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The impact of health technology made simple

The Impact on R&D Investment of the CMS Draft National Coverage Determination for Amyloid-directed Monoclonal Antibodies in Alzheimer's Disease

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Disclosure

- This research and analysis was commissioned and funded by Biogen, Inc.
- Vital Transformation LLC, an international health economics and strategy consultancy, conducted an analysis of the impact of CMS' draft decision on the reimbursement of amyloid-directed monoclonal antibodies under evidence on the biopharmaceutical innovation ecosystem, and specifically the impact on investment and new drug pipeline development in Alzheimer's disease.
- The opinions included in this work are those of Vital Transformation LLC, and not necessarily those of the project's sponsor, Biogen.
- The analysis was performed by Vital Transformation Consulting Economist Dr Harry Bowen and Vital Transformation Managing Director Duane Schulthess.
- The raw data behind this research can be found here.

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Executive Summary

- The Centers for Medicare and Medicaid Services (CMS) has introduced a draft national coverage determination (NCD) for amyloid-targeting Alzheimer's disease (AD) therapies which brings new uncertainties into investment decisions / ROI calculations.
- This analysis measures the potential impact of this NCD - using assumptions based on the current draft language and historical data about AD R&D trials and investment, we assume that the NCD will add 3 or more years to the time it takes for an AD asset to see any return on investment.
- Of the programs currently in development – IF the proposed NCD was in place at the time of program initiation, 93% of investments would have had negative ROI and therefore would not have likely been made.
- Furthermore, the results of our research find that many existing clinical development programs would likely be halted - this is not only true for amyloid-targeting therapies, but all AD treatments, as neurological disorders often use the same endpoint threshold when applying for CMS program participation.
- The NCD, if implemented, reduces our estimated 39 treatments with a net positive ROI to 3, with an assumed three-year delay; with a four-year delay, we find only one therapy with a positive ROI in our model.
- Finally, the NCD introduces new and material risks to the ROI calculations for potentially all products approved under the accelerated approval pathway, which is vital to supporting the development of treatments targeting high unmet medical needs and significant scientific challenges.

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Neuroscience Research Involves High Risks

Those risks have led to many firms exiting the therapeutic area

CNS Program Portfolios in Large Pharma		
Company	**2009**	**2014**
Abbott/AbbVie	17	10
AstraZeneca	21	7
Bristol-Myers Squibb	12	2
GlaxoSmithKline	40	14
Johnson & Johnson	18	17
Lilly	16	9
Merck/Schering-Plough	32	7
Novartis	14	15
Pfizer/Wyeth	46	15
Roche/Genentech	22	21
Sanofi/Genzyme	29	12
Total Programs	**267**	**129**

- Biopharma companies have downsized their neuroscience research even before the impacts of CMS' proposal are considered
- Developing drugs to treat brain diseases is more difficult and often more time-consuming and expensive than developing drugs for other therapeutic areas

Neuron, Volume 84, Issue 3, Medicines for the Mind: Policy-Based "Pull" Incentives for Creating Breakthrough CNS Drugs; Dennis W. Choi, Robert Armitage, et al.; 2014, Pages 554-563; ISSN 0896-6273, https://doi.org/10.1016/j.neuron.2014.10.027. (https://www.sciencedirect.com/science/article/pii/S0896627314009477)

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Project Background

- This study investigates the potential impact of the recent draft national coverage determination (NCD) by the Centers for Medicare & Medicaid Services (CMS) on willingness of investors to continue to fund the development of new treatments in Alzheimer's disease.
    - On January 11, 2022, "CMS [proposed] to cover FDA approved monoclonal antibodies directed against amyloid for the treatment of Alzheimer's disease (AD) under Coverage with Evidence Development (CED) in CMS approved randomized controlled trials."
- This draft decision exacerbates the challenges related to the development of new AD therapies.
- According to both published research and the data sources used in this study, the total length of time from entering the FDA process for approval of a new AD treatment through to confirmatory phase III clinical trials was 12 – 13 years, leaving approximately 8 years of patent life in the asset to obtain a return-on-investment (ROI).
- Given the high failure rate of Alzheimer's RCTs (>99%), the added delay in market access if the CMS draft guidance is implemented will increase the risk associated to early stage investments, likely driving many out of the sector, which has already declined by 50% in the last 10 years.

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Former FDA Director Scott Gottlieb Pointedly Critical of CMS Decision

Scott Gottlieb criticizes CMS in feud over Aduhelm coverage, calls out their lack of expertise

Paul Schloesser
Associate Editor

"It leaves the entire field of Alzheimer's drug development in a state of limbo... CMS is now using the issue of whether or not a drug is approved under regular approval versus accelerated approval as a basis potentially going forward for denying coverage to drugs."

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CMS Draft Decision and Alzheimer's R&D

How does the CMS draft NCD potentially alter the ratio of risk/reward for investors?

- Investors are sensitive to the need of new therapies to provide a return on their investment and will dedicate the most capital to those assets with the greatest probability of successfully creating profits.
- Extending clinical trials in AD, with their historically high rates of failure, adds investment risk and radically reduces returns for investors.
- CMS creates uncertainty by negating the RCT evidence basis that is pre-agreed with the FDA, *ex post facto*.
- While this particular NCD is specific to amyloid-targeting therapies, the draft decision introduces major uncertainty with regards to how CMS will view the evidence of existing clinical trials across all modalities of Alzheimer's disease treatments, especially those that target early stages of the disease.
- Given the long duration required for the clinical development of Alzheimer's therapies, CMS' draft decision will add uncertainty to investments made into current and future AD therapies.
- Investors may react by reducing investments in Alzheimer's, and potentially other neuro treatments and any therapeutic area where accelerated approval is now in question.

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Research Methodology

1. Starting from 1993, a cohort of clinical trials for the treatment of Alzheimer's disease (AD) was extracted – 551 trials in total.
2. All early-stage investments, venture funding, grants, IPOs, and deals involving clinical research in AD were obtained by the date secured and then linked to the specific asset/company that entered into AD RCTs for FDA approval – 729 individual financing rounds and 287 deals in total.
3. The length of time required, from launch to conclusion, of an AD trial was calculated for the entire historical cohort, and the increase of time, increase of costs, and reductions of revenue caused by the CMS draft decision was incorporated into our assessment.
4. The impacts of the CMS draft decision were applied to a revised estimate for investor ROI, taking into consideration several scenarios for reduced revenue and patent life.

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Clinical Trials for AD Launched Since 1993

Trial Type	Total
Suspended	330
Preclinical	65
I	39
II	37
Development Outside U.S.	27
III	11
Investigator Initiated	9
II/III	8
I/II	7
IND	6
Program Hold	3
Approved	**3**
NDA	2
IIb	2
Withdrawn from Market	1
BLA	1
Grand Total	**551**

- Data taken from the BioMedTracker database, filtering out generic treatments.
- 3 remaining patented drugs from 551 clinical trials in our sample represents a 99.5% rate of failure
- Two of the three approved drugs are reformulated versions of otherwise generic treatments.
- Donepezil, Galantamine, Rivastigmine, and Memantine are now generic and thus filtered out of our dataset.
- Suvorexant is also filtered as AD was not its lead indication, which was insomnia.

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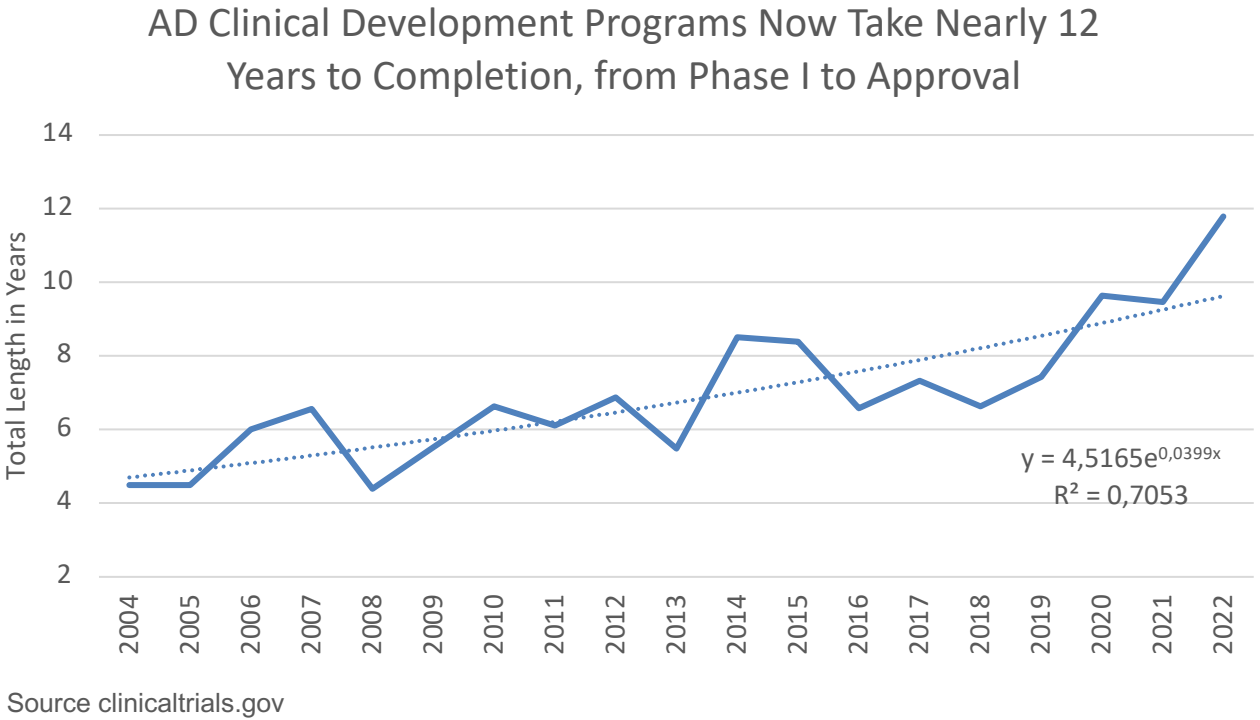
Alzheimer's RCTs – How Long Have They Taken Historically?

The length of an average AD development program is increasing by 4 % per year



Source clinicaltrials.gov

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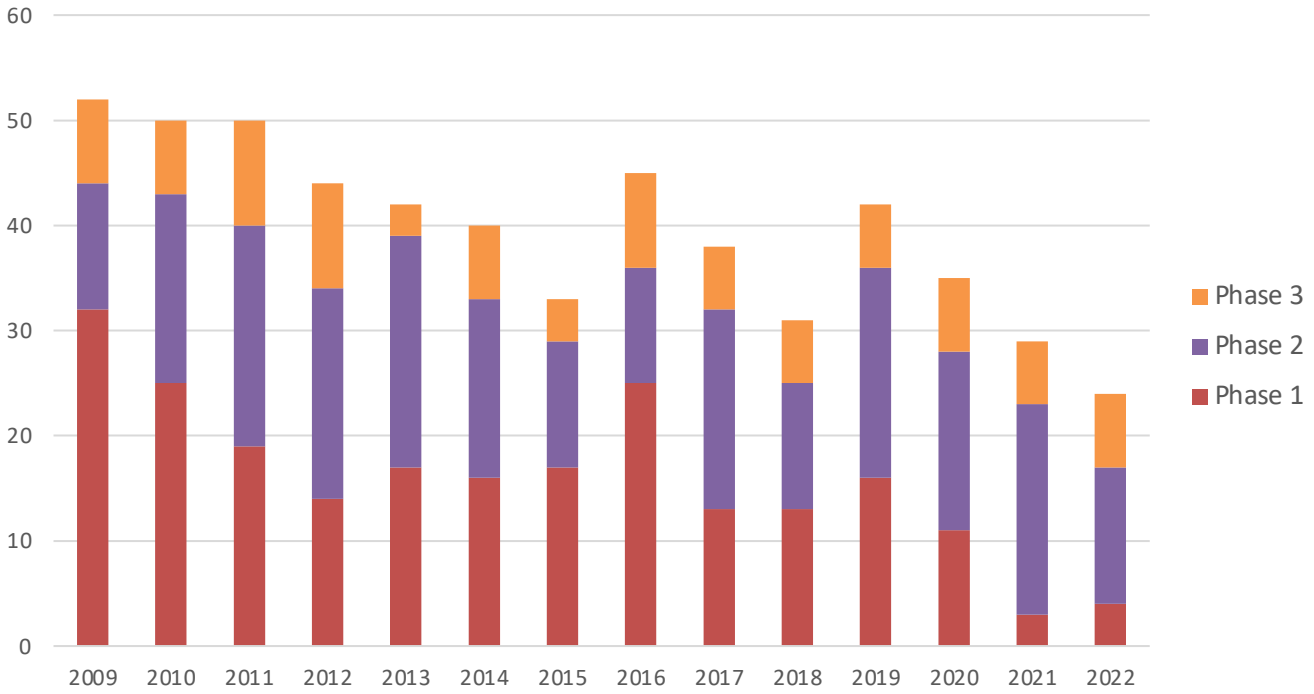
The number of Alzheimer's RCTs had dropped by 50%



Source clinicaltrials.gov

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The US is Dominant in Global Alzheimer's RCTs

Country	Total RCTS
United States	282
Japan	37
United Kingdom	30
Switzerland	29
Canada	22
France	20
Korea (South)	16
Spain	14
Germany	13
Ireland	13
Sweden	12
Israel	12
Australia	12
Denmark	11
India	6
Italy	5
China	4

Source: BioMedTracker by Informa

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RCTs are trying to find an answer

Top 15 AD Target Areas	Total
Amyloid Beta/Amyloid Plaques	**15**
Cholinesterases	**12**
Tau proteins	**5**
Stem Cells/Other Cell Therapies	**4**
NMDA Glutamate Receptor Serotonin 5-HT3 receptor	**3**
Amyloid Beta/Amyloid Plaques Immune System	**3**
Protein Kinase C (PKC)	**2**
Nerve growth factor (NGF)/receptor	**2**
TREM2	**2**
Immune System Tau proteins	**2**
Tumor Necrosis Factor-alpha (TNF-alpha)	**2**
NMDA Glutamate Receptor	**1**
Acetylcholine Cholinesterases	**1**
Serotonin 5-HT4 receptor	**1**
B-APP Synthesis Cholinesterases	**1**

Source: BioMedTracker by Informa

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Modeling the Impact on Investors – Assumptions

1. All trials in our dataset were filtered to focus on non-generic new molecular entities or biologics currently enrolling for RCTs in Alzheimer's, leaving a set of 100 ongoing clinical trials at various stages of delivery; all suspended trials and those for generic treatments were removed, a sample of 45 trials were individually modeled by phase using a Net Present Value financial calculation.

2. Based on our research for average RCT length, all trials were modeled assuming an 11-year period of research of 3, 4, and 5 years for phases 1 – 3 respectively where not indicated in ClinicalTrials.gov, through their ending of patent life.

3. The cost per enrolled trial subject of $100,000[1] per person per year was used as a proxy for cash costs; where a phase was not yet launched, the average time and enrollment of 55, 200, and 1800 subjects for phases 1 – 3 was used; cash costs were offset by all investments, IPO, licensing agreements, and grants that were researched in several subscription financial databases.

4. Although CMS does not propose mandating a specific duration of trial, our research suggests that 3 to 4 years will likely be needed to conduct an additional RCT; for the purpose of this assessment, we have modeled both scenarios.

5. To account for failure rates, the estimated average reimbursement per patient per year based on industry analysts[2] was used with the potential market of 1,000,000 subjects, with sales growth due to annual increased uptake compounding at 20% per year. The potential market revenue of $32,500,000,000 was deflated by 99.5% in each trial to accurately adjust for investor risk.

6. All trials starting from phase 1 were modeled to assume a 20-year patent life; the model does not account for sales beyond patent expiration.

7. The ROI was calculated using an 11% cost of capital, revenues were then delayed by 3 and 4 years to model the impact of the CMS guidance on final ROI. We assume a two arm trial of 1800 subjects, with 900 subjects being compensated for the therapy while participating in a CMS guided RCT under evidence.

[1] Number drawn from Scott 2014 data for average phase 3 out of pocket costs adjusted for inflation, and confidential discussions with several leading VCs currently funding trials in neurological disorders.
[2] Earnings guidance, Mathew Harrison of Morgan Stanley, "assumed net price to $35,000 from $20,000", 6/8/21

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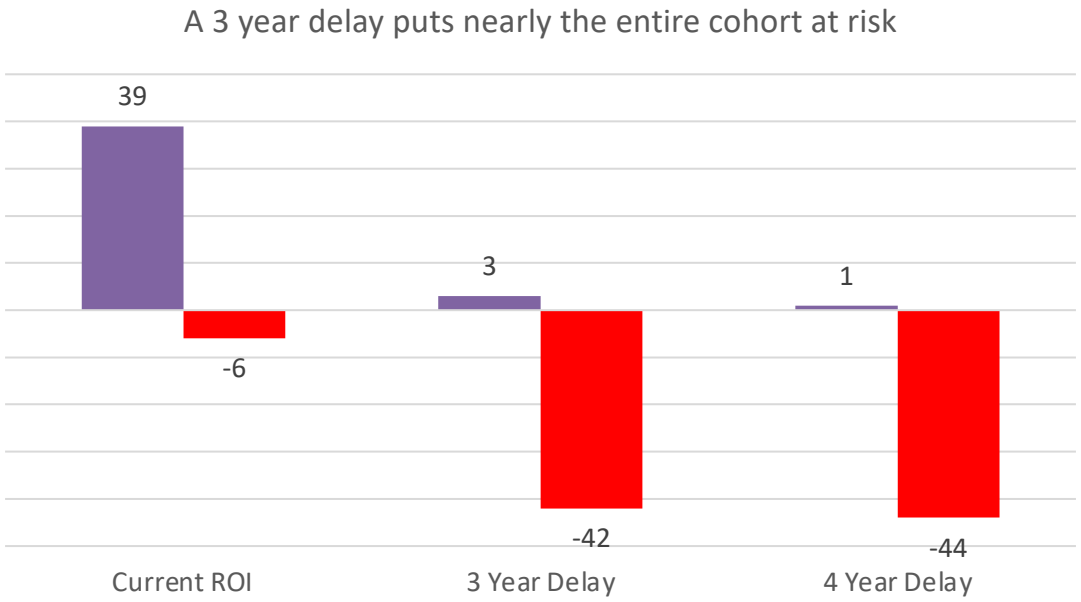
CMS Coverage with Evidence Development (CED)

What is the Impact for Investors?



- Investors require a positive return on their investment – 39 of 45 therapies in active clinical AD development, based upon the FDA approval pathway, are 'good' investments in our analysis.
- However, when we model a three-year delay in market access due to the proposed CMS decision, 42 of our 45 assets are no longer good investments.
- An investor would likely not support their continued development as they are no longer profitable.
- A large company would also likely halt or pause a live AD development program in those therapies as it would no longer be profitable and sustainable.

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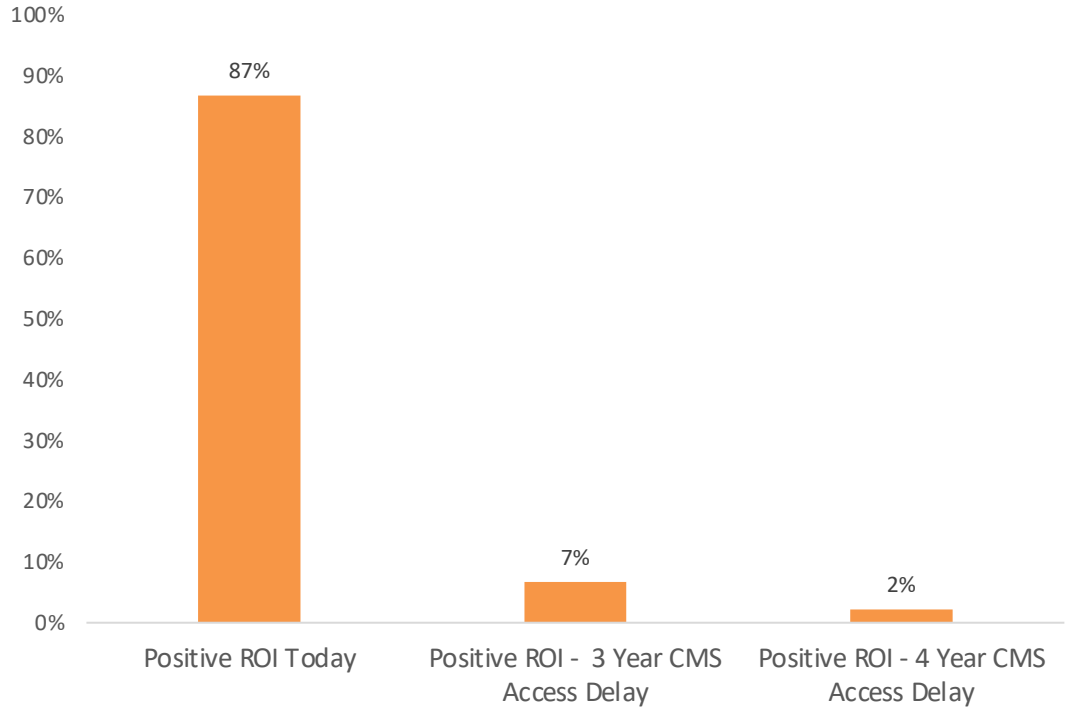
CMS Coverage with Evidence Development (CED)

Alzheimer's RCTs become even more risky



This graph shows the change in the percentage of 'investable' therapies currently in development that are 'good' investments before and after modeling the theoretical impact of the CMS' guidance proposal.

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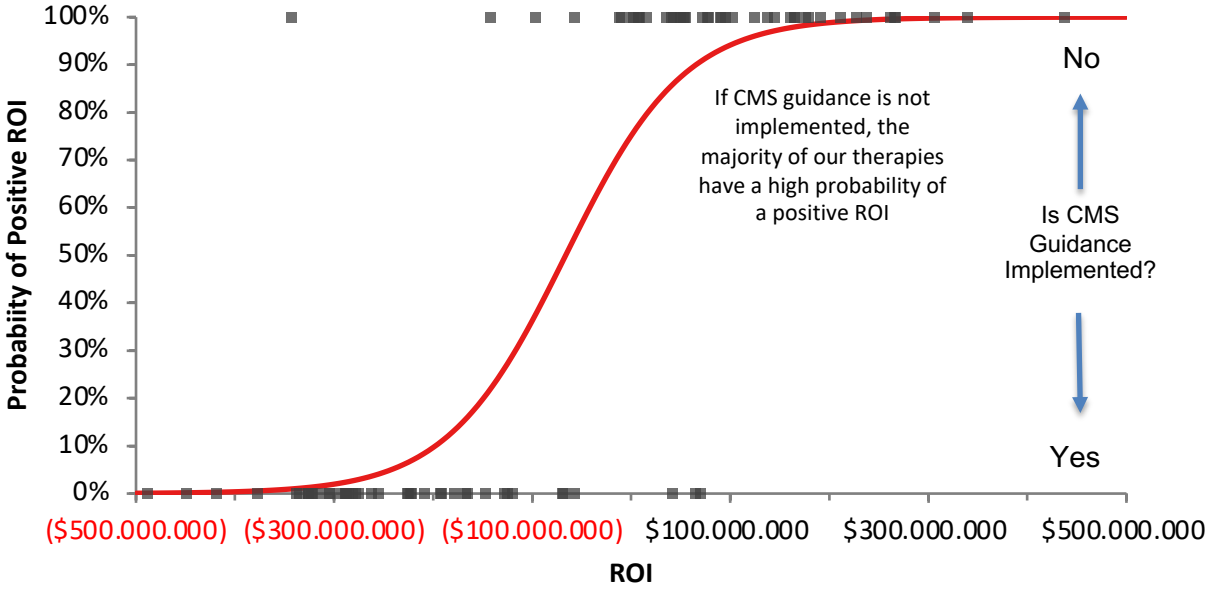
Does the CMS decision impact ROI with statistical certainty?



Source	-log Likelihood	DF	G^2 statistic	p
Difference	38.761	1	77.52	<0.0001
Fitted model	23.622	88		
Null model	62.383	89		

- This chart shows how a “yes or no” by CMS to implement their guidance will impact future value of a therapy.
- The black dots are the ROI of a therapy if CMS does or does not implement their guidance.
- The statistical relationship is very strong: 78% of the change in the probability of having a positive or negative ROI is determined only by the decision by CMS (i.e. the G^2 Statistic).
- The p value ($p < 0.0001$) means there is less than a one in 100,000 chance that this relationship between the CMS guidance and the investment value of a therapy is random.

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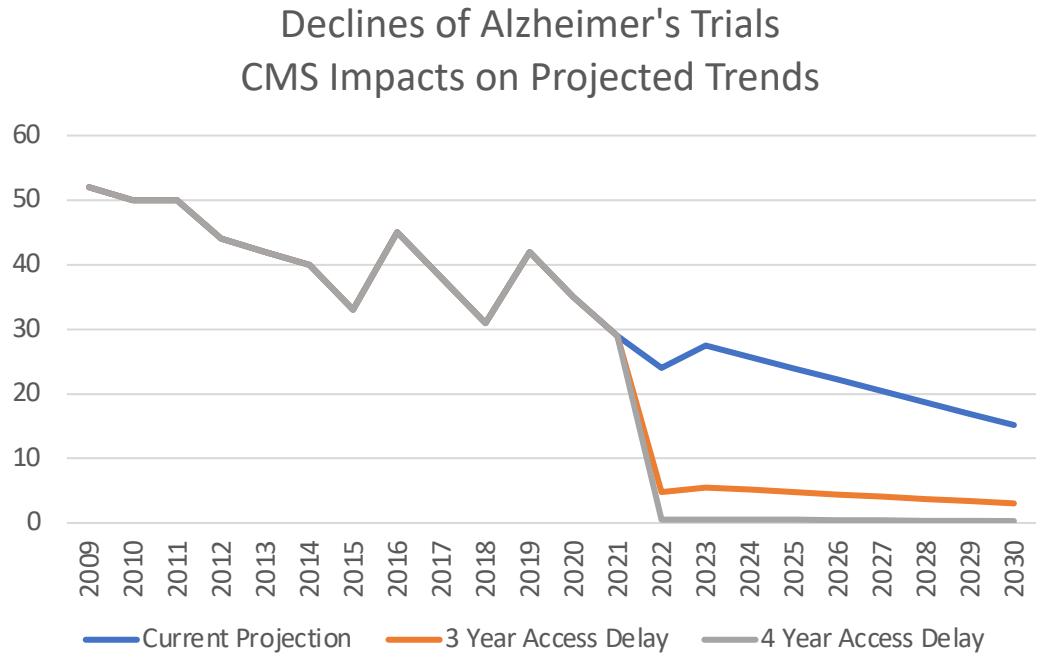
Far fewer RCTs to find cures for patients

CMS' CED would accelerate the decline in AD development, hurting those most in need



- Clinical trials for Alzheimer's disease will continue to halve in number every 10 years at current trends.
- An 80% decline in ROI if the CMS draft decision is implemented, i.e. the delay of 3 years, essentially brings the number of AD therapies under clinical development near to zero.
- Given the success rate for trials is currently less than one in one hundred, removing the ROI from this class of therapeutics will likely see an exodus from early stage investing.

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Conclusions

- Given their high failure rate, a delay of three or more years in the period of revenue realization for new Alzheimer's therapies renders the majority those under clinical investigation financially untenable, according to our model.
- The decision to potentially overturn an FDA decision further adds uncertainty to investors, as the evidence challenges for other neurological disorders is similar to that of amyloid-based AD treatments.
- Even though the proposed CMS guidance applies specifically to amyloid-targeting antibodies, it introduces material risks to the ROI calculations for other assets in development, including other Alzheimer's treatments as well as neurology more broadly, and all products approved under the accelerated approval pathway.
- The proposed guidance puts at risk the entire US Government's strategy to create incentives via the prescription drug benefit to promote the adaption of targeted therapies, orphan drugs, and difficult areas of research such as neurological disorders.
- CMS' guidance, if implemented, will have cooling effect on R&D, and funds will likely move to larger indications with lower risk profiles; it will push risk capital and biopharma away from areas of high unmet medical needs, into other 'me too' categories not seen since the 1990s.
- The use of accelerated approvals is vital to the financial viability of treatments with challenging economics such as orphan diseases and hard to treat neurological disorders; ultimately, these policies were put in place to promote the development of cures in clinical areas with the most challenging science with high probabilities of failure – the effect of this guidance, if implemented, will be less innovation where it is needed most.

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Data Sources Used

Datasets used in this research include proprietary data and publicly available information:

1. BioCentury
2. BioMedTracker/Informa
3. ClinicalTrials.gov
4. https://www.alzforum.org
5. SEC 10-K Annual Financial Disclosures
6. FDA Orange Book
7. FDA Purple Book
8. Company press releases

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