Strengthening the FDA's Accelerated Approval Pathway: Progress and Unfinished Business

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Introduction

The prices of drugs and the innovation that leads to their availability are reliable sources of controversy in American public discourse. In 2023, the United States spent $723 billion on thousands of branded and generic prescription drugs approved by the Food and Drug Administration (FDA).[1-3] Few of these drugs generate as much public scrutiny as the small minority approved through the accelerated approval (AA) pathway.

Accelerated approval is an FDA pathway that allows approval of drugs for serious conditions based on surrogate or intermediate endpoints considered reasonably likely to predict clinical benefit to give patients faster access to promising new treatments. Accelerated approval comes with a requirement that manufacturers conduct confirmatory trials to verify the expected clinical benefit. Between 1992 and 2021, FDA granted AA only 278 times, a small percentage of overall marketing approvals.[4,5] Although the prices of AA drugs are often high, they do not account for the majority of financial outlay for medications. Recent estimates place spending on these products at between 2.5-16% of overall prescription drug spending, depending on the payer and treatment setting.[6,7]

The pathway can be credited with early patient access to several revolutionary treatments, notably including anti-retrovirals for Human Immunodeficiency Virus (HIV) and imatinib (Gleevec®, Novartis) for chronic myeloid leukemia. In more recent years, the program's success also includes early access to immuno-oncology agents, including pembrolizumab (Keytruda®, Merck). Merck credits the pathway with making Keytruda available to patients approximately 3 years sooner than would have been possible under traditional approval and another study estimates that early access to drugs approved under AA for oncology indications resulted in the gain of 263,000 life years across 911,000 patients by 2022.[8,9] A recent analysis looking at the AA pathway from 1992 to 2021 showed that half of AAs converted to full approval in a median time of 3.2 years.[10]

Yet certain drugs with AA have captured public attention in ways that are becoming emblematic of larger challenges troubling the pharmaceutical and health insurance industries. Aducanumab (Aduhelm®, Biogen), approved in June 2021 for Alzheimer's disease (AD) at an initial annual cost of $56,000 per patient, prompted fierce debate over FDA's use of AA and whether the agency had inappropriately collaborated with the manufacturer.[11,12] More recently, delandistrogene moxeparvovec (Elevidys®, Sarepta Therapeutics), a gene therapy for Duchenne muscular dystrophy (DMD) approved in 2023 at a cost of $3.2 million per patient, raised questions about both safety and efficacy after several children died following treatment.[13,14]

These high-profile cases reflect broader questions surrounding the sustainability and return on investment of pharmaceutical innovation. Pharmaceutical Research and Development (R&D) productivity has been declining for decades, with fewer new molecular entities approved per billion dollars invested.[15,16] Industry experts have attributed the trend to exhaustion of readily addressable

areas of unmet need, stepwise advances in medical knowledge and technology, rising costs of enrolling clinical trial subjects, and investment crowding into certain therapeutic areas.[17]

Meanwhile, use of the AA pathway, which has a lower threshold for evidence at initial approval, has been growing dramatically since the late 2010s, with approximately 200 drugs currently marketed under AA.[18,19] These shifts come against a backdrop of mounting questions about the prices and value of drugs more broadly, as well as under AA specifically.[20-22]

Americans increasingly find themselves caught in the push-and-pull between high prices and access restrictions that have come to characterize our health care system, including but not limited to drugs. Surveys consistently show that substantial majorities report difficulty affording medications or consider drug prices to be unreasonable.[20,21] Nearly one-third of adults report not taking medicines as prescribed due to cost.[20] Others struggle to obtain drugs they need because of growing access restrictions, which also frustrates physicians.[23-26] Perhaps unsurprisingly, Americans distrust this system: six out of 10 Americans blame both pharmaceutical companies and health insurers for problems with the health care system. [27,28]

Against this backdrop of public distrust, both FDA approval and post-approval monitoring of certain drugs with AA, as well as payer coverage restrictions on such drugs, invite heightened scrutiny. In April 2021, ICER published a report on the accelerated approval pathway that identified several areas needing reform, including concerns about the selection of surrogate endpoints, lagging confirmatory trials, low levels of evidence, and problematic financial incentives that required greater accountability of the U.S. regulatory system as well as pharmaceutical companies and payers.[29] Other reports and investigations issued around the same time echoed these findings, including a Congressional inquiry and a report by the Office of Inspector General (OIG). [19,30] Following the Aduhelm controversy, Congress passed reforms that gave the FDA greater oversight and enforcement authorities over AA. FDA subsequently issued several new guidances in direct response to critiques about the selection of surrogate endpoints and development of confirmatory data.

In this report, we examine the evolution – and perception – of AA since these Congressional and regulatory reforms, and offer updated policy options that remain relevant for continuing to strengthen the AA pathway.

Background

The creation of the AA pathway was a policy response to the HIV/AIDS crisis, during which patient access to new treatments, including those for serious, debilitating, and even fatal conditions was delayed by the rigorous clinical trial standards of the Kefauver Act.[31] Accelerated approval relies on surrogate endpoints, which are intermediate measures of disease activity thought to be

"reasonably likely" to predict clinical benefit. Drugs that receive AA must go on to produce confirmatory evidence of their efficacy and safety in clinical trials to be converted to full "traditional" approval.

What Are Surrogate and Clinical Endpoints?

Clinical Endpoint: A clinical endpoint "directly measures a therapeutic effect of a drug in humans – an effect on how a patient feels (e.g., symptom relief), functions (e.g., improved mobility), or survives." Clinical endpoints in AA generally capture the effects of treatment on "**irreversible morbidity or mortality**" (IMM).[32]

Surrogate Endpoint: Surrogate endpoints are intermediate clinical endpoints or measures of disease activity that precede and predict a treatment's eventual effect on a clinical endpoint. An extensive body of literature has proposed criteria for identifying surrogate endpoints for use in clinical development. While there are some variations, all require surrogate endpoints mediate the treatment effect. In other words, it is not enough for a surrogate endpoint to be correlated with the clinical measure; it must have the ability to predict how the clinical measure changes after treatment or medical intervention.[33-36]

Validated Surrogate Endpoint: A validated surrogate endpoint has a body of evidence showing that it reliably predicts the effects of treatment on a clinical endpoint. FDA accepts validated surrogate endpoints for traditional approval. For example, lowering low-density lipoprotein (LDL) cholesterol levels is accepted as a surrogate for lowering the risk of cardiovascular events.[37]

Unvalidated Surrogate Endpoint: An unvalidated surrogate endpoint does not have evidence to show that it mediates the effect of treatment on a clinical outcome, but may be considered for clinical development of a drug in certain circumstances. For example, the 6-minute walk test (6MWT) is an unvalidated surrogate endpoint used in clinical development of drugs for pulmonary arterial hypertension, lysosomal storage disorders, and other rare diseases, but studies have not established that it explains clinical outcomes.[38,39] Unvalidated surrogate endpoints may be used for AA if they are "reasonably likely to predict" an effect on a clinical endpoint, typically one reflecting IMM.

Accelerated approval has evolved from its initial uses in HIV and other infectious diseases. Over time, the pathway has grown to include a significant number of oncology approvals and is now commonly used in rare diseases as well. Today, its application extends to treatments that might not otherwise be developed because logistics or costs complicate the study of efficacy and safety. In particular, the pathway has created a viable path for small biotech companies with limited

resources to begin earning revenue sooner. What began as a solution to a timing problem is now also solving an economic problem.

Uncertainty is inherent to the pathway; failing to confirm efficacy and safety is a known risk. As a result, stakeholders in the process generally accept that some drugs with AA will not benefit patients. To ensure that patients aren't exposed to undue harm, the pathway is restricted to conditions with severe and irreversible outcomes, including death, with few existing treatment options.

But by 2020, several controversial decisions by the FDA prompted questions about whether prevailing uses of AA were appropriate. Controversy surrounding the pathway grew when FDA granted AA to Aduhelm, a treatment for Alzheimer's disease with such uncertainty about its efficacy and safety that three members of the FDA advisory committee resigned over the approval.[40] Around this time, numerous studies and reports (including our 2021 white paper) identified concerns with low quality evidence and a high price that failed to account for uncertain patient benefits.[29]

Federal investigations followed. In 2022, a report by the Office of the Inspector General (OIG) found that 35 of the 104 drugs with AA that had yet to complete their confirmatory trials had fallen behind their original completion date.[19] The same year, the House Oversight and Energy and Commerce committees published findings of their investigation into the Aduhelm approval. The report raised the possibility that AA was misused as a work-around for approving the drug despite evidence that its effect on clinical outcomes was insufficient for full approval.[30]

In late 2022, Congress passed the Food and Drug Omnibus Reform Act (FDORA), which included several provisions reforming the AA pathway. Among other things, the Act gave FDA the power to expedite withdrawal of drugs with AA from the market and require that confirmatory studies be under way at the time of AA.[41] In addition, it called for the formation of an AA coordinating council to oversee the pathway and issue annual reports, and called for FDA to issue guidance on AA surrogate endpoints, clinical trial design, and confirmatory studies used in AA. The law also required that study sponsors update the FDA on their confirmatory trials every 180 days, as opposed to the previous cadence of annual updates.[41]

By 2025, the FDA had issued several new guidance documents to clarify its position on clinical evidence development requirements for AA. This includes guidance for developing surrogate endpoints that can be considered "reasonably likely" to predict clinical benefit under AA, aspects of study design that sponsors should consider in clinical development, and conditions and processes for expedited withdrawal.[42,43] The agency also established that it will require prescribing information for drugs with AA to describe uncertainties surrounding ultimate clinical benefits,[42] and described its expectations for demonstrating that confirmatory trials be underway at the time of approval.[43] FDA notes that it will consider confirmatory trials to be ongoing if they meet three

criteria, including a target completion date that is "consistent with diligent and timely conducts of the trial," evidence of progress towards timely completion, and initiation of enrollment. Exemptions are considered only in limited circumstances and require "appropriate justification" from the study sponsor. [43]

The agency also responded to concerns specific to oncology, which had come under scrutiny for the use of surrogate outcomes such as progression free survival (PFS) as the primary endpoint and single arm trials to generate confirmatory evidence.[44-46] The Oncology Center of Excellence (OCE) issued guidance describing its preference for randomized controlled trials (RCTs) over single-arm trials in support of AA for oncology products, as well as conditions under which it could consider evidence from single-arm trials instead.[47] The agency also clarified expectations for extensions of the same RCT initially used to support AA to generate confirmatory data for traditional approval, as well as confirmatory evidence requirements from a different line of therapy for the same cancer type.[47] This guidance also recommends that confirmatory trials be underway at the time of AA in order to avoid undermining enrollment of the trials through commercial availability of the drug.

Methods

This paper relies on information and perspectives gathered from interviews with members of ICER's Policy Leadership Forum (PLF) – which includes life sciences companies, health plans, pharmacy benefit managers, and purchasers – as well as patient groups, and regulatory and clinical experts. We used a structured discussion guide to collect input during interviews with 15 respondents about their views on AA, changes in response to recent reforms, and challenges and potential policy solutions that remain since our prior report. We also conducted a targeted literature review focused on AA and clinical development in the U.S.

The ICER research team summarized findings identifying improvements, ongoing challenges, and emerging issues in AA and compared these to policy options identified in our prior report. From this, we developed updated policy options to build on improvements from recent reforms and meet ongoing and emerging challenges.

Finally, discussion and further input from ICER's Policy Summit convened in December 2025 was used to refine and finalize policy options. Senior leaders of 29 payer and life sciences companies joined patient advocates and employer, regulatory, and Medicaid experts at a two-day meeting to deliberate on this topic and provide suggestions for revisions. Meeting participants are shown in the Appendix. None of these participants or their organizations should be considered as approving of any element of this paper. The perspectives and recommendations presented here are those of the editorial team at ICER and Verdant Research alone.

Findings: Evolution of Accelerated Approval

A consensus view from our previous report was that, under ideal circumstances, drugs with AA would reach patients within a timeframe that would not be achieved through traditional approval. Most patients would benefit from better clinical outcomes, although some will not because faster approval at lower levels of evidence inherently implies that some drugs will not produce the hoped-for treatment effect. In this tradeoff, benefits of successful drugs are expected to be substantial, and prices correspond with level of uncertainty and magnitude of clinical benefit.

Most respondents at the time felt that use of the pathway fell short of that ideal. Payers, who view AA as too often producing high-priced drugs with uncertain benefits, limit access. Manufacturers and patients see these restrictions as creating unfair delays and barriers to treatments that were being made available precisely because there was potential for significant benefit. Several controversial AAs, including for drugs used to treat Duchenne muscular dystrophy (DMD) by the pharmaceutical company Sarepta Therapeutics, heightened these tensions.

Interviews for this updated report showed that stakeholders still largely agree on the ideal vision of AA and that recent changes to the pathway are seen as aligned, encouraging faster development of evidence without hindering faster access to promising therapies. But many previously raised issues remain unaddressed, including concerns about pricing and access. Meanwhile, we also found that use of the pathway is evolving along different paths according to therapeutic area, creating challenges that may require tailored solutions.

Views On Predictors of Success in Accelerated Approval

Respondents had clear ideas about what predicted success in conversion to full approval or faster withdrawal after AA:

Favorable:

- Big effect size in surrogate endpoint
- Study sponsor works proactively and with the FDA to develop evidence in support of surrogate endpoint

Unfavorable:

- Small effect size in surrogate endpoint
- Poorly designed confirmatory trial
- Clinical endpoint doesn't reflect patient preferences
- Use as a "salvage option" when drug fails to demonstrate evidence sufficient to justify full approval

Recent Changes

Several policies identified in our 2021 report were at least partially adopted in FDORA reforms or FDA guidance. (See Table 1) These reforms have been well-received and give reason to believe that better perception and performance of AA is possible without sacrificing the objectives of faster access to promising new therapies.

Table 1. Reform Options Identified in ICER's 2021 Paper on AA

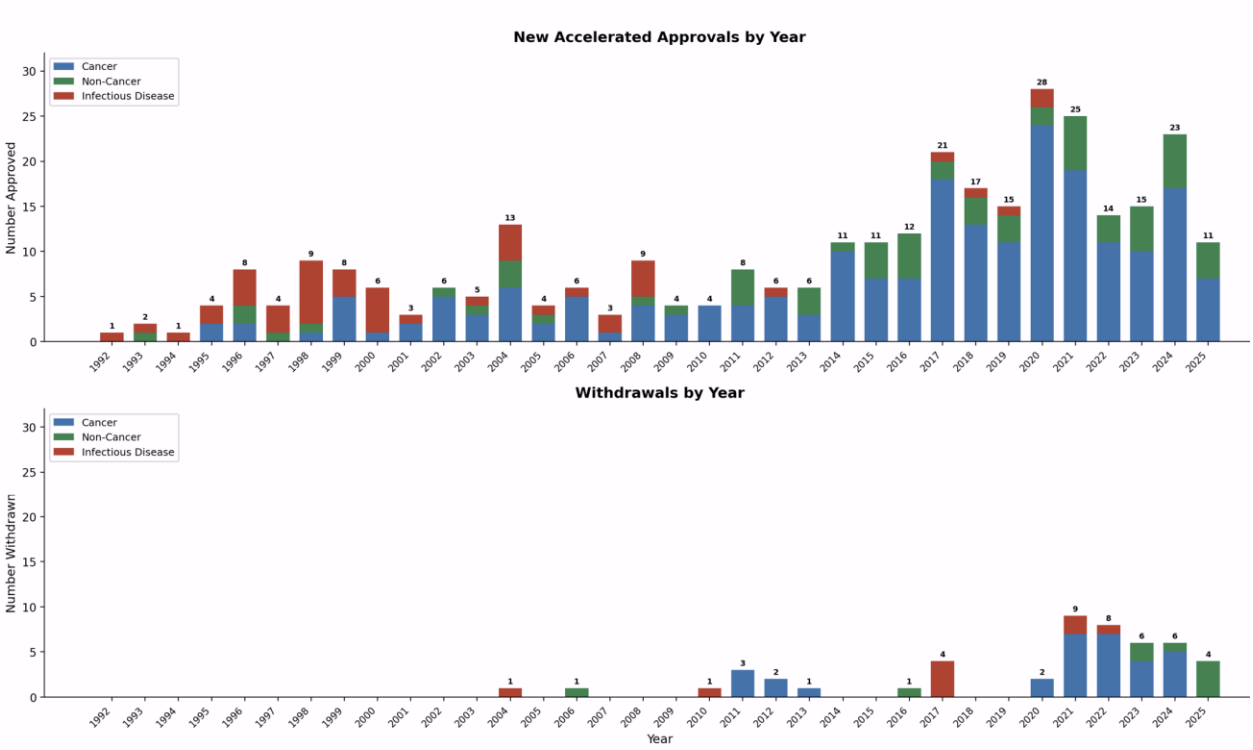
Policy Option	Changes in New FDA Guidance
Strengthen the Selection of Surrogate Endpoints	• Describes conditions and characteristics that would allow FDA to consider a surrogate endpoint to be "reasonably likely" to predict a clinical outcome[42]
Require Greater Use of Randomized Controlled Trials	• Clarifies that FDA prefers randomized controlled trials when it is possible to conduct them for oncology indications under AA, and describes conditions under which a single arm trial is acceptable[47] • Describes design considerations to allow study sponsors to use a single trial for both AA and full approval in oncology[47] • Recommends confirmatory trials be underway at time of AA[42]
Create a New Label Alert and Patient Material for Accelerated Approval Drugs	• Requires manufacturers to describe uncertainties surrounding clinical benefits as part of the Indications and Usage section of the drug's label[42]
Increase Enforcement of Requirements to Complete Confirmatory Trials	• Describes how study sponsors can demonstrate that confirmatory trials are underway and under what circumstances FDA would consider waiving the requirement[42] • Describes conditions and processes under which FDA would pursue expedited withdrawal[48]

FDA's increased use of its existing and new authorities to require confirmation of benefit has been particularly well-received. Even before FDORA was passed, FDA had begun to review and withdraw approval for certain drugs or indications with AA. Between 1999 and 2021, the agency withdrew six approvals for oncology indications; it has withdrawn 25 since 2021.[49] (See Figure 1) In most instances, manufacturers have withdrawn products voluntarily upon FDA's request. For example,

when sacituzumab (Trodelvy®, Gilead Sciences) failed to show an overall survival benefit in urothelial cancer, Gilead withdrew the indication after discussions with the FDA.[49]

FDA's recent actions also built on existing trends towards faster conversion to traditional approval (i.e. approved through the traditional FDA pathway following the release of data from confirmatory trials) or withdrawal in AA for oncology products. One analysis found that average time from accelerated to full approval for oncology indications decreased from 4.3 years between 1992-2013 to 2.3 years between 2014-2024; time to withdrawal decreased from 9.5 to 3.2 years over the same timeframe.[50]

Figure 1. Yearly Approvals and Withdrawals of AA (1992 – 2025)[51]



Newly adopted requirements that confirmatory trials be underway are also seen positively, particularly by payers, who have long voiced frustrations with delays in confirmatory evidence. Manufacturers largely agreed that this change was positive because it improves trial enrollment. Participation in clinical trials typically declines when a therapy becomes commercially available; having trials underway encourages enrollment before this trend takes hold.

Regulatory Flexibilities

While a number of recent AA decisions have been controversial, respondents also acknowledged that flexibility to keep drugs on the market may sometimes be acceptable when confirmatory trial results are ambiguous. Regulatory flexibility as a means of preserving oversight and providing

equitable access to treatments also emerged as a common theme. Many see the pathway as the FDA's "last line of defense" because it allows for ongoing assessment of uncertain benefits and risks over the course of risky clinical development. It was also seen as protecting against a policy shift to "safety-only" approvals that may not entail coverage requirements, which were unanimously rejected as incompatible with the premise of faster access to benefit more patients. Virtually all stakeholders raised the concern that safety-only approvals would mean that only patients who can afford to pay for treatments without insurance coverage would have access to them. Even those patients would have little assurance of efficacy, since manufacturers would have few incentives to produce confirmatory evidence.

Weighed against this alternative, AA was seen as a critical tool for spurring scientific progress as well as patient access. In our prior report, many respondents viewed flexibilities as readily abused. In this iteration, they were viewed as an acceptable tradeoff.

Failed Trials

When a drug does fail in confirmatory trials, stakeholders consider AA successful if the product is removed from the market according to FDA procedures and in a timely manner. The withdrawal of bevacizumab (Avastin®, Genentech/Roche) for the treatment of metastatic breast cancer was frequently described as an example in which the pathway worked as intended, even though this is one of the few examples in which the drug's manufacturer contested the withdrawal, keeping it on the market through a year-long appeals process. Granted AA in 2008 for this indication, Avastin showed some initial promise on the basis of progression free survival (PFS), albeit not on overall survival (OS).[52] Four confirmatory trials subsequently failed to show evidence of a PFS or OS benefit and in late 2010, the FDA announced it would seek withdrawal of the indication.[53] After public hearings to weigh Genentech's appeal, the withdrawal of the indication was completed in late 2011.

Contested Withdrawals

FDA proposals to withdraw AA have only been appealed three times, for Avastin for the treatment of breast cancer, hydroxyprogesterone caproate injection (Makena®, Azurity Pharmaceuticals) for prevention of preterm birth, and melphalan flufenamide (Pepaxto®, Oncopeptides) for multiple myeloma. The withdrawals of Avastin and Makena both occurred before FDA was granted expedited withdrawal authority under FDORA, and took 11 and 30 months, respectively. Makena's lengthy withdrawal process became an illustrative example of problems with AA.[54] Resolution was reached more rapidly with Pepaxto under the FDA's new expanded authority. It was withdrawn from the market seven months after the agency's initial proposal.[55]

In some instances, confirmatory trials produce ambiguous results: neither clear evidence in support of conversion to traditional approval nor to suggest the drug should be withdrawn. For example, in 2016, FDA granted AA to obeticholic acid (Ocaliva®, Intercept Pharmaceuticals) for primary biliary cholangitis (PBC). In 2024, confirmatory trials failed to show improvements in the rate of death, liver transplants, and other disease-related outcomes, although a comparison to real world data from untreated patients did show improvement in these outcomes. In addition, serious liver injuries were observed in patients taking the drug, and FDA declined to grant it approval for a different indication, nonalcoholic steatohepatitis (NASH).[56] An advisory committee voted that data from confirmatory trials in PBC did not support full approval and FDA went on to issue a complete response letter (CRL) denying conversion to traditional approval in PBC.[57] However, the agency allowed the drug to remain on the market with AA for PBC while it considered additional data. In 2025, the agency identified additional safety concerns, halted further clinical development of the drug, and requested that Intercept, its manufacturer, voluntarily withdraw it. Intercept obliged.[58]

Stakeholder Input

Whether Ocaliva should have been allowed to remain available to patients while the FDA followed procedure is an open question. But although regulatory flexibilities can slow the removal of a drug from the market, they also provide opportunities for stakeholders to weigh in on the decision and prepare for changes in access. Recent experience with Elevidys, a gene therapy for Duchenne muscular dystrophy (DMD), illustrates problems raised by abrupt changes outside of procedural norms. Elevidys was initially granted AA for children over the age of four who remained ambulatory.[59] Although confirmatory trials failed to achieve the primary endpoint, FDA nevertheless granted traditional approval and also expanded the label to include non-ambulatory patients under AA.[60] The product then remained in the headlines as several patients died of acute liver failure.[13]

The FDA, recently under new leadership, took the unusual action of demanding that shipping of the drug be halted, rather than propose withdrawal through the processes laid out in guidance. The controversy was heightened by several other factors. One is that Elevidys is highly sought after by parents of children with DMD. Another is that it is manufactured by Sarepta, whose prior use of the AA pathway has been the subject of regulatory and policy controversy regarding evidentiary standards and demonstrated clinical benefit. The FDA's abrupt announcement precipitated even more controversy, with patients and their parents advocating to have access restored.[61] The agency ultimately reversed course to allow treatment of patients who remain ambulatory.

Public Perception of Repeated Reliance on Flexibilities

Company track record shapes public perception. Many view Sarepta, Elevidys' manufacturer, with suspicion, since the company's numerous accelerated approvals have been contentious. The company's products aim to replace dystrophin, which DMD patients lack, with truncated forms of the protein. Its products have stirred controversy since 2016, when FDA approved its first drug, eteplirsen (Exondys 51®, Sarepta Therapeutics) despite significant scientific uncertainties and a very small effect size in the surrogate endpoint. Sarepta has since failed to produce confirmatory data for the drug, an exon-skipping therapy, within the specified timeframe, but continues to market the drug.

In the more than 10 years working on this target and disease, Sarepta has struggled to produce evidence of effect in any of its marketed products. Confirmatory trials for its other exon-skipping therapies, approved on similarly low levels of evidence, have been delayed. Until recently, the only confirmatory trial it has completed is for its gene therapy, Elevidys, which failed to achieve its primary endpoint. In November 2025, the company finally published results of confirmatory studies for two of its exon-skipping therapies, which failed to show any statistically significant difference in the ability to climb stairs among patients treated with the drugs for 96 weeks as compared with placebo.[62] The company nevertheless plans to pursue conversion to full approval.[63]

Evidence Standards and Expectations

FDA's use of regulatory flexibilities can also invite controversy when used to grant AA to drugs with existing but underwhelming evidence of clinical benefit. The 2021 approval of Aduhelm exemplifies this dynamic: after the FDA's advisory committee voted against traditional approval, the agency pivoted to AA. The move raised questions of how AA could be justified when evidence of clinical benefit had already accrued and was deemed inadequate to support full approval. Several prominent members of the committee resigned in protest of the decision and Congress began an investigation into use of the AA pathway. High prices also contributed to the controversy: Biogen initially set Aduhelm's price at $56,000 a year despite significant uncertainties, serious safety concerns, and low promise of meaningful efficacy. Amidst these concerns, the Centers for Medicare and Medicaid Services (CMS) announced that it would be using a Coverage with Evidence Development (CED) approach for all monoclonal antibodies used to treat Alzheimer's disease – including Aduhelm – because of the uncertainties surrounding the relationship between the surrogate endpoint of clearance of beta amyloid plaque and clinical outcomes.[64] The decision set off a debate about the role of CMS, not only in breaking precedent by not granting unconditional

coverage of a drug with FDA approval, but by demanding the development of clinical data that the FDA had not.[65-67]

Flexibility in applying evidence standards becomes particularly contentious when it runs counter to expectations for improvement in the surrogate endpoint, as it did for Sarepta's Exondys 51. Exondys 51 was designed to produce a truncated form of dystrophin in patients with Duchenne muscular dystrophy (DMD), whose bodies otherwise cannot make meaningful amounts of the protein. Clinical trials evaluated changes in dystrophin level as the surrogate endpoint, which was developed based on evidence from Becker muscular dystrophy (BMD). BMD is a less severe condition in which cells produce a shortened but partially functional form of dystrophin, at levels typically ranging from 10-50% of normal.[68] Other scientific evidence suggested that a minimum of 15% in dystrophin levels would be needed, and key FDA staff thought that at least a 10% dystrophin level would be "reasonably likely to predict clinical benefit".[69,70] The FDA nevertheless granted AA on the less than 1% dystrophin levels seen in clinical trials and no evidence of improvement on the clinical endpoint, improvement in a six-minute walk test (6MWT).[71] Internal FDA documents revealed sharp disagreement about this decision, which prompted significant controversy.[72]

Asymmetric Uncertainties

Regulatory flexibilities are often deployed when information about treatment risks and benefits emerges at different rates. Surrogate endpoints serve as predictors of clinical benefit, not as indicators of treatment-related risks. This has two critical implications for the AA pathway.

First, clinical outcome measures in confirmatory trials often capture the net effect of both benefit and harm from treatment. As a result, even when surrogate endpoints suggest promise, confirmatory studies may yield disappointing results if toxicity offsets clinical gains. In fact, this was an underlying reason for the withdrawal of Avastin for breast cancer: the lack of benefit in overall survival was related to increased treatment-related mortality.[73]

Second, evidence of adverse events often accrues more rapidly than data demonstrating clinical benefit, especially when therapeutic effects are modest and adequately powered studies require larger sample sizes and longer follow-up. While it may become clear over the course of a trial that treatment-related adverse events are unexpectedly common or severe, their overall effect on the clinical endpoint remains unknown until the confirmatory trial reads out. In the meantime, higher than expected rates of adverse events can call into question whether the balance of risks and benefits expected at the time of AA can be achieved. In clinical trials, these questions fall to data safety monitoring boards, which are tasked with determining whether to continue or discontinue a trial based on interim data. While patients participating in confirmatory trials may be protected by these safeguards, their contemporaries receiving treatment covered by insurance are not.

Challenges by Therapeutic Area

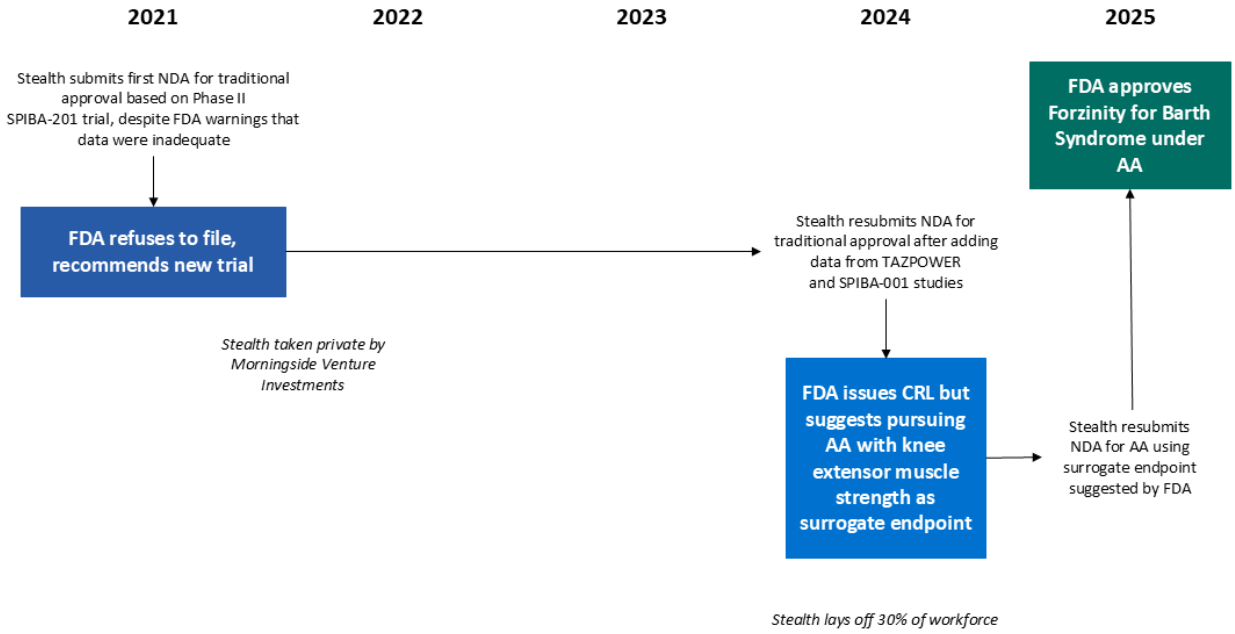
Non-Oncologic Rare Diseases

Accelerated Approval faces particular challenges in non-oncologic rare diseases, where the traditional pathway, often combined with breakthrough designation and priority review, has been proven highly successful. Treatments including nusinersen (Spinraza®, Biogen) for spinal muscular atrophy and enzyme replacement therapies for lysosomal storage disorders such as Fabry disease and Hunter syndrome all reached patients without AA.

But not all rare diseases lend themselves to traditional approval, especially when early treatment is thought to prevent irreversible disease progression. In many such cases the disease is not well-understood, and the evidence to inform the development of surrogate endpoints is limited. This is particularly true of ultra-rare diseases, where small numbers of patients further confound the ability to gain scientific understanding about disease biology, let alone study clinical outcomes. Uncertainty arises from both not knowing how much clinical outcomes can be improved, and limited evidence to link surrogate endpoints to clinical ones. Moreover, a significant number of study sponsors are early stage biotechs with specialized expertise in a specific condition or therapeutic platform. Backed by venture capital, financing these companies' operations and clinical development programs depends on milestone payments associated with progress and results from their clinical trials.

Elamipretide (Forzinity™, Stealth BioTherapeutics), recently approved by the FDA under AA for the treatment of Barth Syndrome, illustrates the give-and-take between scientific and practical considerations. Barth Syndrome is an X-linked genetic disorder that causes, among other things, cardiomyopathy and growth delays in boys. Stealth BioTherapeutics originally submitted its New Drug Application (NDA) for Forzinity to the FDA in 2021, despite FDA's warning that it considered the evidence in support of its application to be inadequate.[74] The FDA responded to the submission with a refusal to file, noting that the submission depended on data from the Phase II clinical trial SPIBA-201, which was negative during the randomized controlled portion.[75] While Stealth argued that it was reasonable to consider the positive result from the subsequent open label extension of the same trial to historic controls, FDA recommended the company conduct a new trial. Instead, the company resubmitted the NDA in 2024 with additional results from the open-label extension period of another study, the Phase II TAZPOWER trial.[76,77] While it accepted the second NDA, FDA issued a Complete Response Letter (CRL) after first delaying its decision to review additional data.[78] In its rejection of full approval, however, the FDA suggested the company consider knee extensor muscle strength as a surrogate endpoint for accelerated approval.[79] The company went on to resubmit its NDA taking this approach in August 2025, and FDA granted AA in September.[80] (See Figure 2)

Figure 2. Regulatory Timeline From First Submission to AA of Forzinity for Barth Syndrome



The fraught back-and-forth exemplifies not only scientific uncertainty, but the economics of small, early-stage biotechs that account for a disproportionate share of rare disease drug development.[81] Both FDA and Stealth expressed concerns about a mutually agreeable scientific path forward, and the company's engagement with FDA had spanned four different review divisions between 2019-2021.[74,82] The rarity of Barth Syndrome – there are currently fewer than 150 patients alive in the US – likely also constrained study design. Upon receiving the FDA's refusal-to-file, Stealth was taken private by Morningside Venture Investments.[83] The subsequent CRL prompted layoffs of 30% of the company's employees.[79,84] The company had planned to sell a priority review voucher from its approval to fund confirmatory clinical trials, setting it at odds with FDA's new requirements to require that confirmatory studies be underway at the time of AA.[85] (The company must begin enrollment in early 2026.)

Development of evidence to support approval for rare disease drugs can also be frustrating for patients, whose preferences may not match the clinical endpoints used in confirmatory trials. For example, the Phase III EMBARK trial of Elevidys failed to meet its primary endpoint—the North Star Ambulatory Assessment (NSAA), a measure of motor function—with patients on Elevidys improving 2.6 points versus 1.9 points for placebo on a 34-point scale, a difference of 0.65 points that was not statistically significant.[86] Some secondary endpoints that contribute to NSAA, including time to rise and 10-meter walk/run, showed improvement, but the study was not designed or powered to make inferences on these measures. However, patient advocates and caregivers argue that these improvements are meaningful to them, and FDA made the decision to convert Elevidys to full approval for ambulatory patients on this consideration.[60]

Subsequent safety concerns for Elevidys have renewed questions about its benefit-risk balance. While the safety profile has become clearer over time, evidence generation to better characterize the treatment's benefits have not kept pace, despite the company's decade of experience developing dystrophin replacement therapies for patients with DMD and treating nearly 1,000 patients with Elevidys.[87] The absence of clearer data from confirmatory trials, including Sarepta's other dystrophin replacement therapies, leaves patients and clinicians unable to form expectations about the benefits of treatment, crucial information for decision-making when treatment can result in severe liver damage or death.

Oncology

Surrogate endpoints used in AA for oncology are considered more well-established. It is possible that the FDA's Oncology Center of Excellence (OCE) Project Confirm, which launched in 2021 and provides guidance and monitoring of AA in oncology, contributes to this view.[88] Several oncology drugs approved through AA in recent years have dramatically improved patient outcomes. For example, Keytruda, which received AA for advanced melanoma in 2014 and full approval in 2015, significantly improved 10-year survival of the disease as compared with previously available treatment options.[89] Similarly, improvements in lung cancer mortality have been tied to the rapid uptake of targeted therapies and checkpoint inhibitors for non-small cell lung cancer (NSCLC), many of which were first approved under AA.[90]

Yet AA for oncology is freighted with its own uncertainties, and studies continue to raise questions about whether patients ultimately experience clinically meaningful benefits, even with drugs that are ultimately converted to traditional approval. One third of oncology drugs that were approved under AA on progression-free survival (PFS) between 2013-2017 and subsequently converted to regular approval failed to demonstrate improvements in overall survival (OS) or quality of life (QOL).[91] The rationale for approving such drugs even when they fail in clinical trials is often related to clinical trial design.[92] In some cases, patients enrolled in trials for molecularly-targeted drugs did not benefit from the drug's mechanism of action.[92] Lack of statistical power and certain trial designs may also contribute to less dramatic improvements in OS than PFS. For example, trials that allow rescue medication and crossover between treatment arms may underestimate survival benefits, as patients in the control arm often receive the experimental therapy upon progression, which can dilute observed OS differences. Finally, difficulties in trial recruitment for later-line use within an indication may force the deployment of confirmatory trials in earlier-line, less severe disease, which may make demonstration of substantial OS improvement more difficult.

In other instances, treatment with oncology products with initially positive signals on PFS has led to reductions in OS. This occurs most often when the magnitude of effect in tumor response or PFS is relatively small or treatment entails significant toxicity.[93] The latter is often related to the long-standing industry practice of using maximum tolerated dose (MTD) in oncology trials. Dosing to MTD became an established norm in oncology during the development of cytotoxic

chemotherapies, in which efficacy was inevitably linked with its adverse effects. The targeted therapies under development today break with that paradigm. Higher doses do not necessarily increase efficacy but do increase toxicity, which limits adherence to oral treatments delivered over longer timeframes, undermining clinical outcomes.[93,94] For example, sotorasib (Lumakras®, Amgen), which received AA in 2021 for NSCLC, later became the subject of FDA concern regarding high-dose toxicity, leading the agency to request investigation of lower-dose alternatives. While survival on the higher dose was nominally longer than on the lower dose, side effects were also significantly more severe. Amgen nevertheless pushed ahead with developing the higher-dose version.[95]

Despite their frequent use, the correlation between surrogate endpoints such as PFS, objective response rate (ORR) and event-free survival (EFS) and OS varies widely, both within and across cancers and treatment types.[96] While AA is designed to accept some degree of uncertainty, this raises questions about when and how to validate surrogate endpoints in oncology (and to varying degrees the other therapeutic areas of interest in AA as well). The FDA accepts validated surrogate endpoints, such as cholesterol lowering as a surrogate for cardiac events, in due course of regular approval, without the need for additional confirmatory trials. Although not rising to the level of validation, PFS and other intermediate endpoints may be more reliable predictors of OS in some types of cancers than others. Better understanding of these differences, which could be developed through meta-analyses of trials and/or observational studies, could allow FDA to manage AA more adaptively for cancer indications.

Neurology

Some of the most controversial recent instances of AA have been in neurology, including aducanumab for Alzheimer's disease and tofersen (Qalsody®, Biogen) for amyotrophic lateral sclerosis (ALS).

As a therapeutic area, neurology faces unique challenges, particularly in studying the central nervous system (CNS). The brain is one of the most challenging organs to study; it is complex, cannot be biopsied without harming patients, and the blood-brain barrier limits the development of biomarkers and therapeutic interventions. Many CNS conditions are also rare and progress slowly, making them difficult to detect in individual patients and challenging to characterize and study.[97] Slow progression and difficulty in obtaining the data needed to understand the root causes of brain diseases hamper clinical development even in more common conditions, such as Alzheimer's disease.

In the case of AD, development of treatment has mostly centered on the amyloid beta cascade hypothesis, which posits that amyloid beta plaque formation in the brain triggers inflammation which then damages neurons. Under this paradigm, treatments to clear plaque should slow or prevent cognitive decline, and plaque-clearing has become an accepted surrogate endpoint for AA of AD therapies.[98] The combination of high unmet need, lack of treatment options, long timeframe,

and a measurable surrogate endpoint that appears reasonably likely to mediate treatment response make a strong case for development through the AA pathway.

Yet Phase III randomized clinical trials of eight different plaque-clearing monoclonal antibodies have largely been disappointing. Despite showing a strong effect of plaque clearance, trials for only two drugs, donanemab (Kisunla®, Eli Lilly) and lecanemab (Leqembi®, Eisai Co., Ltd), showed any signal that treatment slowed cognitive decline.[99] In fact, there has long been disagreement about the role of amyloid beta plaque in cognitive decline and whether drugs to clear it hold promise.[100-102] In its most recent update to guidance on development of AD therapies, FDA acknowledges amyloid beta plaque clearance as a potential surrogate endpoint, but also encourages study sponsors to investigate new biomarkers that could be used for AA and other clinical development in AD.[103]

Recent advances give some reason for optimism about the development of new biomarkers to improve diagnosis, refine patient selection, and monitor response to therapies as surrogate endpoints.[104] However, the challenges in understanding CNS diseases, the lack of treatment options, long timeline to progression, and demands of monitoring patients being treated will continue to make clinical development in this area both uniquely suitable to AA and uniquely challenging.

Resolving Uncertainty

Under AA, a certain percentage of confirmatory trials are expected to produce no evidence in support of conversion to traditional approval. Possible causes are myriad, but common hypotheses include ineffective treatments, unsuitable clinical trial designs, and inaccurate predictions about the effect size on the clinical endpoint based on changes in the surrogate endpoint. While failed confirmatory trials are disappointing to patients and study sponsors, they may offer information to inform scientific advancement. Attempting to distinguish between potential causes is a worthy exercise.

Unfortunately, opportunities to do so are fairly limited. In some cases, FDA requires study sponsors to conduct additional studies while the drug remains under AA, which may offer some evidence to inform understanding. But when approval for the drug or indication is withdrawn, little information is revealed to further the scientific thought process, in part due to constraints in the agency's ability to share confidential and proprietary data. FDA lacks a process for revisiting endpoints that appear not to predict or mediate clinical outcomes when confirmatory trials fail. Patients, payers, and providers view this as a lost opportunity to advance understanding of the disease, inform the development of more promising surrogate endpoints, and avoid futile development efforts.

Learning From Failed Clinical Trials

Only rarely are data from failed clinical trials used to inform the commercialization of other manufacturers' clinical development programs. Actions taken by Amicus Therapeutics are a notable exception. After their clinical trial for a topical cream to improve wound healing in epidermolysis bullosa (EB) failed to demonstrate effect, the company declined to further pursue commercialization of the product. However, they shared the data with Amryt Pharma, which was developing its own candidate topical treatment for EB.[105] Insights from these data prompted Amryt to refine their clinical trial to focus on patients with slower wound healing rates.[106] Amryt went on to obtain marketing approval for oleogel-S10 (Filsuvez®, Amyrt Pharma) from the European Medicines Agency (EMA).[107] Filsuvez was later also approved by FDA.[108]

Delays in confirmatory trials also attenuate learning. Although time to study completion and conversion to traditional approval has decreased in recent years,[50] this remains problematic because delayed confirmatory evidence is correlated with low levels of clinical benefit and safety concerns at the time of AA.[109] Delays in producing these data slow understanding of the disease and which surrogate endpoints and treatments do and do not hold promise and lead to health system spending on therapies that ultimately do not benefit patients.

Pralatrexate (Folotyn®, Acrotech Biopharma), which was granted AA in 2009 for peripheral T-cell lymphoma (PTCL), illustrates several of the factors that can lead to a delay.[110] FDA revisited this drug in 2023, when even 14 years after its initial AA, confirmatory trials had still not been completed. The agency found several causes, with the most important being that trials were not underway at the time of AA, making enrollment increasingly difficult as standard of care came to include the use of Folotyn. The study sponsor had also failed to establish a combination dose for study, and the drug changed hands to another manufacturer in 2019. Although FDA and the new study sponsor agreed on the details of a new confirmatory trial, it will not be completed until 2030 — 21 years after the original approval. Whether the study produces clinically valuable information by that point remains to be seen.

Transparency Needs

Concerns that regulatory flexibilities could be misused to benefit study sponsors rather than patients may also be related to misunderstandings about FDA policies and pathways and appear to contribute to confusion and concerns about the AA pathway.

For example, payers noted that they often had little information to allow them to rapidly distinguish between different types of FDA approvals and designations and understand their implications. Meanwhile, manufacturers reported having to educate payers extensively when lack of knowledge

leads to misconceptions about their products. One former company executive noted that they and their team had to work extensively to educate payers about their drug. Payers assumed that the drug was approved under AA and managed it assuming that its clinical benefits were highly uncertain, even though it had received traditional approval and a breakthrough designation.

Stakeholder confusion extends to the development and review process as well. In this report, we identified several instances in which FDA and study sponsor expectations were effectively mismatched, suggesting that study sponsors may have misunderstood the agency's processes and requirements. FDA officials see the development of study design, including surrogate endpoints, to be the responsibility of study sponsors. The sequence of FDA rejections of Stealth BioTherapeutics' drug for Barth Syndrome suggests that the company may have misjudged the agency's willingness to rely on its flexibilities in certain situations. Although the initial submissions were for regular approval, the agency ultimately relied on AA, paving the way for patient access but requiring Stealth to develop confirmatory data.[74,82]

According to reporting by Fierce Biotech, Stealth's CEO was taken aback by the decision: "*I just don't really understand… It seems like accelerated approval on the basis of muscle strength, data that we already submitted, should have just meant an approval instead of a CRL*."[82]

FDA's inability to explain some of its decisions publicly may contribute to confusion about the agency's authorities and flexibilities, and when they might be used. Agency officials do have some leeway to explain controversial approval decisions, as they did in the case of Aduhelm and Elevidys.[111,112] However, this flexibility does not extend to decisions to deny approval. The terms of Investigational New Drug (IND) applications limit what can be disclosed. When the agency makes decisions that seem counterintuitive in the face of the evidence, these terms can limit its response to public inquiry.

Guidance issued in response to FDORA suggests that the agency will require study sponsors to deliver strong arguments in favor of exceptions and other flexibilities under AA.[32,43] The stricter stance has been accompanied by some efforts to reduce uncertainty about the agency's reasoning. In July 2025, FDA Commissioner Marty Makary announced the publication of more than 200 Complete Response Letters (CRLs) (redacted for trade secrets) to provide transparency on the types of deficiencies and recommendations detailed in these documents.[113] Dr. Makary noted, "*drug developers have long been playing a guessing game when navigating the FDA*," suggesting that this administration sees greater transparency as a means of giving insight on agency judgment.[113]

Pricing and Access

In our previous report on AA, pricing and spending on drugs approved under the pathway was one of the most contentious topics. Conversations for this report showed that this remained a top concern for respondents, particularly among patients and payers.

Although AA is intended to bring promising treatments to patients more rapidly, many report extensive delays while working through prior authorization, step therapy, non-coverage, and appeal processes. In some cases, uncertainty around reimbursement or delays in payment could slow treatment initiation even when coverage criteria are met. In progressively disabling and fatal conditions, speed is critical; even if treatment is eventually authorized by the payer, process delays can mean lost quality of life, function and survival.

Both high prices and high uncertainty associated with drugs with AA contribute to these delays, and appear to be particularly problematic for drugs to treat orphan diseases. Payers reported that orphan drugs are often a focus of their management efforts because they perceive them as being less certain to provide benefit than drugs with AA for other conditions, such as cancer. They would like prices at launch to reflect the evidence available at that time until confirmatory trials are completed. Several payers pointed to their experience with voxelotor (Oxbryta®, Pfizer), which received AA in 2019 for treatment of sickle cell disease (SCD).[114] Net annual cost of treatment with the drug was estimated to be approximately $93,000 per patient at the time of launch.[115] Despite its initial promise, confirmatory data showed that patients taking Oxbryta experienced higher rates of vaso-occlusive crises, which cause severe pain, organ damage, as well as greater risk of death. In 2024, the drug's maker, Pfizer, voluntarily withdrew it from the market.[116] According to payers, many patients used crizanlizumab (Adakveo®, Novartis), another drug for SCD, concomitantly with Oxbryta, prompting them to question whether patients were benefiting even before the drug was withdrawn.

Pricing concerns may contribute to more restrictive coverage for orphan drugs overall, regardless of whether they are approved under AA.[117,118] Still, because few patients use them, orphan drugs with AA contribute less to spending than other forms of medical care, even among people living with rare diseases. A study commissioned by Every Life Foundation estimates that the economic burden of prescription and provider-administered drugs (including but not limited to drugs with AA) used by individuals with rare diseases was $96 billion in 2019, or 23% of their medical costs.[119] Spending on oncology drugs is higher, amounting to $99 billion in 2023 and projected to reach $180 billion by 2028.[120] In Medicare alone, spending on oncology drugs with AA that had not yet converted to full approval was $9.1 billion in 2019.[6]

Payers may be less able to manage access to oncology drugs because of their higher volume and state laws that limit their use of prior authorization and step therapy.[121] In interviews for this report, several payers mentioned that they have reduced their management of oncology drugs because of the high rate of overturn on appeal, which extends to drugs approved under AA. In addition to prevailing concerns about being able to manage access to products with uncertain safety and benefits, this makes it difficult to curtail use of drugs after confirmatory trials have proven them ineffective. One study estimates that between 2017-2019, Medicare spent $224 million on withdrawn indications for 10 cancer drugs that had previously been granted AA.[122]

Concerns about the financial implications of paying for treatments that ultimately provide no patient benefits have prompted some payers to take a firm stance. Independence Blue Cross Blue Shield announced that it would not cover drugs with AA for the first 18 months following approval.[123] This approach manages the tension between drug pricing, clinical certainty, and patient access, by abrogating responsibility for the latter. While non-coverage avoids spending on drugs that don't work, it conflicts with the intent of the AA pathway to speed access to treatments that do work.

Fortunately, studies suggest that such restrictive approaches to management are relatively uncommon. After controlling for multiple characteristics of newly approved drugs, three different papers show that health plan coverage and access restrictions are driven mostly by pricing and to some extent cost-effectiveness, not by a drug's approval under expedited FDA review processes.[117,118,124]

This offers little solace to patients, however, since drugs with AA usually have high prices. Although patient respondents reported that they understood the need to control costs from high-priced drugs, to them, delayed access to drugs with AA was not an acceptable cost containment strategy. But their opposition also extended to high prices, not only because they encourage access restrictions, but because high prices create financial toxicity for patients.[125-127]

Trust

To work as intended, the AA pathway requires the cooperation of many different stakeholders, all of whom are asked to share some form of risk associated with the pathway's uncertainties. Sharing risk, however, is not the same as sharing interests. In the case of AA, stakeholder goals often conflict, making it more difficult to establish the trust necessary to accomplish cooperation. In our interviews, two factors emerged as the leading sources of mistrust: unclear rationales for deploying regulatory flexibilities, and delays in confirmatory trial readouts. Stakeholder perceptions of these issues were entwined with their frustrations about transparency and concerns about misuse of regulatory flexibilities.

Payer respondents suspect that some pharmaceutical manufacturers take advantage of FDA's flexibilities, allowing them to obtain initial approval despite scant evidence or to delay the readout of clinical data showing that their drug doesn't work. Payers note – correctly – that the financial incentive for such abuse can be significant. Drugs that are ultimately proven not to work are often used by many patients and still produce significant revenue while they are on the market. One recent study estimates that 17% of Medicare beneficiaries who received treatment for cancer with a drug approved under AA were treated with a product that went on to be withdrawn.[128] The OIG estimates that between 2018-2021, Medicare and Medicaid spent more than $18 billion for drugs with AAs that had failed to complete their confirmatory trials as originally planned.[19]

Many payers also feel that the FDA has become too lenient and influenced by industry. They seek more clinical evidence – often beyond what FDA might require – and greater transparency in regulatory decisions to address their misgivings.

For their part, manufacturer respondents acknowledge the incentive but feel that the vast majority of pharmaceutical companies operate in good faith. They also seek more transparency from the FDA, particularly as they try to navigate growing regulatory unpredictability.[129] At the same time, they argue that some payers use concerns about regulatory flexibility and the status of confirmatory trials to unfairly justify access restrictions on drugs granted AA. Several manufacturer respondents said that they were not confident that providing more evidence to payers would improve access to their treatments. Payers, on the other hand, argue that if the evidence is sufficient, the appeals process will overturn unfounded denials to ensure that patients get appropriate access.

Patients bear the direct consequences of these dynamics. They hope for speedy access to new treatments and instead find themselves caught at the impasse between payers and manufacturers. In addition, they and their providers also want more transparency and information – from FDA, payers, and manufacturers. One respondent representing the patient perspective said that while patients do not expect perfection, they do expect transparency and accountability. To them, delayed confirmatory trials can feel "like a broken promise".

Uncertainties about treatments' benefits and risks also most directly affect patients. Decision-making about treatments for disabling and fatal conditions is inherently dynamic, and both providers and patients want emerging information about the balance in benefits and risks as quickly as possible. They also need to be prepared for the possibility that the drug they are using will be withdrawn from the market, since AA inherently accepts greater risk in the risk-benefit balance than traditional approval. But providers often have limited knowledge about a drug's approval status or don't inform their patients that the drug they are taking remains in clinical trials to confirm its effectiveness. For patients and providers, drugs with the greatest amount of uncertainty should proceed through clinical trials the fastest, but are often the slowest.

Although their motives differ, virtually all stakeholders would like more transparency about the functioning of the AA pathway, the status of individual drugs, and the strength of the relationship between surrogate endpoints and clinical outcomes. In fact, some information, such as status of confirmatory trials, is already publicly available. However, the data are not readily accessible in a comprehensive or digestible format. Instead, they are hosted on different websites and resources that are not connected, and may not be frequently updated.

Where to Find Information about Drugs with Accelerated Approval*

Which drugs have accelerated approval and what is the status of their confirmatory trials?

The FDA lists products with AA here for cancer drugs and indications with AA.[51] This resource documents requirements for AA confirmatory trials, as well as non-AA post-approval studies to confirm a drug's safety or to identify emerging signals of safety risks. The database includes:

- The current status of each requirement (e.g., initiated/delayed/completed)
- An explanation of that status

Additional details about the design and endpoints used in confirmatory trials can be found on ClinicalTrials.Gov.[130]

How can I find out if a drug has known or suspected safety risks?

The Risk Evaluation and Mitigation Strategies (REMS) database is a valuable source of information about a drug's possible safety risks.[131] REMS are FDA-required monitoring programs for approved drugs with safety concerns (both under AA and traditional approval) that require providers and supply chain participants to be educated and registered to provide, handle and/or administer the product. This site provides:

- The goal of the safety monitoring strategy
- An assessment plan
- Educational materials and registration forms for providers and other stakeholders

In addition, the FDA Adverse Event Reporting System (FAERS) provides a searchable public database of reported adverse events by drug.[132]

Where can I find out more about a drug's regulatory history?

The history of FDA approvals for a drug can be found at Drugs@FDA.[133] Here you can find information including:

- Dates and details about changes to a drug's marketing status, including approvals for each drug by indication
- Regulatory materials, including communication from the FDA about changes to the drug's label and the associated updated label

* Note: Information from different FDA sites can occasionally be inconsistent because they serve different purposes. Additionally, some websites have recently seen less frequent updates or have not been consistently accessible.

Policy Options

We identified five areas for continued improvement, including:

1. Strengthen evidence foundations
2. Improve transparency and accountability
3. Improve basis for shared decision-making
4. Align financial incentives with evidence and value, and waive cost-sharing
5. Strengthen oversight and enforcement

While policies are described individually, we urge readers to consider how combining them with other reforms would make them more or less effective. At the present moment, the need for policies to improve trust is particularly urgent. For example, discussions to inform this report revealed that payers are unlikely to abandon defensive postures that limit or delay coverage for treatments with AA if they believe that study sponsors are not required to produce confirmatory evidence that would pass muster under traditional approval. Likewise, without evidence that payers will change their posture when given evidence at this level, manufacturers are unlikely to prioritize endpoints that matter to payers in their clinical trials. Patients will continue to be caught in the middle. This makes policies to strengthen evidence foundations and support greater transparency and accountability prerequisites for the success of other changes, such as realigning financial incentives.

Strengthen Evidence Foundations

Recent changes in FDA guidance were largely welcomed by stakeholders as improving the evidence base for drugs under AA. Many see opportunities for further improvements building from these changes. In particular, there continues to be strong demand for better mechanisms to distinguish promising surrogate endpoints from those more likely to fail, and to incorporate outcomes that most matter to patients. Many also called for greater use of existing FDA resources, such as advisory committees, to bolster AA.

Strengthen the Selection of Surrogate Endpoints

Strengthening the selection of surrogate endpoints remains a top priority among stakeholders. FDA's guidance describing its thinking on surrogate endpoints was viewed as a step in the right direction. Stakeholders expressed a keen interest in using AA to advance scientific understanding of the connection between surrogate endpoints and clinical outcomes.

Four priorities emerged in this category. The first was to establish a more structured process for developing surrogate endpoints, particularly for rare diseases and those with an evolving understanding of a condition's pathology and natural history. As part of this process, the FDA could call on advisory committees to weigh in on scientific considerations and to set expectations for the types of clinical responses that experts might expect based on changes in proposed surrogate endpoints as part of the AA process. This would give both the FDA and study sponsors more information to guide surrogate endpoint development. It would also allow FDA to provide more justification for why it would or would not accept an unvalidated surrogate, and what magnitude of changes to the endpoint might be considered promising before a clinical outcome can be measured.

The FDA could adapt existing frameworks designed to evaluate surrogate endpoints for their promise as predictors of clinical outcomes. A number of institutions and working groups, including the National Academy of Medicine and academic researchers, have processes that lend themselves to systematic assessments across therapeutic areas.[134,135] One such approach, proposed by Ciani and colleagues for evaluating surrogate endpoints in value assessments, first aims to establish the level of evidence available to assess the relationship between the surrogate and clinical endpoint. It then moves on to evaluate the strength of the association between the two. Finally, it quantifies the expected treatment effect on the clinical endpoint based on the effect on the surrogate.[136] Publicly available systematic assessments of surrogate endpoints would allow FDA to share with the larger scientific community information from otherwise confidential meetings and communications between FDA and study sponsors.

The second priority is to publicly articulate hypotheses about the change in clinical endpoints based on changes in surrogate endpoints. This includes *a priori* hypotheses about what would constitute a meaningful change in clinical endpoints, as well as the time horizon for detecting them. Making these theories public would help the FDA establish clearer benchmarks for what is considered success in confirmatory trials. The agency could go so far as to present internal disagreements, such as those about levels of truncated dystrophin needed to improve outcomes in DMD, or to convene public discussions with experts to pressure test working assumptions and data. Although this would likely create its own controversies, greater clarity about expectations – and disagreements about them – creates transparency. The agency could also use these disclosures to explain the later use of flexibilities, should they be needed. It also has the benefit of providing a basis for informing expectations of payers, who can only receive limited information from manufacturers prior to approval.

The second priority lays the groundwork for the third, which is to use failed confirmatory trials as learning opportunities. Currently, FDA is limited in what it can disclose publicly about confirmatory trials that either show a drug doesn't work, or fail to produce the data needed to justify full approval. One respondent suggested that the FDA should conduct publicly accessible meetings and "After Action Reports" discussing why a surrogate endpoint failed to translate to a clinical benefit and what can be learned. This would have two benefits. It would allow FDA to explain its thinking

behind complex decisions, such as keeping a drug on the market without converting it to full approval. It would also create a public good – information to guide both future FDA decisions and manufacturers' plans for future clinical development.

Finally, meaningfully involving patients in the surrogate development process is an important fourth priority. At times, patients are asked to contribute to the development of clinical endpoints, but they are not typically brought into the process for defining surrogate endpoints. However, patient input is critical for identifying and mitigating the burdens and challenges they face in participating in clinical trials, which have the potential to delay the accrual of evidence for confirmation of benefit.

Policy Option: *Strengthen the selection of surrogate endpoints in AA by 1.) conducting systematic evidentiary evaluations of candidate endpoints, 2.) publicly articulating expectations for changes in clinical endpoints, 3.) issuing after action reports when confirmatory trials fail to demonstrate benefit, and 4.) incorporating meaningful patient input into the development of surrogate endpoints*

Use Scientific-Focused Drug Development to Address Disease-Specific Questions

Lack of input from scientific experts and patients throughout the AA review process – or a perceived lack thereof – was a common theme in interviews. Respondents, including former FDA employees, suggested that the application and execution of the AA pathway would be more productive if guidance on surrogate endpoints and clinical development were obtained from scientific experts, patients, and FDA earlier in the process of clinical development.

This could be challenging: bringing together all three perspectives is difficult even for well-resourced companies. Top clinical and scientific experts who might advise on these issues may already be employed by the sponsors or be involved in developing a potential competitor product. Patients and caregivers willing and able to participate may struggle with accessibility and technical aspects of development. Meanwhile, company meetings with FDA may include perspectives gathered from scientific advisors and patients, but do not give agency staff an opportunity to engage with those advisors directly.

This lack of focused scientific and patient input appears to be particularly problematic in rare and ultra-rare diseases. The margin of error for studying rare diseases is tighter than for other conditions: sample sizes are often extremely small and endpoints must be carefully designed to strike a balance between uncertain effect size, statistical power, and clinical meaningfulness. Meanwhile, adding more voices to the clinical development process is challenging for companies developing rare disease drugs that are highly specialized and early-stage. Tight timelines, resource constraints, and competitive pressure can limit their ability to incorporate input from external advisors.

Its challenges aside, respondents familiar with the process of patient input in clinical trial design felt that this approach could be transformative if it "operationalizes patient input, not just invites it." To

do that, patients and clinicians would need to be engaged as soon as development of a surrogate endpoint is contemplated, to determine whether proposed options have any possibility of meaningfully reflecting later effects of treatment on patients' lived experiences. This should happen early enough in development that a core set of surrogate and clinical endpoints can be identified and required by FDA across clinical trials by different competitors, and be supported with education and resources for patients to understand the logic for collecting certain measures, particularly if they are biomarkers that require some explanation.

FDA could bring the relevant viewpoints together by taking on the role of facilitator. It could form advisory committees to review evidence from pre-clinical and early clinical studies and set expectations for approval under AA for particular diseases and treatment modalities. FDA could borrow from the patient-focused drug development program, by bringing stakeholders together for "scientific-focused drug development" meetings, a concept recently proposed at BIO's International Convention.[137-140] These meetings could be open to the public to ensure that the input and information the agency receives is more broadly available. Gathering input from advisors and patients through the agency also has the benefit of helping FDA build the knowledge base needed to advise companies on their future clinical development plans, and allows stakeholders to shape endpoints and study designs not just for one company, but more broadly.

Policy Option: *Establish a scientific-focused drug development framework, modeled on existing approach to patient-focused drug development to align on disease-specific surrogate endpoints and evidentiary expectations for AA*

Require Advisory Committees for Surrogate Endpoint Development and Accelerated Approval Reviews

Many respondents noted that advisory committees play a critical role in evaluating complex scientific questions, but that FDA does not consistently convene them for AA decisions. When advisory committees are used, their recommendations are sometimes overridden without clear public explanation. This opacity undermines confidence in the pathway and deprives stakeholders of the deliberative process that helps establish shared expectations.

To combat this, FDA could convene advisory committees for all AA decisions, particularly for the other purposes identified later in this section, such as evaluating the strength of proposed surrogate endpoints before clinical trials are conducted, guiding confirmatory trial design, and participating in the process of early scientific-focused drug development. These deliberations should be public and result in documented expectations for the product's anticipated clinical benefit, the rationale for accepting the surrogate endpoint, and benchmarks for confirmatory trial performance. Advisory committees for AA decisions would serve multiple purposes: they would bring expertise to bear on difficult scientific judgments, create a public record that can inform future decisions about similar endpoints, and establish a public record of expectations against

which confirmatory trial results can be evaluated. When a surrogate endpoint fails to predict clinical benefit, this documentation would also facilitate the kind of systematic learning that several interviewees identified as missing from current FDA practice.

Realizing this vision requires first contending with structural weaknesses in the broader advisory committee system. Like AA, advisory committees have their own issues with trust, bias, and representation. Committees are largely composed of scientific experts, who are asked to be both knowledgeable and independent reviewers. But these two elements are often at odds: experts are commonly involved with clinical studies and have relationships with study sponsors, and FDA has struggled to strike a balance. Meanwhile, committees are required to include industry and consumer representatives, [141,142] but not patient representatives. Rather, patients wishing to participate are instead encouraged to apply to the FDA's Patient Representative Program for training on an "as-needed" basis. [143]

In practice, the use of advisory committees has been declining over time even for traditional approvals, and FDA has increasingly disregarded committee votes against approvals.[144] Broader reforms to their composition, governance, and authority are likely necessary before they can be successfully deployed for purposes of AA.[145-151]

Policy Option: *Require advisory committees for certain steps at defined stages of development as well as all AA reviews, after reforms to committee composition, governance and role*

Improve Transparency and Accountability

To work as intended, the AA pathway requires trust among stakeholders. Although FDA is the central decision maker in AA, it cannot address the misgivings of the various stakeholders about each other's motives. But instances of lack of transparency and accountability in the agency's processes and decisions regarding AA approvals and confirmatory trials are at the center of some stakeholders' concerns.

The policy options in this section borrow heavily from principles first articulated in 1998 by Norman Daniels and James Sabin, who developed a framework for accountability around managed care decisions that limit access.[152] The concept, dubbed "accountability for reasonableness", identifies four conditions needed to improve trust in decisions about how limited resources are used in health care:

1. Publicity: Coverage decisions for new technologies, and the rationales for making them, should be made publicly accessible.

2. Relevance: Decisions should be based on "evidence, reasons, and principles" that "fair-minded" individuals agree are relevant to decisions about how limited resources are shared across diverse needs.

3. Appeals: There must be a mechanism for challenging decisions that limit access.

4. Enforcement: That regulations exist to ensure the first three conditions be met.

Among these, publicity and relevance appear as gaps that can be addressed by FDA to reduce controversies about AA pathway decisions. The policies identified in this section speak directly to these conditions.

Increase Transparency in Decision-Making

Greater transparency in FDA decision-making was perhaps the most common theme in interviews and discussions. Suggestions by respondents on this topic were similar to a policy option from our first paper, to develop standardized review templates that would provide more detail on the rationales driving FDA decisions, as well as expectations and updates on changes. Calls for a more standardized approach included options to strengthen the selection of surrogate endpoints described here in this report, but also extended to explanations of reasoning behind full approvals, withdrawals, and decisions to keep products on the market despite problems in generating confirmatory evidence.

Similarly, several experts argued for a form of "after-action reports" in which FDA could explore, in a public forum, instances when surrogate endpoints fail to predict clinical benefit, confirmatory trials are delayed for reasons beyond study sponsors' control, or the confirmatory evidence is ambiguous or doesn't support conversion to full approval.

These proposed changes, which were met with broad support throughout discussions, could be useful to a number of other policy options identified in this report. However, they would likely require legislative changes to require FDA to provide a rationale for its decisions and allow the agency to disclose information from INDs as part of these public discussions. Currently, FDA must treat information disclosed in INDs as confidential, which often limits the agency's ability to explain its reasoning. However, the agency's recent release of redacted CRLs suggests that there may be some opportunities to advance transparency reforms through regulation as well.[113]

Policy Option: *Give FDA authority to publicly disclose certain information from INDs; issue standardized explanations of decisions under AA and After Action Reports as mentioned above*

Create Risk Ratings for Accelerated Approval Drugs

The source and level of uncertainty surrounding AAs and confirmatory trials are often unclear to stakeholders, especially patients. To improve understanding, the FDA could develop an ordered

rating system that relates to the strength of evidence supporting each drug or indication with AA. Ratings could be developed from data on past FDA actions, clearly define risks, and take into account the different factors that contribute to uncertainty, including strength of evidence for the surrogate endpoint; the level of risk associated with failure of the surrogate to predict patient-important outcomes, including death; and expected time horizon for measurable effects on clinical benefits.

However, some of the respondents we interviewed noted that ratings could be misinterpreted by patients and providers or used by payers to unduly restrict access. To address the issues of mistrust between AA stakeholders, the FDA would need to set clear expectations for how the information should be communicated. For example, the agency could borrow from its labeling guidance for reporting adverse event information: prioritize the most significant risks that could affect clinical decision-making, provide monitoring recommendations, and describe what can be done to mitigate potential harms of taking a drug.[153]

The ratings – and any communication about them – should also clearly distinguish between scientific uncertainty and execution risk. For instance, for a drug with AA for a rare disease, the risk rating should separate the uncertainty surrounding the relationship between surrogate endpoint and clinical outcomes and the possibility that enrollment in confirmatory trials may be delayed due to the small patient population. In some cases, the distinction would require additional context, such as the severity of potential outcomes of disease and whether uncertainty is structural or applies to an entire group of diseases. To further improve confidence, these elements could be coupled with ratings of study sponsors' prior performance in AA, such as on-time study completion and other measures of success.[154]

Ratings could be developed through a number of methods, including both qualitative and quantitative analysis, and based on factors shown to be predictive of certain outcomes. For example, safety concerns at the time of AA have been shown to predict delays in the development of confirmatory evidence.[109]

A scoring system for clinical trial and evidence quality could allow FDA to track AA pathway performance over time and across study sponsors and might serve as an early warning system to identify trials at risk of delay or failing to provide the necessary data for conversion to full approval. It would also allow FDA to identify problematic or beneficial patterns in clinical trial designs across different therapeutic areas, which could aid in further development of guidance.

Policy Option: *Develop rating system for uncertainty using factors known or expected to influence completion of confirmatory trials and likelihood of achieving meaningful clinical outcomes for patients*

Improve Basis for Shared Decision-Making

Principles of shared decision-making require that providers and patients be educated in the potential benefits and risks of treatment with a drug. Accelerated approval adds two additional demands: understanding the uncertainties inherent to the pathway and receiving emerging information about a treatment in a timely manner. Two proposals emerged from stakeholder discussions: developing educational materials specific to drugs with AA and requiring informed consent of patients treated with drugs that remain in confirmatory trials.

Create Educational Materials for Accelerated Approval Drugs

Patients and providers need clear, accessible information to make informed decisions about treatments approved under the AA pathway. While product labels must now disclose AA status, this alone is insufficient.[48] Patients, clinicians and payers we interviewed noted that the nuances of surrogate endpoints, the strength of evidence, and expectations for confirmatory trials remain opaque to most patients and many providers. As one noted, information about AA products needs to be "more transparent and digestible to the average person."

Risk Evaluation and Mitigation Strategies (REMS) could provide a template for a standardized resource of educational materials tailored to providers and patients. Such materials could describe what is known and unknown about each product and indication with AA, incorporating summaries from advisory committee deliberations, explain the rationale for the surrogate endpoint, and outline the expected timeline for confirmatory data. Like REMS materials, these could be tailored to meet the distinct communication and information needs of providers and patients.

This approach could be especially useful when paired with other options identified in this report, including the development of risk ratings (See Create Risk Ratings for Accelerated Approval Drugs), as well as informed consent requirements for patients using products with AA (See Require Informed Consent for Accelerated Approval Drugs).

Policy Option: *Develop patient and provider educational materials about possible benefits and risks of drugs with AA*

Require Informed Consent for Accelerated Approval Drugs

During discussions with patient advocates, it became evident that patients are often unaware that they are using a drug with AA and/or misunderstand the level of uncertainty surrounding benefit and risk associated with these treatments. Without adequate communication about these concepts, patients cannot fully weigh their options, even if the only alternative is no treatment. Their limited understanding of how the pathway works can also catch patients by surprise when a drug is withdrawn from the market following failure in confirmatory trials or unexpected safety problems.

This is not the case for patients in confirmatory trials for these drugs, who must give their consent to treatment after being informed of the potential risks. To address this gap, providers could also obtain consent from patients treated with an AA drug outside of clinical trials. This process would ensure that patients review and acknowledge the educational materials described above, confirming that they understand both the promise and the uncertainty of the treatment they are considering.

As with the risk rating option described above, informed consent invariably highlights treatment uncertainties, which can erode trust if not communicated clearly. It is therefore critical to pair informed consent with objective, unstigmatized education about the AA pathway and the distinction between scientific uncertainty and execution risk.

Some of this need could be accomplished with educational materials modeled on the REMS program as described in Create Educational Materials for Accelerated Approval Drugs. But even an adaptation of the existing REMS model may be easier said than done, since the conversations required to obtain and sustain informed consent add complexity to the clinical care workflow and increase the already substantial administrative burden of providers. To make matters more complicated, additional tailoring is likely necessary for some types of treatments with AA. For example, patients who initially consent to a one-time treatment such as a gene therapy are unable to revisit their choice the way other patients can when treated at repeated intervals. Not only is the decision to receive treatment irreversible, but uncertainty about durability can also mean long-term monitoring. To accomplish this, informed consent under AA would need to balance affirming FDA approval with transparency about the current level of evidence and ongoing confirmatory efforts. Moreover, while patients may not be able to change their decisions, they should be kept abreast of new developments after receiving treatment.

Systematic adoption of informed consent for treatments with AA would need to be grounded in the relationships between patients and trusted medical professionals who can guide this process over time. This would demand significant time and resources, which are not accounted for in current provider reimbursement and must compete with other clinical and financial priorities. Similarly, the infrastructure to develop the consent framework and informational materials also needs investment, but has no readily apparent source of funding. Still, informed consent could be a powerful way to build understanding and trust in AA, especially if coupled with other policies designed to improve accountability and transparency.

Policy Option: *Obtain consent from patients for treatment with a drug under AA after describing its uncertainties and the possibility that the drug may be withdrawn*

Align Financial Incentives with Evidence and Value, and Waive Cost-Sharing

Pricing of drugs with AA is at the core of tensions between patients, payers, and pharmaceutical companies. Numerous proposals, including two in our prior report, as well as several put forward by Medicaid and CHIP Payment and Access Commission (MACPAC) in 2021, aimed to strengthen financial incentives for completing confirmatory trials.[155] Those proposals outlined offering rebates on drugs prior to the completion of confirmatory trials, and pricing drugs at marginal cost before additional evidence was generated.

Policies in this vein suffer from several limitations. One is that linking rebates to a drug's price can encourage higher list prices because they allow manufacturers to provide rebates without sacrificing net revenues. At least in theory, linking payment to confirmatory trial completion would also disadvantage pharmaceutical companies who complete their studies in good faith, only to find that the drug has no clinical benefit or has significant safety risks.[156] Manufacturers also see such policies as overly burdensome to small companies that rely on early commercialization to fund confirmatory trials and other research.

Setting aside these objections, capping what companies can charge for drugs before they convert to traditional approval is conceptually straightforward. Perhaps the greatest shortfall of proposals is one that plagues all current reimbursement practices: none contend with the underlying question of whether a drug's price reflects the value of its clinical outcomes to patients, and that our understanding of this value evolves over time as we learn more about a drug's benefits and risks. This problem takes on heightened importance in AA because the variation in the value of those outcomes is potentially very high across different treatments. Virtually all drugs with AA are high-priced and many fail – expectedly so.[6,22,155] This creates an environment in which uncertainty also lends itself to price inflation, since it isn't always clear which drugs will succeed and which won't.

However, uncertainty and value can be handled separately. Ideally, confirmatory trials should resolve questions about whether, when, and how much clinical benefit is achieved. Meanwhile, the value of expected outcomes can be established in advance.

The options in this section take a new approach: applying value assessment to questions about pricing relative to anticipated outcomes, and outcomes-based contracts to contend with uncertainty with significant implications for the realized value of a drug's treatment outcomes. Finally, the option to waive copayments for certain drugs addresses the impossible financial choices faced by patients with no other treatment alternatives.

Incorporate Value Assessment

Although the degree of clinical benefit of drugs with AA is uncertain, the expected value of that clinical benefit is knowable in advance and can thus be incorporated into pricing. Several frameworks are available for incorporating uncertainty related to surrogate endpoints into value assessment, drawing on methods to weigh evidence quality, adjust for risk, and develop new information to update estimates.[135,157] These methods are particularly important for gene therapies and other one-time treatments, where benefit durability over time is uncertain, and most patients with the condition might be treated shortly after initial approval under AA.

Linking expected performance of a drug with its price has desirable consequences for patients. Higher prices for better expected outcomes send a signal to innovators about the market opportunity for their products, and can encourage them to better incorporate outcomes that matter to patients into their confirmatory trials. More importantly, it can also provide updated pricing guidance as uncertainty is reduced, creating more flexibility to decrease or increase prices under the ceiling set by value.[158]

While value-based pricing creates desirable incentives, its promise is limited by current payment policies, which constrain both increases and decreases in prices. For systematic use, several federal policies would have to be modified to allow for changes in prices to align with value, including average sales price (ASP) reporting and inflation rebates under Medicare and Medicaid. Another challenge is the lack of a central infrastructure for value assessment that can inform all payers, beyond the existing impact of ICER's comparative effectiveness reports, although there has been progress on this front through the Cell and Gene Therapy Access model, an initiative piloting centralized data collection for gene therapies treating sickle cell disease through CMS.[159] Moreover, Medicare now also has the power to negotiate what it pays for certain drugs based on their benefits and risks. Although this authority is limited to older products and the Medicare population, the infrastructure and institutional knowledge for assessing the value of clinical benefits and risks has nevertheless been established and could be harnessed for other efforts.

Policy Option: *Condition coverage of drugs with AA on pricing at or below expected value of outcomes, consider updating prices as additional information becomes available*

Use Outcomes-Based Contracts Where Impact of Uncertainty Is Greatest

Outcomes-based contracts (OBCs) were the policy option most commonly identified by stakeholders as having promise in managing spending on drugs with AA. As in prior interviews, the appeal of this option is that it addresses concerns about the high level of uncertainty surrounding the clinical outcomes of drugs under AA.

Their practical application, however, is limited. Uptake has been low at least in part because they fall short of addressing payers' financial concerns. To them, OBCs don't offer enough money back relative to the value of the drugs they cover. Moreover, OBCs are not designed to address the fact that small payers struggle to absorb infrequent and high costs. Because they largely rely on clawbacks, OBCs can also be difficult to enforce. For example, if a manufacturer files for bankruptcy or goes out of business, repayment can become impossible. Payers describe "here today, gone tomorrow" situations in which manufacturers have canceled OBCs for poor real-world performance of their drugs. The payer-preferred alternative – withholding or staggering payment according to clinical milestones – is largely unacceptable to manufacturers. This approach is seen as particularly difficult for small pharmaceutical companies, who rely on up-front reimbursement to fund confirmatory studies.

In addition, manufacturers report struggling to develop outcome measures to use in OBCs for drugs with AA, particularly for diseases with heterogenous disease subtypes. Outcomes-based contracts are typically informed by clinical trials, which provide a basis for both manufacturers and payers to work from. But in the case of AA, payers often view data from the clinical studies used to receive AA as inadequate evidence to inform coverage, let alone contracting.

Oversight and management of OBCs is also administratively burdensome. Following patients over time, through different clinical settings, and across different payers is challenging, particularly for conditions and treatments with long time horizons. Patients experience the negative aspects most directly: OBC negotiations and adjudications can delay access to treatment, and require more diagnostics, imaging and interaction with the health care system.

Perhaps the greatest limit to the use of OBCs is that they are least practical where they offer the greatest benefits. Although they may not offer much upside from a payer budget perspective, they can generate data about outcomes and place limits on one important area of concern to payers and patients: spending money on a drug that doesn't work. This makes them particularly promising for rare and ultra-rare diseases, where uncertainty about the relationship between the surrogate endpoint and clinical outcomes is often greatest. However, the small patient population means that most payers would be negotiating one-off agreements with manufacturers, an inefficient outcome for all involved.

To be worthwhile, OBCs must become more practical and efficient. Federal efforts to improve data collection about disease and treatment-specific outcomes may help lead the way. Policymakers have increased their focus on the collection of real-world data in recent years, both through legislation and regulation. For example, the 21st Centuries Cures Act prompted FDA to issue guidance for the collection of real-world evidence through registries, which could inform a more standardized approach to data collection in OBCs.[160] Future FDA adoption of other AA policy options, such as patient and clinical expert input in the development of surrogate and clinical endpoints, could also give stakeholders more information to facilitate efficient data collection.

Centers for Medicare and Medicaid Innovation (CMMI) is also studying a centralized approach that aggregates data across participating Medicaid programs through a standardized OBC for sickle cell gene therapies.[159] These initiatives may offer a starting point for a more fit-for-purpose application of OBCs with standard templates and data collection across payers.

OBCs will also only address value if they are paired with value-based pricing. While the value of an expected outcome can be estimated at the patient level, how many patients will achieve the outcome or at what magnitude, is the key unknown in AA. Resolving the latter uncertainty is where OBCs may be most useful. Setting OBC payments on the value of expected outcomes and adjusting the payments based on the number of patients or average magnitude of benefit would resolve uncertainties in a way that ultimately delivers a value-based price. Using this approach could allow for both lower and higher prices depending on the achieved outcomes. For example, when launching its treatment for beta thalassemia, betibeglogene autotemcel ("beti-cel", Zynteglo™, Genetix Biotherapeutics), bluebird bio, now known as Genetix Biotherapeutics, proposed contracts with five annual payments totaling $2.1 million. An ICER review found that this arrangement would be cost-effective if the manufacturer paid back 80% of its price when patients do not experience the desired outcome, transfusion independence, over five years.[161]

Policy Option: *Target use of OBCs to conditions and treatments with the most uncertain outcomes, use a standard contract template, centralize data collection across payers, condition payments on the value of expected outcomes and adjust based on the magnitude of benefit or number of patients who experience the benefit*

Remove Cost-Sharing Requirements When There Is No Treatment Alternative

Addressing financial incentives and value requires considering the patient perspective. Although cost-sharing is designed to encourage patients to weigh the value of treatments and choose cost-effective options, research shows that it is ineffective at guiding treatment choice when options are constrained. Patients facing life-threatening illnesses will pursue available treatments regardless of out-of-pocket costs. However, burdensome cost-sharing does come at the expense of adherence, reducing the effectiveness of treatment.[162]

Cost-sharing for drugs with AA amplifies these challenges – most drugs with AA are expensive and many have limited therapeutic alternatives or none at all. It also creates its own complications: when a drug is ultimately withdrawn after failing to demonstrate clinical benefit, patients may have spent significant sums on a treatment that did not work, with no mechanism to recover those costs.

Removing or limiting cost-sharing for drugs with AA is one way to limit these forms of financial toxicity. But this policy entails both practical and ethical challenges. For payers, actuarial value constraints make it difficult for plans to selectively reduce cost-sharing for AA drugs without affecting overall plan costs. They would also face the administrative burden of determining when

drugs with a mix of indications with traditional approval and AA require cost-sharing. Meanwhile, patients would have to begin cost-sharing after a drug converts to traditional approval. Finally, waiving cost-sharing for drugs or indications with AA also favors drugs with weaker evidence, creating an incentive to delay traditional approval, as well as to favor development of drugs for AA over traditional review.

Many of these problems could be avoided by more broadly exempting cost-sharing for any drugs or indications with no available treatment alternative beyond supportive care, regardless of their status under AA.

Policy option: *Limit cost-sharing for all drugs or indications with no treatment alternative, regardless of AA status*

Strengthen Oversight and Enforcement

Accountability is critical to any arrangement that relies on stakeholders to cooperate despite differing incentives. The policies in this section aim to address the need for program integrity and include refining the criteria to qualify for AA, increasing enforcement of confirmatory trial requirements, opportunities to sunset lagging AAs that have not converted to traditional approval, and tailoring AA to therapeutic areas to ensure they meet their unique needs and challenges.

Refine Qualification for Accelerated Approval

Expanded use of AA is accompanied by questions about whether all products currently qualifying for the pathway genuinely require its flexibilities.[4,5,19] The pathway was designed for serious conditions with high unmet need where traditional approval timelines would impose unacceptable delays in patient access. However, the criteria for qualification have been applied inconsistently across different treatment modalities and therapeutic areas.

Gene therapies, for example, may receive AA based on single-arm trials in well-characterized conditions, while other promising therapies for similarly well-understood diseases face more stringent RCT requirements.[47,60] This raises questions about whether the pathway's entry criteria adequately distinguish between products that truly need accelerated review to speed patient access and those that could reasonably proceed through traditional approval processes with minimal delay.

One approach to strengthening qualification criteria would be to incorporate more objective measures of disease severity and unmet need, and to update these over time as treatment options become available. Metrics such as equal value of life years (evLY) shortfalls or life expectancy reductions could provide standardized thresholds for determining which conditions warrant the pathway's use. For instance, the pathway might be reserved for conditions that reduce life

expectancy by a specified number of years or impose substantial disability burdens, ensuring that its flexibilities are applied only where the benefit-risk tradeoff of earlier access with less evidence is most justified.[163,164]

More stringent qualification criteria would help preserve the pathway's integrity while focusing its resources on the therapies and patient populations where accelerated access provides the greatest value. This refinement would not prevent innovation in better-understood diseases, but would direct those products toward traditional approval pathways where more complete evidence can be generated before market entry.

Policy Option: *Reserve AA for drugs that treat conditions meeting pre-specified life year shortfalls or survival thresholds*

Increase Enforcement of Requirements to Complete Confirmatory Trials

More assertive enforcement by FDA appears to have contributed to both improved perceptions of AA and its performance. Requiring that confirmatory studies be underway at time of approval facilitates the development of confirmatory evidence because it preempts at least some of the enrollment challenges that can occur once a commercial treatment option becomes available. However, the requirement can also create financial challenges for small companies, who are dependent on meeting milestones such as FDA approval to fund subsequent clinical development.

Expedited withdrawal of products has also been well-received, particularly when drugs fall short in their confirmatory trials or show unacceptable risks. FDA began to use its existing authority to encourage withdrawal even before FDORA was passed, and has since built on these reforms with guidance that outlines the information required from each party and defines a step-by-step process for removing a drug from the market. This includes giving the manufacturer adequate notice and clear reasoning for the proposed withdrawal, as well as opportunities to appeal, and giving the public an opportunity to comment.[42]

FDA's recent attempt to stop Elevidys shipments, rather than use the steps of the expedited withdrawal authority, shows the importance of predictability and input in the withdrawal process. The political backlash from patients and caregivers, who had been given no opportunity to weigh in on the decision, showed the importance of ensuring that enforcement happens within the guardrails of a stakeholder input process.

Policy Option: *Continue to require enrollment in confirmatory trials at time of AA, ensure that proposals to withdraw remain within the guardrails described in FDA guidance, and consider adding a requirement that the withdrawal process be initiated upon FDA determination that a manufacturer has not provided acceptable justification for failing to meet the agreed-upon timeline*

Re-Review or Sunset Accelerated Approvals Lacking Confirmatory Evidence

Our previous report included an option to institute annual review cycles or sunset AAs after a certain period if confirmatory evidence was not forthcoming. FDORA reforms that give FDA greater authority to require that confirmatory trials be ongoing at time of AA and to expedite withdrawal may reduce the need for this option. But the premise nevertheless holds some appeal: periodic reviews of new evidence and the state of confirmatory trials are seen as beneficial for monitoring the pathway's performance and fostering scientific advancement. Several respondents argued that regular re-review would be especially beneficial if it were for specific conditions or therapeutic areas, such as rare diseases.

Respondents also highlighted two concerns. One is that policies that go into effect without agency discretion, such as an automatic sunset for drugs that fail to produce confirmatory evidence within a given timeframe, would reduce the regulatory flexibility FDA needs to manage the pathway. That concern could be addressed by taking an approach similar to the European Medicines Agency (EMA), which requires manufacturers to submit a request for renewal of market authorization, which expires five years after initial approval under the European analogue of the AA pathway.[165]

Resource constraints present the other challenge, and may be more difficult to address in practice: FDA has struggled to sustain programs not directly funded by user fees, and comprehensive re-reviews would require significant resource commitments and compete with other critical priorities. More recently, layoffs and reductions-in-force under the Trump administration have reduced staffing, raising questions about its ability to deliver on existing programs and obligations.[166,167]

Resource constraints could be addressed by increasing funding, which could come from taxes or industry user fees. User fees already fund about 80% of FDA reviewer salaries, but critics argue this gives industry too much influence over the agency. [168,169] Raising taxes, meanwhile, requires political will that is difficult to muster. Another option is to limit the resource-intensity of re-reviews by limiting it only to certain circumstances or drugs. For example, additional reviews could target only drugs where uncertainty is greatest.

Policy Option: *Consider targeted re-reviews at the class or disease level, prioritized by degree of evidentiary uncertainty*

Adapt the Pathway to Specific Therapeutic Areas

A one-size-fits-all approach to AA may not match the evolution of the use of AA in specific therapeutic areas. Each faces distinct challenges in developing surrogate endpoints, designing clinical trials, and generating confirmatory data and would benefit from tailored FDA guidance and processes.

The FDA has already gone down this path for oncology, one of the three therapeutic areas we identified as having unique challenges under AA. The FDA's Oncology Center of Excellence (OCE), established in 2017, coordinates across the agency on cancer drug development, and weighs in on clinical trial design for AA and confirmatory trials.[47,170] Project Optimus, an OCE initiative, specifically aims to improve dosing optimization in oncology, where the MTD approach established for cytotoxic chemotherapies can result in higher than necessary doses for modern targeted therapies, reducing tolerability while not significantly improving treatment outcomes. However, additional guidance may be needed to address situations where PFS improvements don't translate to overall survival gains, and to clarify when PFS or other surrogate endpoints alone might suffice for full approval in specific cancer types.

In rare diseases, particularly ultra-rare conditions, the pathway could benefit from more structured processes for surrogate endpoint development when disease understanding is limited. This might include earlier advisory committee involvement and clearer thresholds for what constitutes acceptable evidence given small patient populations. As we noted above, a "scientific-focused drug development" process might be particularly helpful for rare disease development, where resources are most constrained and patient input is often missed.

For neurology, where brain disease complexity poses unique challenges, guidance could address the validation requirements for novel biomarkers and the role of long-term observational studies in confirming benefit. Disease-specific adaptations would preserve AA's core intent while acknowledging that evidence generation strategies may need to be tailored for certain conditions.

Policy Option: *Develop centers of excellence focused on AA for specific therapeutic areas*

Conclusion

The FDA's Accelerated Approval pathway exemplifies a societal commitment to getting promising treatments to seriously ill patients as quickly as possible – a reflection of our system's capacity for innovation and responsiveness to patient need. Throughout the development of this report – across stakeholder interviews, literature reviews, breaking news coverage, and in-person discussions – it was apparent that the underlying issues that remain for the AA pathway revolve around trust. Between manufacturers, payers, purchasers and regulators, and most especially among patients, there is skepticism, confusion, and frustration. From one perspective, products are being approved with weak evidence and high price tags, and the development of confirmatory evidence is slow. From another perspective, decisions are being made about insurance coverage based on costs, not value, leaving patients with few or no options. And from yet another perspective, shifting regulatory guidance and behavior has introduced more uncertainty to the already risky endeavor of bringing a new drug to market.

Despite the trust deficit, stakeholders also agree that much progress has been made. When our first paper was published in 2021, it could be argued that the many possible reforms identified were politically or practically infeasible, yet the changes from FDORA in 2022 and recently updated FDA guidance have begun to restore trust in the pathway by ensuring confirmatory studies are underway at the time of approval and asserting FDA's expedited withdrawal authority. Time to confirmatory study completion has declined. Manufacturers have withdrawn products voluntarily when confirmatory trials have failed.

The policy options laid out in this updated paper are designed to build on these successes and address the trust deficits that remain. Enforcement must be sustained — the requirement that confirmatory trials be underway, the expedited withdrawal process, and the transparency provisions of recent guidance all depend on an agency with the capacity and will to implement them. The selection of surrogate endpoints remains the critical upstream problem; without systematic approaches to identifying the endpoints most likely to predict clinical benefit, concerns about misuse of regulatory flexibilities will persist. Pricing and access reforms – outcomes-based contracts, value-based pricing, relief from cost-sharing for patients with no treatment alternatives – remain largely unimplemented despite years of discussion, in no small part due to the daunting data collection and infrastructure requirements that accompany them. Greater transparency in FDA decision-making could help rebuild the trust that controversial approvals have damaged, but only if the agency has the independence and resources to make decisions that can withstand public scrutiny.

This paper offers a guide. With input from various stakeholders – manufacturers, payers, purchasers, former regulators, and patients – the policy options outlined above would strengthen the perception and reality of the AA pathway. These options offer an opportunity to build trust across the ecosystem in service to affordable access for patients. Balancing the financial risks undertaken by drug developers with the financial risk assumed by payers and purchasers to ensure patient access is the ultimate goal of a high-functioning accelerated regulatory pathway.

The pathway's core premise remains sound: for serious conditions with high unmet need, earlier access to promising treatments can be worth the risk of greater uncertainty. But realizing that premise requires more than good policy ideas. It requires sustained commitment to enforcement, rigorous approaches to evidence generation, alignment of financial incentives with clinical uncertainty, as well as the institutional capacity to make difficult decisions based on science. Trust in this system — from patients who stake their lives on these treatments, from payers who fund them, from manufacturers who invest in developing them, and from the public whose health depends on a functioning regulatory apparatus — cannot be rebuilt through rhetoric alone. It must be earned through consistent, transparent, science-driven decision-making. We hope that this paper offers a starting point for further policy change in service to rebuilding that trust.

Appendix

In addition to representatives from the following companies and organizations who participate in ICER's Policy Leadership Forum, we were also joined by former FDA officials, patient advocates, and a representative from a state Medicaid department at ICER's 2025 Policy Summit, which was held from December 10 – 12, 2025 in Phoenix, Arizona:

- Abbott
- AHIP
- AstraZeneca
- AT&T
- Bayer
- Blue Cross Blue Shield of Massachusetts
- Blue Shield of California
- Boehringer Ingelheim
- California Public Employees' Retirement System (CalPERS)
- Centene Corporation
- CVS Health
- Elevance Health
- Express Scripts by Evernorth
- Geisinger Health System
- Genentech
- GSK
- Humana
- Intellia Therapeutics
- Kaiser Permanente
- Keenova
- Merck & Co., Inc.
- National Pharmaceutical Council
- Orchard Therapeutics
- Premera Blue Cross
- Prime Therapeutics
- Regeneron Pharmaceuticals, Inc.
- Sanofi
- UnitedHealthcare
- Ventegra

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