models are used in the majority of OECD countries and EU member states (Wenzl and Chapman 2019), performance-based agreements—although less common—are rapidly growing, especially

for oncology treatments and therapies for rare diseases where some of the market failures we describe above are particularly salient (Dabbous et al. 2020; Gamba, Pertile, and Vogler 2020; Lakdawalla 2018).

2.5 Conclusions

Overall, our work finds that although uniform pricing can achieve first-best efficiency in ideal markets, value-based pricing in the form of PBAs and other alternative payment models may help address market failures in practice. We discuss each of the market failure types in detail and indicate how different types of value-based pricing may help overcome them. At the same time, it is important to consider transaction costs, regulatory hurdles, and data challenges which remain significant obstacles to their broader adoption.

Future work may provide empirical estimates of the benefits of alternative payment models, showing how they contribute to social or patient welfare, and build on our analysis of the conditions under which specific types of alternative payment models should be considered.

3 The Economics of Single-Dose, High-Cost Therapies

In this chapter, I discuss the contributions of our work on payment for single-gene, high-cost therapies in an environment with fixed budget constraints (Hlávka, Mattke, and Wilks 2020). The presented work followed the approval of the first gene therapy, Kymriah (tisagenlecleucel) for certain pediatric and young adult patients with a form of acute lymphoblastic leukemia (ALL), in the United States in 2017 (Office of the Commissioner 2020) and increasing calls for making sure that single-dose, high-cost therapies do not destabilize the budgets of insurance plans, as the case of the treatment for hepatitis C (sofosbuvir) illustrated (Schiff 2015).

3.1 Theoretical Background

While the value of modern therapies often surpasses that of the previous generation, the associated costs on a per-unit, per-capita basis also tend to increase. This follows the logic of cost-effectiveness analysis which assumes that higher clinical and economic value of a treatment should be rewarded with a higher price. It has been documented in previous literature that drug prices, translated to revenue and net profits, are a strong driving force of innovation in drug development (Garber et al. 2006; Lakdawalla 2018). Moreover, for conditions that affect smaller numbers of patients, including rare and ultra-rare diseases, researchers and policy-makers have proposed even more favorable reimbursement conditions, such as by raising the cost-effectiveness threshold (a metric of willingness to pay) higher (in the case of the U.S. Institute for Clinical and Economic Review up to $500K per quality-adjusted life-year (QALY) gained for ultra-rare diseases) (Garrison et al. 2019) and developing alternative valuation approaches, some of which may take other perspectives, such as social preferences, into account (Schlander et al. 2014, 2016).

By the end of 2010s, it was estimated that up to 350.000 patients could benefit from gene and cell therapies by 2030 in the United States alone (Quinn et al. 2019), which could pose significant financial risks for the sustainability of healthcare financing, particularly due to the high upfront costs of these therapies. Another more recent analysis suggests

over 1 million patients could be treated by gene therapy alone by the end of 2034, with most of the indications expected in oncology, with the estimated cumulative spending on treating these patients expected to reach $241 billion over the same period (Wong et al. 2023).

This has resulted in calls to "develop precision financing solutions that can ensure appropriate patient access to needed treatments, increase affordability for payers, and sustain private investment in innovation" (Quinn et al. 2019).

Our work contributes to this literature by studying how under fixed budget constraints, innovative payment models such as deferred (installment) payments can improve social welfare by enabling more patients to get treated faster, even if per-patient, per-unit prices remain the same.

3.2 Contribution of Hlávka, Mattke and Wills (2020)

This paper investigates a design for an outcomes-based deferred payment model (DPM) using gene therapy for congestive heart failure (CHF) as a case study. We compare the financial and clinical outcomes of the DPM with those of the conventional upfront payment model, evaluating the perspectives of payers, manufacturers, and patients.

CHF was selected because of its significant treatment-eligible population—about 6.5 million people in the US (Benjamin et al. 2018)—and its poor standard care prognosis, with nearly a 50% 5-year mortality rate (Hernandez 2013). At the time of analysis, regenerative therapies for CHF were in development; for example, Renova Therapeutics' RT-100, an adenylyl cyclase type 6 (AC6) gene transfer, showed promising phase II results in 2017 and a multicenter Phase 3 clinical trial was underway between 2017 and 2019 (Penny et al. 2018).

Our analysis assesses the clinical and financial features of a DPM for hypothetical CHF gene therapy compared to status quo payment. We focus on three stakeholders: payers, who seek to lower per-patient spending; manufacturers, who aim to maximize revenue; and patients, who benefit from better clinical outcomes. We also explore how different payment design choices affect these outcomes.

This study employs a three-pronged analytical approach: (1) an empirical analysis of longitudinal data on cardiovascular admissions and mortality; (2) a Markov transition model to assess patient progression

under varying payment structures; and (3) a discounted cash flow forecast model to evaluate financial implications.

A separate empirical investigation of congestive heart failure (CHF) re-admissions and patient mortality (Dallmann, Wilks, and Mattke 2019) was utilized to parameterize the Markov chain model. This analysis, based on Medicare Provider and Analysis Review (MedPAR) 5% data, estimated 30-day probabilities of mortality and recurrent CHF admissions. It focused on patients with a primary CHF diagnosis (ICD-9-CM code 428.xx) who survived the index admission and had no CHF-related hospitalizations in the preceding 12 months. The study tracked over 91,000 Medicare fee-for-service beneficiaries from 2009 to 2014, monitoring outcomes until death, disenrollment, or study completion.

3.2.1 Markov model design and economic evaluation

The Markov model quantifies life-years gained and reductions in cardiovascular admissions under a deferred payment model (DPM) relative to the status quo, assuming equivalent access to gene therapy. Payment deferral is modeled by adjusting the proportion of the upfront cost, ranging from 25% to 75% of the estimated total therapy cost of US$200,000 (Kish 2017). The analysis accounts for cost offsets from avoided cardiovascular hospitalizations, valued at US$16,000 each (Kilgore et al. 2017), ensuring budget comparability. Over a three-year period, the cumulative per-patient cost of treatment is kept static across the different payment models. Extending the payment duration beyond this horizon is deemed impractical due to high CHF-related mortality. Patient disenrollment, primarily attributed to transitions to Medicare Advantage plans, is assumed to occur at similar rates under both payment models.

For treated patients, the model assumes a relative risk reduction of 0.70 for cardiovascular re-admissions and 0.80 for cardiovascular mortality, derived from clinical outcomes associated with sacubitril/valsartan (Entresto) (McMurray et al. 2014). Payments under the DPM framework comprise an initial down-payment followed by monthly installments, contingent on patient stability. Payments are suspended for one month in the event of cardiovascular hospitalization and cease upon patient mortality. The model is calibrated to a hypothetical annual budget constraint of US$1 billion—aligning with estimated short-term affordability challenges identified by the Institute for Clinical and Economic Review (Pearson 2018)—enabling treatment

for approximately 15,000 patients over three years within a fee-for-service structure. This is a simplifying assumption: given the burden of CHF, actual Medicare expenditures on novel gene therapies would likely exceed this threshold. ***Figure 3.1*** illustrates the DPM structure, while ***Table 3.1*** delineates model parameters and sensitivity analyses.

Figure 3.1. Chart of Markov chain and associated payments under a deferred payment model (DPM)

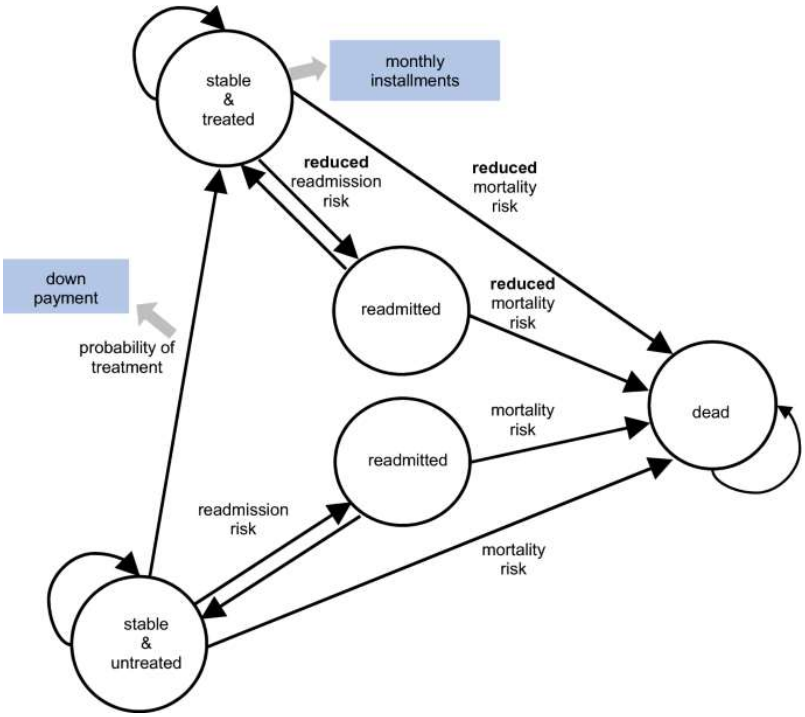


Table 3.1: Model parameters and sensitivity ranges

Parameter	Parameter value	Sensitivity test	References
Down-payment	25%, 37.5%, 50%, 62.5% and 75%	–	Authors' choice
Length of the deferred payment model	36 months	–	Authors' choice (based on high patient attrition beyond 36 months)
Cost of therapy	US$200,000	US$100,000	Baseline value based on the work of Kish [15]
Cost of cardiovascular admission	US$16,000	–	Kilgore et al. [16]

Parameter	Parameter value	Sensitivity test	References
Relative risk of mortality	0.80	–	Comparable to sacubitril/valsartan (Entresto) McMurray et al. [17]
Relative risk of cardiovascular admission	0.70	0.50	Baseline value comparable to sacubitril/valsartan (Entresto) McMurray et al. [17], hypothetical reduction to 0.50
Budget constraint	US$1 billion	–	Approximation based on Institute for Clinical and Economic Review [18]
Discount rate	5%	–	Authors' choice

Finally, the financial implications of the DPM for manufacturers are assessed through a discounted cash flow model. Treatment revenue is discounted at a 5% rate and compared across payment scenarios under identical budgetary constraints, therapy costs, and relative risk reductions. The model assumes that all payments accrue to the manufacturer, with future revenue streams discounted to present value.

3.3 Findings

Our work finds that deferred payment under a fixed budget constraint may allow for more patients to receive treatment sooner, with better clinical outcomes. We explore two different designs of DPM and study their implications.

Drawing on MedPAR 5% data, we find that cardiovascular admission risk is highest in the first several months post-index event, declining from 14.7% in the first month to 5.1% after a year. Mortality follows a similar pattern, decreasing from 8.4% to 2.3% over the same period, with cumulative mortality reaching 33.6% in year one, 20% in year two, and 19.5% in year three.

Figure 3.2 presents patient treatment volumes under different payment models. These include status quo (100% upfront treatment) and range from a down payment of 25% to a down payment of 75% relative to the cost of therapy. Deferred payment slightly increases the number of patients receiving gene therapy (15,043 under a 25% down-payment vs. 15,000 under the status quo) and accelerates access for those who are treated (while in the first year under status quo, just 417

patients are treated, a down payment of 25% allows 866 patients to be treated in the first month in the first year, thus allowing them to benefit from the clinical benefits of therapy sooner).

Figure 3.2: Average monthly number of patients treated by year, by payment scenario (annual budget: US$1 billion)

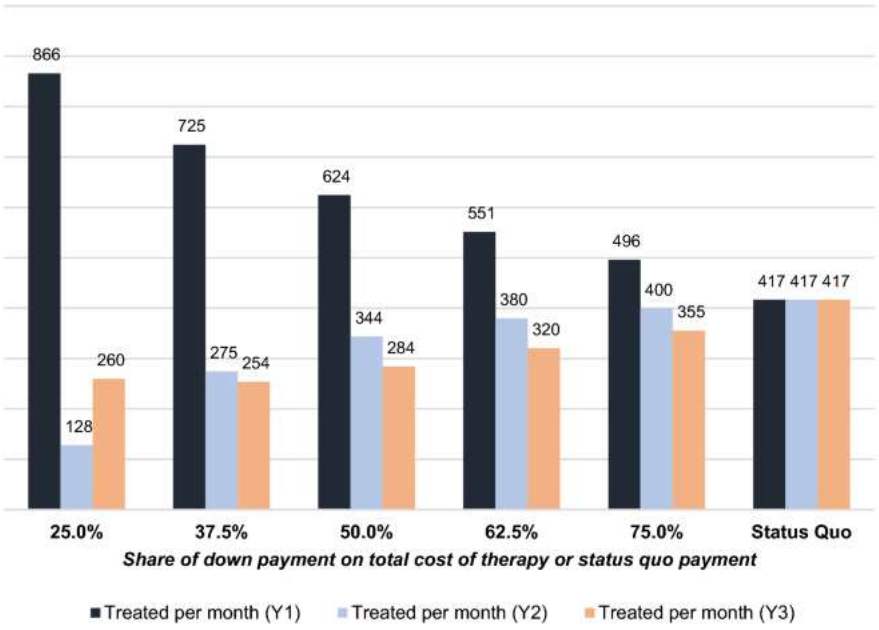


Table 2 shows that a 25% down-payment leads to the highest reduction in cardiovascular admissions (26.1% increase in admissions avoided, or a 0.52% reduction in the simulated patient pool) and mortality (23.3% increase in deaths avoided, or a 0.29% reduction), largely due to earlier treatment. With only 16.5% of eligible patients receiving therapy, cost savings from avoided admissions under the deferred model total $8.64 million.

Table 3.2: Clinical outcomes for patients with congestive heart failure relative to no treatment, by payment scenario (annual budget: US$1 billion)

	Admissions avoided	**Deaths avoided**	**Admissions reduction (%)**	**Mortality reduction (%)**
Status quo	2.071	648	2,00	1,24
75% down payment	2.203	686	2,12	1,32
62.5% down payment	2.287	710	2,20	1,36

	Admissions avoided	Deaths avoided	Admissions reduction (%)	Mortality reduction (%)
50% down payment	2.386	738	2,30	1,42
37.5% down payment	2.501	770	2,41	1,48
25% down payment	2.611	799	2,52	1,53

In our model, a 25% down-payment yields 345.2 life-years gained (51.6% increase relative to status quo), while a 75% down-payment leads to 73.3 life-years gained (11% increase relative to status quo). Earlier treatment under deferred payment reduces three-year mortality, generating societal benefits beyond hospital cost savings. A discounted cashflow analysis shows minimal differences in manufacturer revenue, with a 0.31% gain under the highest discount rate (5%). We also conduct sensitivity analyses, which show greater cost-effectiveness with improved efficacy and lower therapy costs. Reducing the relative risk of cardiovascular admissions to 0.50 increases avoided admissions by 28.5%, while halving therapy costs to $100,000 per patient doubles the number treated, leading to a 26.9% increase in avoided admissions under a 25% down payment relative to status quo.

Overall, our findings indicate that while financial implications of deferred payment and status quo payment are comparable for both payers and manufacturers, deferred payment offers significant advantages to patients by enabling earlier access to life-saving therapies. The lowest down-payment yields the greatest clinical improvements, reducing cardiovascular admissions by 0.52% and mortality by 0.29% in the treated population without exceeding the budget constraint.

3.4 Implications

Our work provides the first empirical assessment of both clinical and financial outcomes of deferred payment (DPM) for hypothetical gene therapy in congestive heart failure (CHF). We find that the primary benefits of DPM will be experienced by patients, as earlier access to treatment improves their clinical outcomes. The smallest modeled down payment reduces cardiovascular admissions relative to the status quo, while maintaining budget neutrality. DPM may also appeal to payers by aligning costs with patient outcomes, as payments cease upon patient death and are suspended during readmissions.

While DPM's financial advantages in CHF remain limited, the model may prove more effective for treatments with higher cost offsets, such as hemophilia, where maintenance therapy costs are substantial (Chen 2016). Additionally, conditions with large prevalent populations relative to incident cases may see greater benefits from DPM, as treatment budgets are concentrated within a shorter timeframe. Budget impact considerations may encourage payers to explore DPMs for emerging, high-cost treatments in both the United States and other countries where such therapies are becoming available.

Our findings suggest that early access is the primary advantage of deferred models in single-dose high-cost therapies, reinforcing their potential role in helping improve timely access to such treatments.

3.5 Conclusions

Our work indicates that deferred payment may be more effective in conditions with high cost offsets (e.g., hemophilia) or large prevalent populations where budget constraints could impose a barrier to access due to the impact such high-cost therapies may have in any given time period (e.g. in the case of Hemophilia C therapy).

The rise of curative and regenerative therapies such as cell and gene therapies is pressuring payers to develop models that facilitate the rapid adoption of high-cost treatments (Jørgensen and Kefalas 2021; Quinn et al. 2019; Young, Quinn, and Trusheim 2022). The Centers for Medicare and Medicaid Services and other payers are exploring innovative pricing strategies to address this issue (U.S. Centers for Medicare & Medicaid Services 2017). Different payment strategies have been considered, including "installments, risk pools, reinsurance, price-volume agreements, expenditure caps, subscriptions, outcomes-based-payments and rebates, warranties, population outcomes–based agreements, and coverage with evidence development" (Horrow and Kesselheim 2023; Zhang and Shugarman 2024).

These payment models have been found to improve market efficiency under specific conditions, but each of these carries specific risks and benefits. Specifically, deferred payments would need to overcome legal challenges as most payers (particularly public ones) operate on annual budgets and in the absence of pay-for-performance clauses, they may not consider the uncertainty of treatment effectiveness in the real world (Antonanzas et al. 2019; Horrow and Kesselheim 2023).

They may also be difficult to introduce in a robust way in a multi-payer system where patients often switch health plans (Horrow and Kesselheim 2023; Koleva-Kolarova et al. 2022). Other barriers to these models include a lack of a clear governance structure and the potential for negative selection of patients with prior treatment that may carry future installment payments (Koleva-Kolarova et al. 2022).

Our work contributes to emerging literature on identifying optimal reimbursement strategies for treatments with high unit costs and their optimal design.

4 The Economics of High-Cost, Population-Wide Therapies

In this chapter, I present our work related to payment for high-cost therapies in Alzheimer's disease, a disease that affects millions of people in the United States and Europe. By 2030, it is estimated that there will be 6,7 million patients with dementia in North America and 15,3 million patients in Europe, and by 2050, these estimates are expected to reach 11,1 and 21,6 million, respectively, in the absence of disease-modification therapies (Guerchet, Prince, and Prina 2020). The majority of dementia cases are patients suffering from Alzheimer's disease, which has several neurological hallmarks: a brain atrophy process, an increased presence of neurofibrillary tangles composed of hyperphosphorylated tau protein located within neurons, and senile plaques (amyloid deposits) (Jahn 2013).

Some of the clinically most promising therapies have targeted both tau tangles and amyloid-β deposits at different phases of aggregation (Abbott 2022). Clinically, the disease does not manifest for several years while biological changes are underway, with early symptoms typically affecting people in their 60s and 70s (however, early-onset Alzheimer's disease has been documented in a smaller share of patients), usually manifesting as subjective memory loss, an impaired sense of smell, followed by more severe cognitive and functional decline (e.g. with transient episodes of amnestic wandering or disorientation, sleep abnormalities) (Jahn 2013).

New disease-modifying therapies (DMTs) have been available to patients since early 2020s, with Aduhelm (aducanumab) approved as the first therapy of its kind (targeting amyloid-β) in June 2021 under the FDA's accelerated approval pathway. In the United States, the approval of Aduhelm was highly controversial, due to ambiguous clinical trial results, high costs, and significant safety concerns, such as amyloid-related imaging abnormalities (ARIA-E and ARIA-H) observed in 35-36% of patients (Budd Haeberlein et al. 2022; Roytman et al. 2023). In Europe, the European Medicines Agency (EMA) rejected aducanumab's application in December 2021, citing insufficient evidence of clinical benefit and safety concerns. Biogen subsequently withdrew its marketing application in April 2022 (Hunter 2024; Vaz et al. 2022).

As of 2025, two disease-modifying therapies (DMTs) for Alzheimer's disease (AD) were available in the United States and one approved in Europe:

- Lecanemab (Leqembi): Approved by the U.S. FDA in January 2023 (accelerated approval) and July 2023 (traditional approval) for early-stage AD, including mild cognitive impairment (MCI) and mild dementia (Office of the Commissioner 2023). It slows cognitive decline by targeting amyloid beta plaques and protofibrils. In November 2024, EMA recommended its approval for a restricted population of early AD patients with one or no copies of the ApoE4 gene, due to risks of amyloid-related imaging abnormalities (ARIA) (European Medicines Agency 2024). Marketing authorization in Europe is pending final confirmation.
- Donanemab (Kisunla): Approved by the FDA in mid-2024 for early AD in the U.S., marking it as the third DMT available after aducanumab and lecanemab (Center for Drug Evaluation and Research 2024). It targets amyloid plaques and is intended for patients in the early stages of AD. As of March 2025, the review of donanemab's application by EMA was ongoing, with potential commercial availability in Europe expected in late-2025 at the earliest (Biogen Inc. 2025).

Emerging AD disease-modifying therapies are administered via intravenous infusions and require biomarker confirmation of AD diagnosis. Both Donanemab and Lecanemab have shown modest benefits in slowing disease progression but come with risks such as ARIA, necessitating careful patient selection and monitoring.

Despite the hope these therapies have brought to millions of patients, significant questions remain about the optimal design of payment models for them and ensuring timely, equitable access to these therapies (Belder, Schott, and Fox 2023; Musiek and Morris 2021) . In the United States, this is a particularly acute issue do the fragmentation of the payer landscape – with many patients ageing into Medicare as they turn 65, providing a discontinuity in coverage and a potential disincentive for commercial health plans to offer timely access to patients under 65, given the limited time to accrue the economic benefits of such therapies.

We investigate this issue using a microsimulation model which allows us to model the value of therapy by age groups, and study how

alternative payment model design may address the potential risk to patients.

4.1 Theoretical Background

In the United States, commercial health plans (which cover the majority of the population) have to consider the value that interventions provide over a relatively short time period, particularly because their members often switch plans and because patients age into the public Medicare program, typically at the age of 65. Hence, for patients with an earlier disease onset, covering treatment to Alzheimer's therapies may be particularly difficult to justify, even if they are priced cost-effectively. Moreover, adopting innovative payment mechanisms may be crucial to mitigate the significant financial risk posed by the drug's steep price and the uncertainty surrounding its benefits (Hlávka et al. 2022). To address this risk, commercial plans might narrow coverage to specific patient subgroups, such as individuals with mild cognitive impairment (MCI), who are likely to remain insured for a longer duration. This scenario is emblematic of broader issues, as similar challenges are expected with future FDA-approved disease-modifying therapies for Alzheimer's disease, potentially resulting in delayed or restricted patient access.

Our prior work explored how these challenges might be addressed through alternative payment models (APMs), including risk-sharing arrangements (Hlávka et al. 2021). However, implementing APMs has proven difficult in the USA and other countries due to high transaction costs, challenges in accurately measuring outcomes, and deficiencies in the data infrastructure required to support these models (Bohm et al. 2022; Neumann et al. 2011). According to an analysis conducted in 2023, about half of select U.S. commercial plans did not cover lecanemab, with 15 plans covering the treatment with a variety of conditions and stipulations (Shaw 2023). Prior to its commercial withdrawal, an analysis found that only 41% of Medicaid fee-for-service plans issued a publicly available coverage policy for aducanumab and that only five commercial plans covered aducanumab for their enrollees (Lin et al. 2023).

4.2 Contribution of Hlávka et al. (2022)

In our work, we draw on the Future Elderly Model (FEM), a healthcare microsimulation which incorporates nationally representative data from the U.S. Health and Retirement Study (HRS) along with other sources, to forecast clinical and economic outcomes for adults aged 51 to 85 with mild cognitive impairment and mild dementia across four different treatment effectiveness scenarios. This allows us to model the hypothetical long-term effects of a disease-modifying therapy in Alzheimer's disease (given the uncertainty about effect sizes, we show the effects of varying magnitude in the cognitive and functional domain, drawing on clinical trial evidence) by the age of individuals treated.

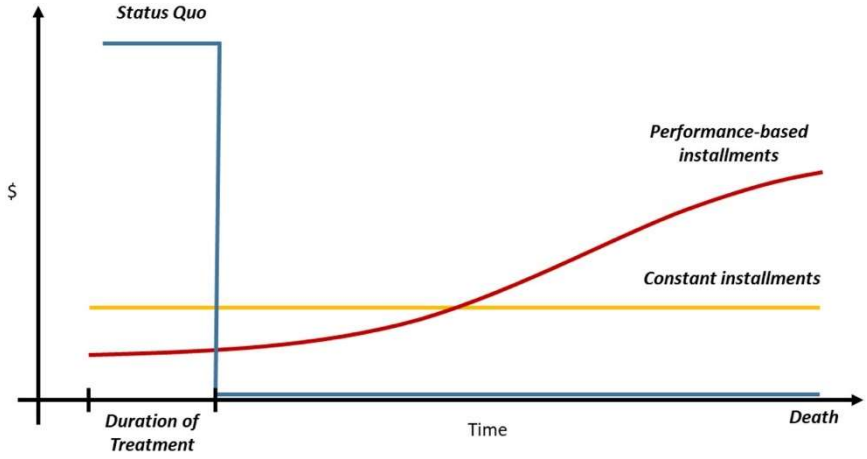
Cognitive benefit is quantified as a reduction in expected decline using the TICS-27 scale, a cognitive measure in the HRS study, while functional benefit is measured by a decrease in the expected development of difficulties with activities of daily living (ADLs). In Scenario 1, a 20% reduction in cognitive decline and a 40% reduction in functional decline are applied, mirroring benefits observed in the aducanumab EMERGE trial (Haeberlein et al. 2022). Scenario 2 adopts a more conservative approach with a 10% cognitive effect and a 20% functional effect, essentially halving the improvements of Scenario 1. Scenario 3 tests an inverse relationship by simulating a 40% reduction in cognitive decline paired with a 20% reduction in functional decline, and Scenario 4 scales these effects down to a 20% cognitive reduction and a 10% functional effect.

We also create a payment model that estimates the net benefit or loss potentially attributable to AD DMTs by age, payer type, and payment model. We construct an economic model that measures treatment benefits across 5-year age cohorts by attributing a value of $150,000 to each quality-adjusted life-year (QALY) gained (Neumann, Cohen, and Weinstein 2014), representing the social welfare benefit from treatment. Leveraging FEM, the model assesses the impact of each intervention on direct healthcare costs—including expenses related to nursing home stays—and determines the net value accrued before and after age 65 as the balance among the social welfare gain, the differences in healthcare expenditures, and the cost of therapy.

The therapy cost is modeled differently under three payment approaches—status quo (payment upon treatment), constant installment payments, and pay-for-performance installment payments (see ***Figure 4.1.*** for a notional description)—with both installment

methods assumed for the patient's remaining lifetime without accounting for a possible termination of effect. This strategy is explored in light of the unique age profile of patients with AD-related cognitive impairment, where benefits may accrue later while costs are incurred early, a scenario particularly relevant for the most advanced disease-modifying drug candidates, many of which are biologic therapies.

Figure 4.1. Notional allocation of treatment costs by payment model



This is done to analyze the benefits and costs of Alzheimer's disease-modifying treatments, focusing on the direct costs and benefits that both private and public payers will experience, and the resulting incentives for them to cover the treatment.

Simulated individuals enter the model according to their cognitive status. We select HRS respondents with a TICS-27 score of 7 or higher—as referenced in Crimmins et al (2011), indicating a likely CDR score of 0.5. Individuals with a recent heart condition, stroke, or congestive heart failure are excluded. HRS does not allow patient selection based on amyloid status—a key marker of AD pathology and a common inclusion criterion in AD clinical trials. Select demographic characteristics of patients in our simulation are presented in ***Table 4.1.*** below.

Table 4.1. Demographic characteristics of the simulated population

Cohort	Simulated observations at entry	Mean age at entry (years)	Median life expectancy (years)	Male % at entry	Mean years education at entry	Mean TICS at entry	Any ADL at entry, %	Any IADL at entry, %
51-55	2.288	53,8	27,0	26,4	12,74	11,80	17,4	11,0
56-60	16.432	58,6	23,0	25,1	11,90	11,60	26,5	15,0
61-65	20.488	62,9	19,0	27,5	11,79	11,10	28,2	16,5
66-70	37.960	68,3	15,0	31,5	11,68	11,62	20,6	8,1
71-75	63.752	73,0	13,0	34,4	11,77	11,79	19,3	8,2
76-80	63.752	78,0	9,0	33,2	12,17	11,73	20,1	10,2
81-85	53.040	83,0	7,0	41,2	12,43	12,26	24,1	14,0
All	**257.712**	**71,3**	**13,0**	**32,5**	**11,96**	**12,06**	**22,2**	**11,2**

ADL indicates activities of daily living; IADL, instrumental activities of daily living; TICS, Telephone Interview for Cognitive Status.

4.3 Analysis and Results

In our analysis, we find that the application of AD DMTs has variable clinical and economic outcomes in different patient populations and under different treatment effectiveness scenarios.

We present these findings briefly below and discuss their implications for possible market failures of status quo payment (in the absence of alternative payment models such as constant and pay-for-performance installment payments).

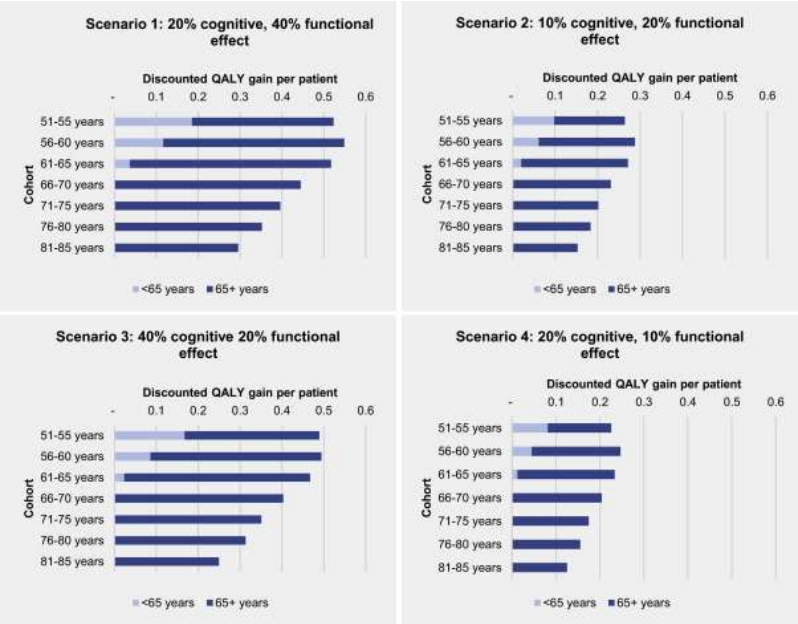
4.3.1 Quality of Life Effects by Age and Scenario

Using the FEM, patients across the four treatment scenarios achieve discounted QALY gains that vary according to the assumed treatment effect, as shown in the Figure below. In baseline scenario 1—assuming a 20% cognitive and 40% functional effect—patients are projected to obtain the highest discounted QALY gains, with those aged 56 to 60 realizing 0.55 QALYs and those aged 81 to 85 gaining 0.30 QALYs, assuming a persistent treatment effect. Halving the treatment effect in scenario 2 reduces QALY gains by approximately 47% to 50% across age groups, with patients aged 56 to 60 achieving 0.29 QALYs and those aged 81 to 85 achieving 0.15 QALYs. In scenarios 3 and 4, although the clinical benefit follows a similar trajectory, the QALY gains are somewhat lower

relative to scenarios 1 and 2; for example, patients aged 56 to 60 in scenario 3 gain 0.49 QALYs—about 10% less than in scenario 1—while the same age group in scenario 4 gains 0.25 QALYs, roughly 14% less than in scenario 2.

Moreover, as the ***Figure 4.2.*** also illustrates, patients treated before age 65 accrue most of their QALY gains after turning 65, confirming the hypothesis that the status quo payment model—where therapy is paid for at the time of treatment—may create an incentive misalignment between payment timing and benefit accrual.

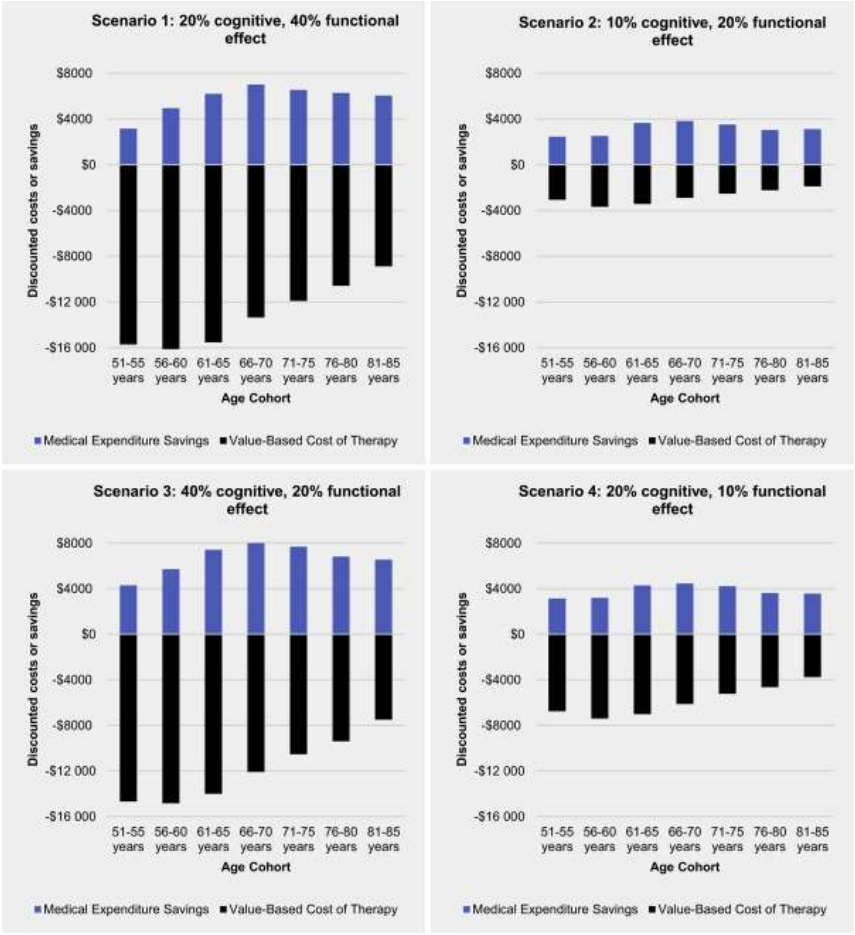
Figure 4.2. Share of discounted QALY gain before and after 65 years of age, by treatment scenario and age cohort



4.3.2 Economic Consequences of AD DMTs

In ***Figure 4.3*** below, we demonstrate the impact of each treatment scenario on medical expenditure savings and the value-based cost of therapy, which is estimated based on the average QALY gain and the previously described treatment cost estimation. Across all four scenarios, patients are expected to achieve medical expenditure savings—even with increased longevity—with savings reaching up to $7.020 for patients aged 66 to 70 in Scenario 1 and $8.017 in Scenario 3, suggesting that cognitive benefits may drive greater savings than equivalent functional benefits.

Figure 4.3. Medical expenditures estimates and value-based cost of therapy, by treatment scenario and age cohort



Although the smallest medical expenditure savings are observed for younger patients, this may be influenced by the timing of cost savings and discounting effects in the analysis. Overall, patients aged 61 to 75 typically realize the highest savings, making them potentially the most attractive from a reimbursement perspective. The figure also displays the value-based estimate of the discounted lifetime cost of therapy for each age group and treatment scenario, revealing significant differences; for example, in Scenario 1 the cost ranges from $8.871 for patients aged 81 to 85 to $16.465 for those aged 56 to 60, and in the other scenarios the highest cost is likewise seen for the 56 to 60 age group ($3.673 in Scenario 2, $14.827 in Scenario 3, and $7.406 in Scenario 4). Patients treated at older ages are expected to have a lower value-based cost of therapy when considering only QALY gains and medical expenditure

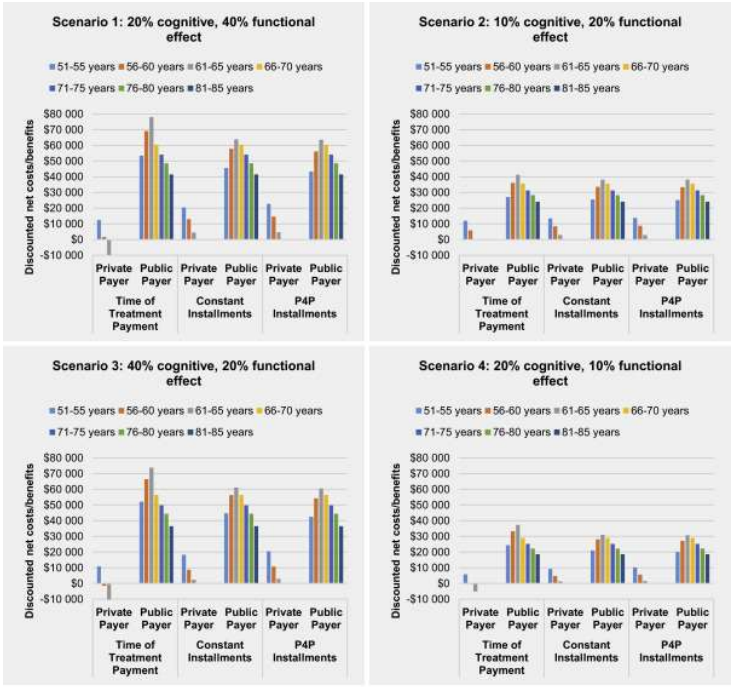
savings, although if manufacturers can appropriate more than 20% of the surplus produced by their therapy, the value-based cost may increase.

4.3.3 Net Impact of AD DMT on Payers by Age of Patients

In ***Figure 4.4.*** below, we compare the net benefit or loss accrued to private and public payers based on treatment scenario, patient age cohort, and payment model. In some age cohorts, a net negative impact on private payers is observed when providing access to an AD DMT, primarily due to patients being near Medicare eligibility, which limits the accumulated benefits relative to treatment costs.

Under the status quo payment model across all four scenarios, payers face net losses for patients aged 61 to 65—estimated at −$9.708 in Scenario 1, −$280 in Scenario 2, −$10.348 in Scenario 3, and −$5.049 in Scenario 4. These losses are entirely avoided with both constant and pay-for-performance payment models, with pay-for-performance installments further enhancing the financial incentive for private payers.

Figure 4.4. Net costs or benefits accrued to private and public payers under treatment scenarios, by age cohort and payment model



Note: P4P = pay for performance

4.4 Implications

Emerging AD DMTs show considerable promise for enhancing patient outcomes, yet current payment design may hinder access—especially for patients under 65 with commercial insurance—because even if these therapies are priced at only a fraction of their overall welfare benefit, they can result in net losses for U.S. private payers, especially for those nearing Medicare eligibility. Since some DMTs require payment at the time of treatment, private insurers might delay treatment, raise premiums, or assign these drugs to higher copay tiers, ultimately limiting timely access.

Our analysis demonstrates that both constant and pay-for-performance installment models could address this issue by spreading the cost of therapy over a patient's lifetime, thereby eliminating the financial disincentive for private payers. Although pay-for-performance installments might represent the actuarially optimal solution, their implementation costs could negate some of their benefits, making constant installments more appealing, particularly when treatment durability exceeds two years.

Given that clinical trials typically provide only short-term outcome data, long-term benefits must be projected using population models such as the FEM, and effective mechanisms for transferring payment responsibilities between public and private insurers will be essential when patients switch plans or become Medicare-eligible.

Additional strategies we discuss include adopting a single-payer model, reallocating costs between payers, subsidizing treatment for younger patients, or establishing an AD risk pool to cover early screening, diagnosis, and treatment—each of which would require regulatory adjustments and cooperation among stakeholders. All of these solutions are particularly challenging in the U.S. context but in the absence of solutions, hundreds of thousands of patients may remain without optimal access to new DMTs for AD.

Our work shows that addressing the misalignment between the timing of costs and benefits could yield significant efficiency gains, and the substantial economic impact of AD DMTs is likely to drive demand for innovative payment solutions and comprehensive health technology assessments (Darius Lakdawalla et al. 2021; Lin, Cohen, and Neumann 2020).

4.5 Conclusions

Our work indicates potential market failures due to the asynchronous accrual of benefits and costs of AD DMTs affecting patient access and the potential alternative payment models have to resolve these. This has been echoed by other authors (Wahlberg et al. 2024) who posit that for such payment models to work, systems for patient follow-up and data collection in routine care will be critically important to develop.

Challenges related to real-world measurement of treatments' effectiveness must also be resolved, with many of the endpoints used in clinical trials possibly too impractical to use in routine clinical practice in diverse settings. In the United States, coordination may be necessary between commercial payers and Medicare, and in Europe, a transparent process for quantifying the benefits of AD DMTs, particularly among younger patients who may benefit the most from them (also due to indirect benefits in productivity of unpaid caregivers).

Specific challenges for AD DMTs will need to be overcome, including the process of diagnosis and identifying treatment-eligible patients (Dobson et al. 2024), incorporating new diagnostic methods such as blood-based biomarkers in the diagnosis process (Mattke et al. 2020) and overcoming likely capacity challenges in both diagnosis and treatment due to specialist and infusion capacity (Hlavka, Mattke, and Liu 2019).

5 The Impact of Regulatory Guidance on Clinical Trial Design

In this chapter, empirical work on trialist behavior following non-binding FDA guidance documents is presented. Our work fills a gap in literature on the effects of soft law (documents that are not legally binding) on clinical design choices in a large disease area, Alzheimer's disease. Our analysis suggests that although guidance documents do not set new legal standards or impose binding requirements, our findings indicate they are broadly followed by AD trialists.

5.1 Theoretical Background

The choice of a primary endpoint in clinical trials determines the type of evidence generated and is a key factor in regulatory review by agencies like the FDA (Brody 2016). Researchers select endpoints based on the trial's main goals, the relevance to patients, ease of measurement, and the likelihood of success (Evans et al. 2018; McLeod et al. 2019). Regulatory authorities also shape these choices through both formal policies and informal guidance, which is the focus of this study. In the United States, the FDA supervises clinical trials for drugs, biologics, and medical devices using various regulatory tools (Center for Drug Evaluation and Research 2023). One important tool is the publication of guidance documents, which outline the FDA's current thinking on issues ranging from trial design and recruitment to ethics and endpoint selection (Noah 2022, 2022; Office of the Commissioner 2024). Although these guidances are not legally binding, trialists can choose to follow or deviate from them as long as they comply with applicable laws.

For example, in 2013 the FDA issued draft guidance for early Alzheimer's disease (AD) trials recommending that drugs show benefits on both cognitive and functional or global assessment scales (Food and Drug Administration 2013). This guidance recognized the difficulty in measuring cognitive improvements in early stages of AD, such as mild cognitive impairment (MCI), and proposed using a combined cognitive-functional score like the Clinical Dementia Rating–Sum of Boxes (CDR-SB). A later draft in 2018 moved away from fixed recommendations, suggesting a broader range of endpoints—including biomarkers and coprimary measures—to suit different types of early AD (Food and Drug

Administration 2018). This study uses these two guidances as a case study to assess how trial designers respond to FDA recommendations.

Because guidance documents are not enforceable and often remain in draft form, their practical impact on clinical trial practices is unclear (Noah 2015). Additionally, the decision-making process within the FDA involves multiple stakeholders, which complicates the influence of non-binding opinions. For instance, despite the FDA's approval of Aduhelm, an influential external panel opposed the drug (Joseph 2021). Moreover, if trialists follow one set of guidance that is later replaced by conflicting recommendations, they cannot hold the FDA accountable for earlier advice (Noah 1997).

Our paper also explores whether the FDA is reacting to trends in clinical research by issuing guidance documents or proactively shaping trial designs, particularly in Alzheimer's Disease (AD). By examining changes in primary endpoint selection in AD trials over time—specifically around the issuance of the two guidance documents—and comparing responses between private and public sponsors, our work represents the first empirical investigation into how trialists respond to FDA guidances and provides a framework for assessing the impact of such non-binding recommendations.

5.2 Contribution of Yu, Hlávka et al. (2022)

We evaluated the impact of the 2013 and 2018 FDA draft guidances on pivotal AD trials by compiling a chronology of trials, assigning primary endpoints to relevant outcome domains, and applying regression discontinuity in time (RDiT) analyses.

Pivotal AD trials (phase II/III, III, III/IV) were identified from the Citeline TrialTrove database (extracted June 2020) using ICD-10 codes G30.0, G30.1, G30.8, and G30.916. We confirmed our dataset by comparing it to prior AD pipeline reviews (Cummings et al. 2020). When start dates were unavailable, they were imputed based on trial length derived from sample size and site regions, with sensitivity analyses confirming the robustness of the findings.

Primary endpoint data came from TrialTrove, supplemented by manual review of trial registries, manuscripts, and abstracts when necessary. Endpoints were collapsed into broader categories (e.g., ADAS-Cog) to track trends, and trials focused solely on safety/tolerability or lacking primary endpoint data were excluded.

Primary endpoints were categorized into cognitive, functional, behavioral, and biomarker domains based on instrument documentation, literature, and neurologist expert opinion. Trials were classified as either disease-modifying therapy (DMT) or non-DMT, based on published classifications (Cummings et al. 2020) and expert opinion.

A RDiT framework, using piecewise linear regression, estimated the effects of the FDA guidances by regressing the use of cognitive and functional composite endpoints (or CDR-SB) on trial start date with knots at March 1, 2013, and March 1, 2018. Models were stratified by DMT status and controlled for AD staging (based on the 2011 National Institute on Aging–Alzheimer's Association guidelines (Sperling et al. 2011)), FDA registration status, and trial phase. Model robustness was tested with alternative specifications and knot P-values.

5.3 Analysis and Results

A total of 3227 unique Alzheimer's disease (AD) trials were identified in the TrialTrove dataset, with 487 trials classified as phase II/III, III, or III/IV (Figure 1). After excluding 13 trials with start dates before 1997, 62 trials focused solely on safety and tolerability, 39 trials lacking a start date, and 59 trials missing primary endpoint information, 314 trials remained eligible for analysis.

Among these 314 trials, 34 (10.8%) were phase II/III trials, 279 (88.9%) were phase III, and 1 (0.3%) was phase III/IV. The initiation of AD trials peaked between 2001 and 2005, and 124 (39.5%) of the trials examined disease-modifying therapies (DMTs). Approximately half of the trials used a single primary endpoint, while the other half employed two or more. In terms of geographical distribution, 58.0% of the trials had at least one site in North America, 47.8% in Europe, and 31.9% in Asia.

Our work identified 128 unique primary endpoints. Throughout the study period, the five most commonly used primary endpoints were ADAS-Cog (n = 145), the Mini-Mental State Examination (MMSE; n = 45), the Clinician's Interview-Based Impression of Change–Plus Caregiver Input (CIBIC+; n = 36), the Neuropsychiatric Inventory (NPI; n = 35), and the Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL; n = 33). ADAS-Cog was by far the most frequently selected cognitive-only endpoint, while the most common multi-domain endpoints were the CIBIC+ (n = 36), Clinical Dementia Rating–Sum of

Boxes (CDR-SB; n = 30), and the Clinical Global Impression of Change (CGIC; n = 21). A selection of the most common primary endpoints identified in late-stage clinical trials is shown in ***Table 5.1.*** below.

Table 5.1: List of most used primary endpoints used in pivotal Alzheimer's disease trials, grouped by domain classification

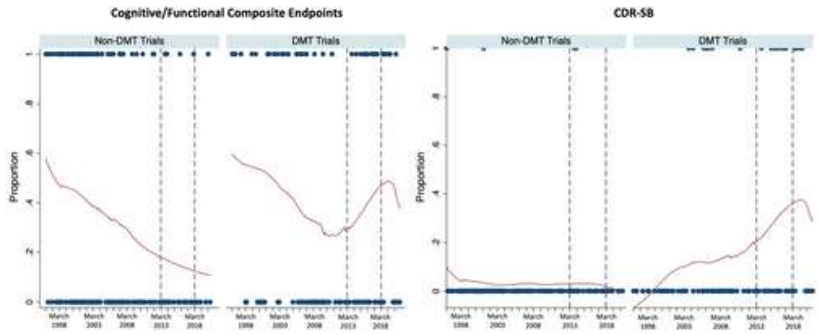
Domain classification	Frequency
Cognitive only	
Alzheimer's Disease Assessment Scale–Cognitive Subscale	145
Mini-Mental State Examination	45
Severe Impairment Battery	24
Global Deterioration Scale	6
Neuropsychological Test Battery	3
Trail Making Test	3
Behavioral only	
Neuropsychiatric Inventory	35
Cohen-Mansfield Agitation Inventory	19
Brief Psychiatric Rating Scale	4
Geriatric Depression Scale	4
Behavioral Pathology in Alzheimer's Disease	3
Functional only	
Alzheimer's Disease Cooperative Study–Activities of Daily Living	33
Activities of Daily Living	9
Disability Assessment for Dementia	9
Instrumental Activities of Daily Living	7
Physical Self-Maintenance Scale	2
PROs only	
Nighttime Total Sleep Time	4
Progressive Deterioration Scale	3
Caregiver Stress Scale	2
Quality of Life–Alzheimer's Disease	2
Biomarkers only	
Magnetic Resonance Imaging	3
Positron Emission Tomography	2
Total Antioxidant Capacity	2
Multi-domain	
Clinician's Interview-Based Impression of Change–Plus Caregiver Input	36
Clinical Dementia Rating Scale–Sum of Boxes	30
Clinical Global Impression of Change	21
Clinical Global Impression	16
Clinical Dementia Rating Scale	7

We first examined trends in using the recommended primary endpoints over time. ***Figure 5.1.*** below shows LOWESS (locally weighted

scatterplot smoothing) plots that display the proportion of trials using a cognitive/functional composite endpoint (and CDR-SB) for both DMT and non-DMT trials. Over time, non-DMT trials steadily reduced their use of these endpoints.

In DMT trials, cognitive/functional composite endpoint use began declining before the March 2013 guidance, but then both composite endpoint and CDR-SB use sharply increased afterward. The plots also show that both endpoints were used less after March 2018, reflecting that guidance's alternative options for early AD trials.

Figure 5.1: Locally weighted scatterplot smoothing (LOWESS) plots of the use of cognitive/functional composite endpoints and CDR-SB



CDR-SB, Clinical Dementia Rating–Sum of Boxes; DMT, disease-modifying therapy

A regression discontinuity in time (RDiT) model was then used to study the effects of the 2013 and 2018 draft guidance documents, as shown in ***Table 5.2.*** below. In DMT trials, the yearly use of a cognitive/functional composite endpoint increased significantly (+12.9%; P < .001) from March 2013 to March 2018 and then decreased significantly (–19.9%; P = .022) after March 2018. Similarly, the yearly use of CDR-SB in DMT trials increased significantly from March 2013 to March 2018 (+11.5%; P < .001) and decreased significantly after March 2018 (–14.8%; P = .017). These effects were not observed in non-DMT trials. Additionally, CDR-SB use was significantly higher (+25.2%; P < .001) in FDA-registered DMT trials.

Table 5.2. Regression discontinuity in time linear model to investigate the impact of the 2013 and 2018 FDA draft guidances on the selection of primary endpoints in AD DMT trials

	Cognitive/functional composite endpoint				CDR-SB			
	DMT		Non-DMT		DMT		Non-DMT	
Independent variables	**Coefficient**	***P*-value**	**Coefficient**	***P*-value**	**Coefficient**	***P*-value**	**Coefficient**	***P*-value**
Intercept	2.015 ***	.000	1.292 ***	.001	0.278	.518	−0.057	.686
Years prior to March 1, 2013	−0.037 ***	.002	−0.022 **	.012	−0.013 **	.042	0.001	.730
Years between March 1, 2013, and March 1, 2018	0.129 ***	.000	−0.021	.418	0.115 ***	.000	−0.005	.509
Years after March 1, 2018	−0.199 **	.022	0.105	.459	-0.148 **	.017	−0.006	.451
AD stage (Reference = overt AD)								
Presymptomatic	−0.016	.933	—	—	−0.240 ***	.002	—	—
Prodromal/MCI	0.075	.506	0.240	.124	0.145 ***	.098	0.367 **	.033
FDA registered trial	0.065	.557	0.074	.329	0.252 ***	.000	0.041 *	.092
Phase (reference = phase III)								
Phase II/III	−0.124	.226	−0.077	.513	−0.203 ***	.005	−0.032	.101
Phase III/IV	0.739 ***	.000	—	—	-0.239 ***	.000	—	—
Number of observations	124		190		124		190	
R-squared	0.141		0.087		0.293		0.228	

Abbreviations: AD, Alzheimer's disease; CDR-SB, Clinical Dementia Rating–Sum of Boxes; CI, confidence interval; DMT, disease-modifying therapy; FDA, Food and Drug Administration; MCI, mild cognitive impairment. * P < .10, ** P < .05, *** P < .01.

The model's robustness was tested by checking model fit and spline P-values under different specifications, adjusting the policy-relevant spline where needed. The base-case model had the highest R^2 and lowest spline P-value, indicating a strong fit.

For DMT trials with private sponsors, the use of cognitive/functional composite endpoints increased significantly each year from March 2013 to March 2018 (+17.0%; p = 0.001), as did the use of CDR-SB (+13.3%; p = 0.005). However, in DMT trials with only public sponsors, no significant increase was observed for cognitive/functional composite endpoints (–12.4%; p = 0.137) or CDR-SB (–5.8%; p = 0.337) after the 2013 guidance. No significant effects were found for DMT trials with either sponsor type after the 2018 guidance.

Additionally, trials using cognitive/functional composite endpoints (+140.1%; p = 0.020) or CDR-SB (+227.9%; p = 0.005) had significantly larger sample sizes than those without these endpoints.

5.4 Implications

Our study provides the first quantitative evidence that FDA draft guidances in AD significantly influence clinical trial design. We show that the 2013 guidance led to an increased use of cognitive/functional composite endpoints, while the 2018 guidance reversed this trend, demonstrating a strong but imperfect influence of non-binding recommendations on trialist behavior. Unlike previous anecdotal observations, our findings quantitatively confirm that regulatory guidance can shape industry practices.

A key insight from our work is that FDA guidances may be perceived as *de facto* requirements rather than mere recommendations. The significant uptake of CDR-SB after the 2013 guidance suggests that trialists may have interpreted the FDA's suggestions as necessary for regulatory approval, potentially shaping how clinical benefit is measured and influencing future innovation in AD trials. This effect is particularly relevant in early AD, where standardized research practices are still emerging (Chen et al. 2024; Ellison et al. 2023).

We also highlight a disparity in how private and public sponsors respond to guidances. Private sponsors, who are more likely to seek FDA approval for marketed products, showed strong adherence to guidance recommendations, whereas public sponsors, often more focused on mechanistic or exploratory research, were less influenced. This distinction underscores the role of FDA guidances in shaping industry-driven clinical development strategies. Our study extends previous work on AD trial endpoints (Harrison et al. 2016) by demonstrating that trials using composite or CDR-SB endpoints tend to have larger sample sizes, suggesting a potential cost impact of the 2013 and 2018 guidances. This raises important questions about whether regulatory recommendations inadvertently increase trial costs, warranting further investigation.

5.5 Conclusions

Our findings contribute to broader regulatory science by offering a framework for evaluating the impact of FDA guidances beyond AD and addressing a gap identified in literature on the evaluation of FDA regulatory actions (Briesacher et al. 2013).

To our knowledge, this study was the first to quantitatively assess how trialists respond to FDA recommendations in any disease area, adding a new dimension to research on regulatory influence, trial design choices, and industry compliance with evolving standards. Future work could expand this analysis to other therapeutic areas and explore how FDA guidances affect additional aspects of trial design beyond primary endpoints and whether specific types of non-binding FDA guidances for industry may contribute to higher costs of drug development.

6 Key Trends in Primary Endpoint Selection by Clinical Trialists in Alzheimer's Disease

The pursuit of disease-modifying treatments for Alzheimer's disease (AD) has been ongoing for decades, with private drug development costs exceeding $42 billion between 1995 and 2021, alongside substantial public funding, primarily from the NIH (Cummings et al. 2022). The growing impact of AD underscores this urgency—Medicare and Medicaid spending on AD is projected to rise from $231 billion in 2024 to $637 billion annually by 2050 without effective interventions (Alzheimer's Association 2024).

Despite extensive efforts, most drug candidates have failed (Cummings et al. 2022). Aducanumab, the first potential disease-modifying therapy, received accelerated FDA approval in 2021 but was discontinued in 2024 following controversy over its approval (Biogen Inc. 2025). This decision was likely influenced by the FDA's full approval of lecanemab (July 2023) and donanemab (July 2024), both of which significantly slowed cognitive decline in early AD.

The EU/US/Clinical Trials in Alzheimer's Disease (CTAD) Task Force emphasized that AD's complexity and the variability of clinical trials remain major obstacles (Aisen et al. 2021). While these challenges persist, this work evaluates the late-stage therapy pipeline and introduces a classification system based on treatment paradigms—grouping candidates by biological mechanism and disease target—to guide future research, policy, and clinical strategies. Our work aims to expand the understanding of late-stage clinical trials in AD, with a particular emphasis on characterizing their trial design, such as inclusion criteria and endpoints used to measure efficacy. It builds on previous work which provided a narrative review of the clinical trial pipeline in AD (Schneider et al. 2014) and work conducted in other disease areas, such as advanced non-small cell lung cancer (Aggarwal and Borghaei 2017).

6.1 Theoretical Background

Previous reviews of the AD clinical trial pipeline have focused on Phase 1, Phase 1/2, Phase 2, Phase 2/3, and Phase 3 trials in AD, including DMTs or as symptomatic therapies (Cummings et al. 2024) but have

focused on select aspects of trial development and are missing data on eligibility criteria, endpoint domains and other relevant information. Horizon scanning has been a method used to inform policy making as well as private investment by commercial entities, given the significant unmet need in Alzheimer's disease globally (Cole and Seabrook 2020). Other work has noted the importance of a diversified pipeline and strategic policies to ensure affordability while fostering innovation in AD through measures such as include postmarket surveillance, disease registries, innovative payment models, streamlined regulatory processes, and conditional coverage for promising treatments (D. Goldman, Fillit, and Neumann 2018).

6.2 Contribution of Hlávka et al. (2024)

We extracted data on AD clinical trials from the United States National Library of Medicine (NLM) clinical trials database on April 10, 2021, and March 28, 2023. Trials listing AD as a condition and targeting AD progression were included. We systematically reviewed late-stage (Phase 2 and 3) clinical trials of disease-modifying therapies for AD. The NLM database was searched using "Alzheimer" in the study description and applying these filters: (i) "Recruiting," "Not yet recruiting," or "Active, not recruiting"; (ii) "Enrolling by invitation"; (iii) "Interventional"; and (iv) "Phase 2" or "Phase 3."

We assessed studies to determine whether they tested disease-modifying or symptomatic therapies. Disease-modifying treatments aimed to alter AD-related biological features (e.g., amyloid plaques, tau tangles), while symptomatic therapies targeted symptom relief (e.g., agitation, fatigue) without affecting disease progression. Studies on symptomatic therapies, imaging, and behavioral interventions were excluded, retaining only those testing disease-modifying therapies for data extraction.

For the 175 disease-modifying trials identified and included in our review, we extracted key variables from the NLM database and categorized studies into treatment paradigms. Data collected included: therapeutic candidate, therapy type (biologic, small molecule, cell/gene therapy, other), target category (amyloid, tau, other), primary outcome measures (e.g., ADAS-Cog, MMSE, amyloid levels) and clinical domains (cognitive, behavioral, functional, biomarker, other), eligibility criteria

(age, MMSE, CDR scores), trial phase, projected duration, funding sources, and U.S.-based study sites.

Therapies were grouped by therapy type and target under a "treatment paradigm" variable, reflecting shared mechanisms and biological targets (amyloid, tau or other). If a paradigm had few candidates, broader categories were used (e.g., a combined Cell and Gene Therapy paradigm). The eight treatment paradigms for analysis were:

- Biologic–Amyloid
- Biologic–Tau
- Biologic–Other
- Small Molecule–Amyloid
- Small Molecule–Tau
- Small Molecule–Other
- Cell and Gene Therapy
- Other

6.3 Analysis and Results

We find that among the 175 late-stage clinical trials analyzed, biologic (30%) and small molecule drugs (54%) were the most frequently studied therapy types, while cell and gene therapy and the other category had fewer trials. Of the 123 unique intervention candidates, biologic drugs accounted for 24% and small molecule drugs for 56%. The most common therapeutic target was amyloid, comprising 54% of biologic trials and 29% of small molecule trials, followed by tau at 19% and 10%, respectively.

6.3.1 Endpoints in AD DMT Trials

The Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) was the most frequently used primary outcome measure, appearing in 29% of trials. The Clinical Dementia Rating (CDR) (15%) and amyloid level (13%) were the second and third most common. Across all paradigms, the cognitive domain was the most frequently assessed, appearing in 54% of trials, while functional (26%) and biomarker (35%) measures were also prevalent. The behavioral domain was the least represented (9% of trials).

The most common primary outcome measures by treatment paradigm are shown in ***Table 6.1.*** below (where primary outcome measures appear with equal frequency, multiple measures are listed).

Table 6.1. Most common primary outcome measure by treatment paradigm for late-stage clinical trials of potentially disease-modifying therapies for Alzheimer's disease

Treatment Paradigms	Most common primary outcome measures	
	1st	**2nd**
Biologic–Amyloid	Amyloid (36%)	CDR (25%)
Biologic–Tau	ADAS-Cog, ADCS-ADL/iADL, tau (30%)	
Biologic–Other	ADAS-Cog (29%)	CDR-SB, amyloid (21%)
Small Molecule–Amyloid	ADAS-Cog (37%)	CDR-SB, ADCS-CGIC, amyloid, PK/PD (15%)
Small Molecule–Tau	PK/PD (33%)	ADAS-Cog, ADCS-ADL/iADL (22%)
Small Molecule–Other	ADAS-Cog (36%)	Homeostatic Biomarkers (19%)
Cell and gene therapy	Homeostatic biomarkers (25%)	—
Other	ADAS-Cog (24%)	CDR-SB (14%)
Grand total	ADAS-Cog (29%)	CDR (15%)

Notes: The Cell and Gene Therapy paradigm did not have other repeated primary outcome measures. CDR is listed when both CDR-SB (Sum of Boxes) and CDR Global Score were used as measures within a paradigm; CDR-SB is listed when only CDR-SB was used.
Abbreviations: ADAS-Cog, Alzheimer's Disease Assessment Scale—Cognitive Subscale; ADCS-ADL/iADL, Alzheimer's Disease Cooperative Study—Activities of Daily Living/Instrumental Activities of Daily Living Scale; ADCS-CGIC, Alzheimer's Disease Cooperative Study—Clinical Global Impression of Change; CDR, Clinical Dementia Rating; CDR-SB, Clinical Dementia Rating—Sum of Boxes; PK/PD, pharmacokinetic or pharmacodynamic properties.

6.3.2 Eligibility Criteria in AD DMT Trials

Most trials (over 90%) included participants aged 60–80 years, with 54% extending eligibility to ages as young as 50 years, and 33% to as old as 90 years. MMSE scores were used as an eligibility criterion in 69% of trials, with scores 22–24 eligible in 80% and 20–26 in at least 70% of such studies. CDR scores were eligibility criteria in 43% of trials, primarily including 0.5 (very mild dementia) and 1 (mild dementia), with higher and lower scores being less common. Scores 0 (normal), 2 (moderate dementia), and 3 (severe dementia) were rare, further

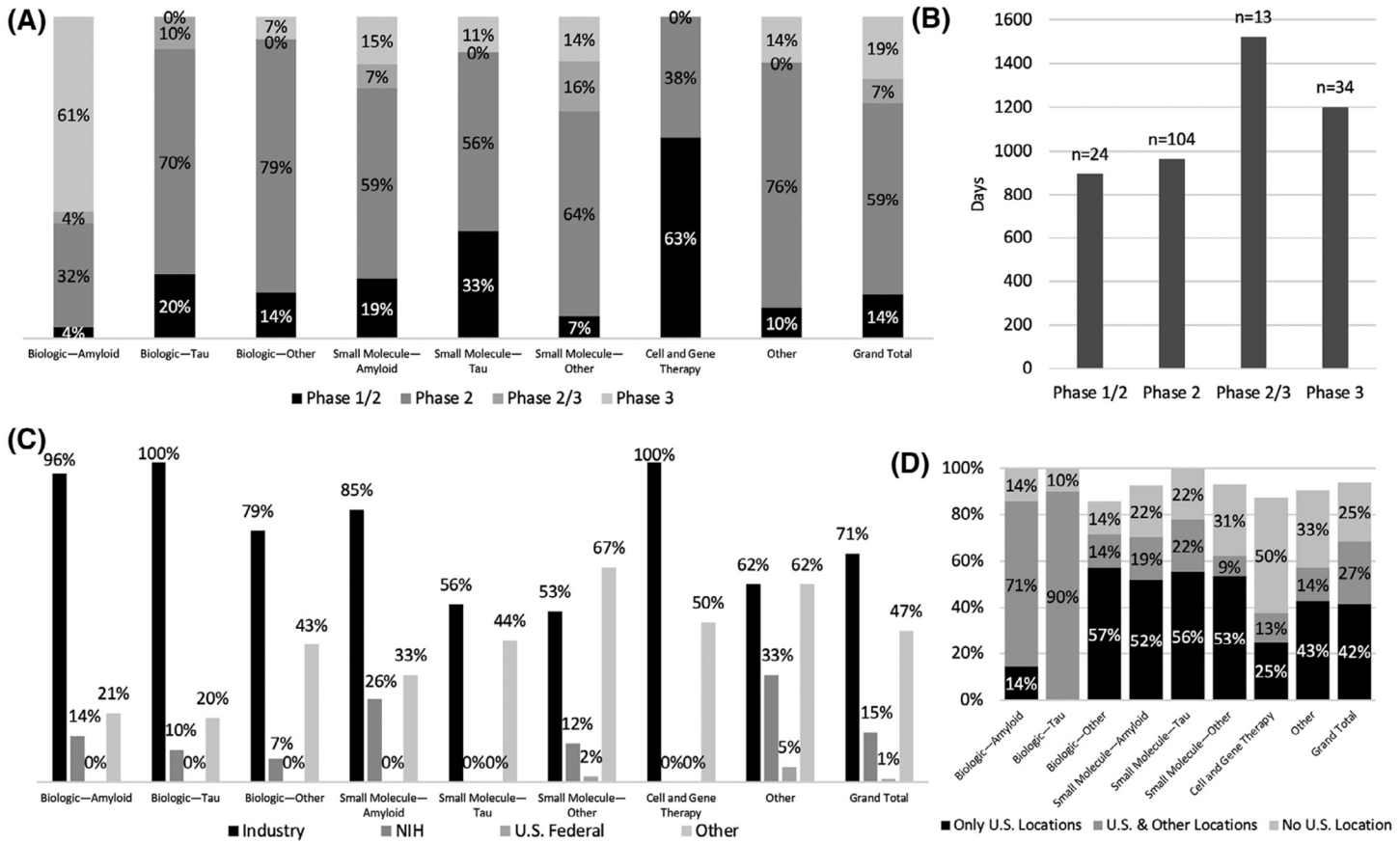
emphasizing the selection of patients with mild disease. Key trial characteristics, including inclusion criteria (age, MMSE and CDR ranges) are shown in ***Table 6.2.*** below.

Figure 6.1. further below describes the key characteristics of clinical trials studied, namely the distribution of clinical trials by paradigm and phase, the average length of trials by phase, funding by treatment paradigm and location of trials as reported by clinicaltrials.gov (not all studies listed locations and totals may not add up to 100%).

Table 6.2. Descriptive characteristics by treatment paradigm for late-stage clinical trials of potentially disease-modifying therapies for Alzheimer's disease

			Inclusion criteria			Trial phase				U.S. site included	
Treatment paradigm	**Count**	**Unique intervention candidates**	**Modal age range**	**MMSE, range (mode)**	**CDR, range (mode)**	**1/2, *n* (%)**	**2, *n* (%)**	**2/3, *n* (%)**	**3, *n* (%)**	**Yes, *n* (%)**	**No, *n* (%)**
Biologic–Amyloid	28	10	60–80	18–30 (27–28)	0–2 (0.5)	1 (4%)	9 (32%)	1 (4%)	17 (61%)	24 (86%)	4 (14%)
Biologic–Tau	10	9	60–75	16–30 (22–30)	0–2 (0.5)	2 (20%)	7 (70%)	1 (10%)	0 (0%)	9 (90%)	1 (10%)
Biologic–Other	14	10	65–80	10–30 (22–24)	0.5–2 (0.5–1)	2 (14%)	11 (79%)	0 (0%)	1 (7%)	10 (71%)	2 (14%)
Small Molecule–Amyloid	27	17	65–75	0–30 (22–24)	0–2 (0.5)	5 (19%)	16 (59%)	2 (7%)	4 (15%)	19 (70%)	6 (22%)
Small Molecule–Tau	9	7	65–80	12–30 (24)	0.5–2 (0.5–1)	3 (33%)	5 (56%)	0 (0%)	1 (11%)	7 (78%)	2 (22%)
Small Molecule–Other	58	49	65	0–30 (21–22)	0–2 (1)	4 (7%)	36 (64%)	9 (16%)	8 (14%)	36 (62%)	18 (31%)
Cell and Gene Therapy	8	3	55–70	10–30 (22–24)	0.5–1 (0.5–1)	5 (63%)	3 (38%)	0 (0%)	0 (0%)	3 (38%)	4 (50%)
Other	21	18	75–80	10–30 (24–26)	0–3 (0.5)	2 (10%)	16 (76%)	0 (0%)	3 (14%)	12 (57%)	7 (33%)
Grand Total	**175**	**123**	**65–70**	**0–30 (24)**	**0–3 (0.5–1)**	**24 (14%)**	**104 (59%)**	**13 (7%)**	**34 (19%)**	**120 (69%)**	**44 (25%)**

Figure 6.1. Characteristics of late-stage clinical trials of potentially disease-modifying therapies for Alzheimer's disease



6.3.3 Trial Phases, Duration, Funding and Site

Of the 175 trials, 81% were in Phase 2 and 27% in Phase 3. The Biologic–Amyloid paradigm had the highest proportion of Phase 3 trials (64%), while most other paradigms were predominantly in Phase 2. The average trial duration varied by phase: Phase 2 lasted 2.6 years (965 days), Phase 3 lasted 3.3 years (1202 days), and combined Phase 2/3 trials averaged 4.2 years (1521 days).

Funding was primarily from industry (71%), followed by the NIH (15%) and other U.S. federal agencies (1%), with 47% receiving funding from other sources. 100% of Biologic–Tau and Cell and Gene Therapy trials had industry funding, while Small Molecule–Tau and Cell and Gene Therapy trials received no NIH funding.

Of trials reporting location data, 69% included at least one U.S. site, while 42% were exclusively conducted in the U.S.. 25% of trials had no U.S. locations, and 6% did not report site data at the time of extraction.

6.4 Implications

Our work finds that late-stage clinical trials in AD continue to prioritize amyloid as the leading therapeutic target, with 55 trials focused on amyloid-modifying biologics and small molecules. This aligns with the decades-old amyloid cascade hypothesis, which suggests that amyloid plaque accumulation drives AD progression (Zhang et al. 2023). While this hypothesis has led to three FDA-approved *Biologic–Amyloid* therapies—aducanumab (2021), lecanemab (2023), and donanemab (2024), their clinical benefits remain modest (Sims et al. 2023). The need for careful patient monitoring is also a barrier, as these therapies are associated with amyloid-related imaging abnormalities (ARIA-E, ARIA-H), requiring safety oversight (Filippi et al. 2022). Despite setbacks, next-generation amyloid therapies such as trontinemab, designed for better blood-brain barrier penetration, reflect the field's commitment to refining this approach (Grimm et al. 2023).

However, as amyloid-focused treatments dominate the landscape, researchers have struggled to advance tau-targeting therapies, another hallmark of AD pathology. Although several tau-directed drugs, including zagotenemab, tilavonemab, and gosuranemab, were investigated, all failed to meet primary endpoints, leading to discontinuation (Cummings

et al. 2023). The complexity of tau's role in neurodegeneration may explain why, at the time of data collection, no tau-targeting therapy had advanced past Phase 2. Some companies remain optimistic, particularly Ionis/Biogen's BIIB080, which suppresses tau production at the RNA level, and Janssen's JNJ-63733657, an antibody targeting tau's microtubule-binding region. But compared to amyloid, tau remains a more elusive and difficult therapeutic target.

Beyond biologics, small molecules have long been a preferred therapeutic modality due to their cost-effectiveness and oral bioavailability. While small molecules comprised 54% of trials, biologics were more likely to advance to Phase 3 (38% vs. 25%), underscoring the pharmaceutical industry's increasing focus on antibody-based interventions. Notably, *Biologic–Amyloid* had the highest number of Phase 3 trials (n = 18) and nearly 100% industry funding, reflecting strong commercial interest. Meanwhile, *Cell and Gene Therapy* approaches remain experimental, with five of the eight trials testing mesenchymal stem cell (MSC) therapies—a promising yet still unproven method for promoting amyloid clearance and neuronal survival (Chakari-Khiavi et al. 2019). Other cell and gene therapies, including antisense oligonucleotide BIIB080 and regulatory T-cell approaches, are still early in development, and no trials had moved past Phase 2.

While mainstream drug development has fixated on amyloid and tau, alternative approaches exist in the *Other* paradigm, which captures interventions that do not fit traditional biologic, small molecule, or gene therapy mechanisms. These trials included dietary antioxidants (n = 8), non-invasive brain stimulation (n = 5), and GLP-1 agonists (n = 3). Though these interventions lack the industry momentum of amyloid-targeting drugs, their diverse mechanisms highlight a broader recognition that AD may require multi-faceted treatment strategies.

Regulatory guidance also plays a crucial role in shaping clinical trial design. In 2013, the FDA recommended that AD trials incorporate both cognitive and functional outcomes to better capture disease impact (Yu et al. 2022) yet adoption has been slow. Within this analysis, only 35% of trials integrated multiple-domain primary outcomes, suggesting that many still rely on narrow cognitive assessments. Notably, the iADRS composite scale, featured in donanemab's Phase 3 trial, was used in six studies, indicating some adherence to regulatory suggestions. Nevertheless, broader use of functional and biomarker-driven endpoints may be necessary to fully evaluate therapeutic benefits.

Funding priorities also reveal contrasting investment strategies. Industry funding overwhelmingly supports *Biologic–Amyloid* (96%), *Biologic–Tau* (100%), and *Cell and Gene Therapy* (100%), reflecting a commercial push for high-risk, high-reward innovations. Meanwhile, the NIH has focused on *Small Molecule–Amyloid* (26%) and *Other* (33%) trials. This division underscores the tension between pharmaceutical companies, which prioritize marketable biologics, and public institutions, which often fund alternative or lower-cost interventions.

Ultimately, AD research remains at a crossroads. While amyloid-directed therapies have made it to market, they offer only incremental benefits, and alternative strategies—whether targeting tau, leveraging small molecules, or exploring novel mechanisms—have yet to deliver a breakthrough. The field's future may hinge on its ability to integrate multi-targeted treatment strategies, improved patient monitoring, and more inclusive clinical endpoints, ensuring that emerging therapies translate into meaningful improvements for those affected by AD.

6.5 Conclusions

As our population ages and the prevalence of AD increases, efforts to develop disease-modifying therapies have intensified, with 175 late-stage trials and 123 unique candidates included in our review of clinical trials in the United States.

Amyloid remains the dominant target, supported by FDA approvals of lecanemab and donanemab (though real-world effectiveness is yet to be comprehensively described). Tau-targeting therapies face significant challenges, with no candidate progressing beyond Phase 2. While small molecules make up the largest share of trials, biologics are more likely to reach Phase 3. Trials focus on secondary intervention, with participants primarily aged 60–80 years and mild cognitive impairment. We find that the pipeline remains relatively narrow, with limited exploration of alternative mechanisms like neuroinflammation, synaptic repair, and metabolic pathways. Expanding trial diversity and investing in non-amyloid approaches, such as immune system modulation, may be critical, as confirmed by earlier work (Gauthier et al. 2022).

Even with more therapies on the horizon, concerns persist regarding cost, specialized administration, and healthcare system readiness. This review adds to the understanding of clinical trial design and trends, highlighting ongoing efforts to balance investment between

high-profile biologics and underfunded yet promising therapies such as cell and gene therapies (Cao et al. 2024). A more diverse and well-supported pipeline could broaden the treatment landscape and improve outcomes for Alzheimer's patients.

7 Scholarly and Policy Implications

The presented body of work contributes to the intersection of health economics, pharmaceutical policy, and regulatory science, offering critical insights into the challenges and opportunities of financing and access to high-cost therapies in developed healthcare systems.

Across the five papers, several overarching themes emerge, notably the need for alternative payment models to address market inefficiencies in reimbursement of high-cost therapies, the impact of regulatory guidance documents on clinical trial design, and the consequences of payer fragmentation on patient access. I also document important trends in clinical trial design in Alzheimer's disease – an area of significant policy interest given the unmet need in treating this condition. Our findings have several policy implications, in both the United States and other countries where rising costs may result in suboptimal access to innovative treatments and where regulatory incentives may affect the type of clinical research conducted and the nature of new treatments development (together with the evidence on their clinical efficacy which may consequently inform reimbursement).

One of the contributions of the presented work is in the analysis of alternative payment models (APMs) for pharmaceuticals. While traditional cost-effectiveness models assume rational pricing strategies, our work highlights the limitations of uniform pricing when real-world market failures—such as asymmetric information, agency problems, and patient non-adherence—intervene. In the specific case of a gene therapy with high upfront costs, our findings suggest that deferred payment models may allow for earlier patient access while maintaining financial sustainability for payers. Similarly, for Alzheimer's disease-modifying therapies (AD DMTs), our work demonstrates how misalignment between costs and benefits accrued by commercial health plans may result in barriers to patients.

Our work suggests that policy solutions could mitigate existing inefficiencies, particularly in the U.S. healthcare system. Some of these solutions need to be explored in future research and may include proposals such as shared financing mechanisms between public and private payers (particularly in the U.S. context), installment-based payment models (where budget impact and uncertainty about real-world effectiveness may be a challenge) or government-backed risk pools (e.g. in the case of rare disease treatments). Additionally, our work

emphasizes the need for robust data collection, particularly where risk-sharing agreements may be required to address existing market failures and real-world data will be needed to inform such payment models. Such data would also contribute to a more robust evaluation of the cost-effectiveness of high-cost treatments, which currently face challenges in many countries, resulting in potentially delayed patient access.

Our work also provides empirical evidence on the influence of non-binding regulatory guidance on clinical trial design. In a specific case study, we find that trialists follow draft guidance of the FDA, which has broader implications for the regulatory ecosystem in the United States and internationally. We conclude that such regulatory acts may potentially shape innovation pathways and trial costs and should be investigated in future empirical studies.

8 Conclusions

Our work makes several contributions to ongoing policy debates on pharmaceutical pricing, payer sustainability, and regulatory efficiency. It highlights that access to high-cost, high-value therapies remains constrained not only by pricing strategies but also by systemic inefficiencies in payment (reimbursement) mechanisms.

Understanding how the interactions of innovators, healthcare payers and government regulators shape drug innovation and access to approved therapeutics will be essential for ensuring that health systems remain both financially sustainable and capable of delivering timely access to life-saving treatments in the future, in the United States and other developed regions. Yet, more research is needed to address gaps in knowledge identified by our work, particularly in areas related to the design of reimbursement models for specific disease-modifying therapies in Alzheimer's disease.

Overall, our work illustrates that economics may provide useful tools in understanding and potentially solving some of the challenges healthcare systems increasingly face and can help expedite access to emerging treatments while ensuring financial sustainability of healthcare systems around the world.

9 Authorship Contribution Statements

Hlávka, J. P., Yu, J. C., Goldman, D. P., & Lakdawalla, D. N. (2021). The economics of alternative payment models for pharmaceuticals. *The European Journal of Health Economics*, 22, 559-569.

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Appendix A The economics of alternative payment models for pharmaceuticals

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Appendix B The Potential Benefits of Deferred Payment for a Hypothetical Gene Therapy for Congestive Heart Failure: a Cost-Consequence Analysis

Hlávka, J. P., Mattke, S., & Wilks, A. (2020). The potential benefits of deferred payment for a hypothetical gene therapy for congestive heart failure: a cost-consequence analysis. *Applied Health Economics and Health Policy*, *18*, 669-677.

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Appendix C Access to Disease-Modifying Alzheimer's Therapies: Addressing Possible Challenges Using Innovative Payment Models

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Appendix D Impact of non-binding FDA guidances on primary endpoint selection in Alzheimer's disease trials

Yu, J. C., Hlávka, J. P., Joe, E., Richmond, F. J., & Lakdawalla, D. N. (2022). Impact of non-binding FDA guidances on primary endpoint selection in Alzheimer's disease trials. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*, 8(1), e12280.

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Appendix E Emerging Alzheimer's disease treatment paradigms: A late-stage clinical trial review

Hlávka, J. P., Kinoshita, A. T., Jeyasingh, D., Huang, C., Mirsafian, L., & Jacobson, M. (2024). Emerging Alzheimer's disease treatment paradigms: A late-stage clinical trial review. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*, *10*(4), e70022.

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