Applying Real-World Data and Real-World Evidence for Accelerated Approvals and Coverage Decisions

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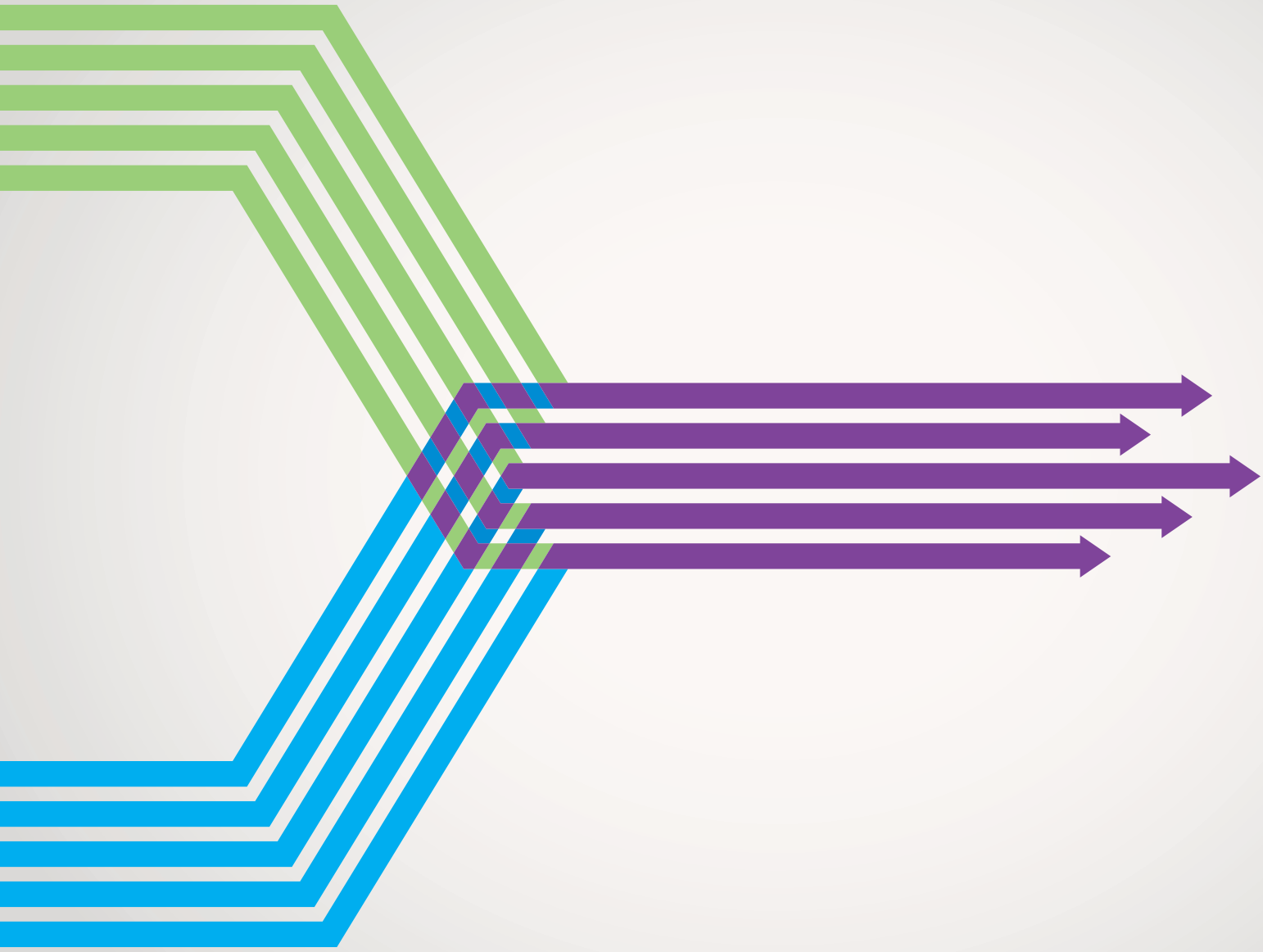

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Disclosures

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Executive Summary

Medical products granted accelerated approval by the United States Food and Drug Administration (FDA), and the evidence guiding such approvals, have been subject to controversy in recent years. Meanwhile, there is an ongoing need to deliver rapidly effective products to patients with unmet medical needs while also addressing the need for demonstrable safety and effectiveness in the real world. In parallel, federal agencies are developing guidance on the use of real-world data (RWD) to drive initial and confirmatory evidence generation that supports evaluation of safety and effectiveness. This paper explores the landscape of accelerated approval decisions by FDA, related payer considerations, and three medical product use cases (Elevidys, Vijoice, and Keytruda). In doing so, it offers considerations, based on current events, for RWD submitted as part of a total evidence package to inform both regulators and payers as they evaluate therapies within the FDA accelerated approval pathway. Such considerations warrant a close examination of how RWD sources address shared evidentiary needs among regulatory and payment stakeholders. In this white paper, we specifically examine real-world endpoint selection, generalizability of evidence, approaches for registries and data repositories, point-of-care trials, external control arms, and private payer considerations in the context of leveraging RWD sources.

Highlights

Real-World Context in Endpoint Selection

- Accelerated approval and payment decisions are context dependent, rendering it difficult to extrapolate recommendations from one use case to another, especially when considering the selection and use of endpoints. Thus, endpoint and measurement selection must consider reliability, validity, sensitivity to treatment effects, and align with data quality specifications to reflect real-world outcomes to ensure that endpoints are relevant for decision-makers.

Generalizability and Representativeness

- Generalizability and representativeness are important factors to consider when assessing clinical benefit and value. RWD can provide larger data sources to strengthen the totality of evidence for products granted accelerated approval.

Data Repositories and Registries

- Registries can be a potential source of RWD to support clinical trials and generate confirmatory real-world evidence (RWE) on the clinical value of medical products with accelerated regulatory approval. **Registries can provide information needed to determine sample size, selection criteria, and study endpoints needed to power both initial and confirmatory evidence generation.**
- Medical product developers may consider using or building registries for the purpose of sourcing or storing fit-for-purpose RWE that is complete, reflective of the patient journey, and available when an appropriate external comparison group is untenable.
- For either newly built or repurposed registries, it would be vital to ensure that patient registry data linked to electronic health records (EHRs) is relevant and reliable through a direct evaluation or comparison trial based on current data collection initiatives.

- General data collection standards for data registries and guidance on disease-specific elements that should be collected along with frequency of data collection would be beneficial to advance the field and practice of caring for rare disease patients.
- **CMS could spur action on more robust registries by updating its legal framework to require registry designs that collect more complete comparator data.** Additional guidance from CMS could be helpful, as well as collaboration between CMS and manufacturers early in the medical product development life cycle would also be helpful to develop registries that address evidentiary gaps.

External Controls

- Though external control arms hold promise, it is often difficult to match heterogenous patient populations across trial treatment arms and external controls. External control arm data could be collected concurrently with a treatment arm to minimize matching challenges. However, important limitations exist for leveraging concurrent external controls in the context of rare diseases. Future efforts should involve the development of methods to support using historical or concurrent external control data from RWD sources, even where assessment timelines might not align, or uses of hybrid external control arms, where a small control arm of the trial is supplemented by external data to lessen the need for a larger sample size in the control arm.

Postmarket Point-of-care Trials

- Point-of-care trials can serve as a means to efficiently generate practical evidence in postmarket settings to confirm benefits and risks of a product granted accelerated approval. Under favorable conditions (e.g., products with well understood safety profiles, endpoints that are collectable in routine care), RWE-based approaches, such as point-of-care, may be appropriate to address the limitations of more traditional, confirmatory trial approaches.

Considerations for Private Payers

- **Private payers should consider how they might support evidence generation that enables them to make decisions to improve patient care.** As concerns about the affordability of new and expensive products continue to rise, payer involvement in evidence generation in postmarket settings will be critical.

How This Paper Was Developed

This paper draws upon insights from the 2023 Real-World Evidence in Accelerated Approvals and Coverage Decisions workstream within the Duke-Margolis Institute for Health Policy's RWE Collaborative, which met monthly from May-November, 2023. Appendices A and B contain a list of 2023 workstream and the RWE Collaborative Advisory Group members who contributed their expertise to the development of this concept and publication.

Introduction

The FDA accelerated approval pathway has been a focus of attention for stakeholders across the drug development space, including Congress, in recent years. Accelerated approval inherently comes with uncertainty, and efforts to confirm therapeutic benefit have often been slow and incomplete.[1, 2] Meanwhile, the Center for Medicare & Medicaid Services (CMS) which oversees state managed Medicaid programs and the federally administered Medicare program,[3] has likewise faced many questions about how to make coverage decisions with limited evidence in light of new medical products, especially for Alzheimer's disease. In parallel, efforts to advance the use of RWD–Information on patient health and health care delivery, which is routinely collected from a variety of sources, and RWE–clinical evidence about usage, benefits, and risks of a medical product derived from RWD analysis, have benefited from new regulatory guidance. Increasingly numerous examples exist, both successful and unsuccessful, of RWE use in regulatory and payer decision-making.[4, 5] However, many unanswered questions remain about how to apply RWD to questions related to accelerated approval and subsequent decisions by payers. As the Institute has noted in past work, significant value exists for major decision-makers who leverage RWD to address shared evidentiary needs, and this holds true for accelerated approval therapies as well.[6]

In light of these deliberations, in 2023, the Duke-Margolis Real-World Evidence Collaborative conducted a year-long Accelerated Approvals and Coverage Decisions workstream focused on potential uses of RWD/E from the FDA accelerated approval to payer coverage decisions. In this paper, we first provide an overview of the FDA accelerated approval pathway and related evidence generation topics. We then discuss the potential utility of RWD/E within an accelerated approval and payer coverage pathway. Next, we provide a close assessment of RWD/E utilization within three distinct accelerated approval and private/public payer coverage instances or use cases. Lastly, we provide policy considerations and recommendations for the development of modernized data infrastructure that can address shared evidentiary needs along accelerated approval and private/public payer coverage pipelines.

Background

Before medical product developers, or sponsors, are allowed to market a new drug, they are legally required to demonstrate substantial evidence that their new treatment safely and effectively works as intended.[7] The traditional pathway for FDA approval of a new treatment is to develop evidence that consists of comprehensive studies based on three phases of research. Phase 1 emphasizes treatment safety and optimal dosing, Phase 2 focuses on treatment safety and side effect identification while providing some information about efficacy, and Phase 3 builds further evidence on safety and efficacy in larger, ideally representative, patient populations.[8] Two adequate and well-controlled studies generally provide a general basis for substantial evidence, that is evidence generated from adequate and well-controlled investigations that evaluate the effectiveness of a drug, for FDA approval.[9] This traditional path can take years to complete, which can delay much needed therapies from reaching patients. However, guidance from the FDA allows for a single adequate and well-controlled study, with follow-up confirmatory evidence to demonstrate substantial evidence of a drug's effectiveness, in specific circumstances.[10] This type of study is especially helpful when randomized control trials—the traditional gold standard for study design—are not reasonable for a treatment due to ethical and practical considerations.

The FDA accelerated approval program offers a more rapid regulatory approval than the traditional approval pathway. Responding to the HIV/AIDS crisis in 1992, the FDA launched the accelerated approval pathway to allow earlier approval of medical products that treat severe conditions and address unmet medical need. Congress expanded the pathway in 2012 by adding Section 901 of the Food and Drug Administration Safety Innovations Act (FDASIA), formally allowing the FDA to base accelerated approval for medical products on whether the treatment has an effect on either a surrogate or an intermediate clinical endpoint.[11] A product that is granted accelerated approval is approved for a specific indication based on a surrogate endpoint or intermediate clinical endpoint that is expected to predict clinical benefit (e.g., progression free survival in cancer). Drugs approved under this pathway are subject to labeling requirements. Sponsors are generally required to conduct further studies, using the same standards as the traditional pathway, to confirm safety risks and clinical benefit in order to gain full approval.[12]

The Food and Drug Omnibus Report Act (FDORA) of 2022 gave the FDA greater oversight and authority over the accelerated approval pathway.[13] It broadly aims to ensure the accelerated approval process is transparent and gives the FDA more authority to oversee the completion of confirmatory studies among sponsors. The FDA now can require a confirmatory, postmarket study to be underway prior to granting accelerated approval. In addition, the FDA now can use expedited procedures to withdraw an accelerated approval if a sponsor fails to conduct any required postmarket study of the product with due diligence or if the postmarket studies produce contradictory evidence to the evidence used for accelerated approval. On March 25, 2024 the FDA exerted its FDORA authority and issued two Complete Response Letters (CRL) to Regeneron Pharmaceuticals related to its application for odronextamab in relapsed/refractory follicular lymphoma and in relapsed/refractory diffuse large B-cell lymphoma.[14] CRLs are an FDA communication to a sponsor that their application is not able to be approved in its current form In this case, Regeneron's application was rejected because it did not have an ongoing confirmatory study.[15] The FDA's rejection of their application could have important implications in reducing delays in confirmatory studies and ensuring sponsors generate confirmatory data about efficacy in a timely manner.

In parallel, CMS has proposed the Accelerating Clinical Evidence model to adjust Medicare Part B payment amounts for accelerated approval medical products to give manufacturers an incentive to expedite and complete confirmatory clinical trials.[16, 17] This model seeks to provide answers to whether targeted adjustments on payments for accelerated approval drugs can accelerate confirmatory trial completion and aims to provide timely information on the safety and effectiveness of accelerated approval medical products on the market, facilitate earlier withdrawals of accelerated approval drugs when appropriate, and reduce Medicare spending on medical products that do not have confirmed clinical benefit.

CMS is working to establish its own approaches for evaluating postmarket evidence for novel therapies. While the FDA bases its approval decisions on whether a product is safe and effective, CMS Medicare coverage for products and services depends on sufficient evidence to support that a product or service is "reasonable and necessary," including whether it is appropriate for use in Medicare beneficiaries.[18] The "reasonable and necessary" considerations go beyond just safe and effective; CMS evaluates evidence on Medicare beneficiaries specifically—if FDA approval data does not have sufficient evidence on Medicare beneficiaries, then it may not meet the reasonable and necessary definition. For novel medical products that do not yet have enough evidence at the time of FDA approval to be considered "appropriate" for use in Medicare beneficiaries, CMS may provide national Medicare coverage to the product through the Coverage with Evidence Development (CED) paradigm.[19] CED is a mechanism, only used for Medicare parts A and B, in which CMS provides Medicare coverage for emerging therapeutics and services on the condition that there is ongoing data collection, often data on long-term safety

and health impacts for Medicare beneficiaries. CED is used only when there is not existing coverage or existing payment structures in place, although most products, even novel ones, can fall under existing payment structures. CMS has used some form of CED since the 1990s, though the modern CED policy was established in 2005, and since then there have been fewer than 30 CED determinations.[20, 21, 22] Additionally, CMS has recently proposed updates to the CED criteria that emphasize that postmarket data that supports coverage should be reflective of the intended patient populations, come from beneficiary expected sites of care, and be selected with attention to bias, completeness, and accuracy.[23]

Meanwhile, both CMS and the FDA have steadily built a set of guidelines for how high-quality RWD/E can be used.[24, 25] Through a variety of study designs and statistical analyses, RWD can be used to generate RWE that can provide insights for stakeholders. CMS continues to "explore how real-world evidence may be used to efficiently meet CED requirements."[26] As RWD collection infrastructure is further developed, and stronger RWE can be produced, these methodologies can provide support for treatments that are difficult to study with randomized controlled trials (RCTs). The FDA has provided source-specific RWD guidance for EHRs, registries, registries, and medical claims, as well as other considerations for external control arms, non-interventional studies, and other concepts. The outlined principles should help sponsors and investigators understand where RWD/E could be useful for their submissions. Furthermore, RWD/E principles can help inform any number of investigative protocols regardless of how reliant the study may be on RWD. A spectrum of study designs exists, and real-world resources can step-in when aspects of traditional, randomized, interventional trials need supplementation.[27]

Given these recent developments at the FDA and CMS, the time is ideal to explore how RWD/E have supported or informed FDA accelerated approval decisions. This exploration involves keeping in mind how broader RWD/E issues (e.g., data quality, cooperative resource sharing, etc.) will affect RWD/E use in final accelerated approval and coverage decisions. Prior Duke-Margolis work identified how shared evidentiary alignment can benefit regulatory and payer decision-makers.[28] The advantages of systematic collection of robust RWD touch all medical product development stakeholders, including patients. As sponsors invest resources in disease treatments that may have limited effect on or limited evidence within small populations and, potentially, limited coverage, it will be critical to ask and answer questions about how to meet patients' highest priority needs. We discuss prominent use cases below that highlight the scope of conversations taking place in the accelerated approval space.

Current Events within the FDA Accelerated Approval Pathway

Cancer

As of September 2023, more than 300 medical products have gone through the accelerated approval pathway. From 2010 to 2020, 85 percent of accelerated approvals were for oncology indications. In October 2021, the Oncology Center of Excellence (OCE) launched Project Confirm, a searchable, public database on the FDA website.[29] This database is divided into separate pages that list ongoing accelerated approvals, those that have verified clinical benefit and have been granted traditional approval, and those that have been withdrawn. Project Confirm aims to promote transparency of outcomes for oncological medical products approved via the accelerated approval pathway. The FDA Oncologic Drugs Advisory Committee has recommended withdrawal of 22 oncology accelerated approval medical products (between 2020-2024) for failure to show confirmatory evidence of clinical benefit. Currently, FDA has issued 61 ongoing cancer accelerated approvals, with 102 products with postmarketing trials that have verified clinical benefit and for which traditional approval has been subsequently granted for the specific indication.[30, 31]

Alzheimer's Disease

Monoclonal antibody (mAb) therapies for Alzheimer's have garnered significant public attention around the accelerated approval program. The FDA granted accelerated approval to Aduhelm (aducanumab) in 2021 on the basis of two Phase 3 clinical trials.[32] This decision was controversial, and an FDA advisory committee did not recommend approval. Some researchers and Alzheimer's advocates do not believe that the surrogate endpoint of amyloid plaque reduction used in the trial is indicative of reductions in cognitive decline, nor that the FDA should presume the drug's ability to reduce amyloid indicates effectiveness. More recently, the FDA granted accelerated approval to Leqembi (lecanemab-irmb) in January 2023 based on the observed reduction of amyloid plaque. This approval was converted to traditional approval in July 2023 based on a clinically meaningful reduction of cognitive decline.[33]

In 2022, CMS finalized a national coverage decision (NCD) to cover mAb treatments directed against amyloid plaque for the treatment of Alzheimer's disease under the CED mechanism. CMS provides Medicare coverage for mAbs approved in accelerated pathways (based on surrogate endpoints) in RCTs under investigational new drug applications. However, the CED requirements for mAbs with traditional approval for the treatment of Alzheimer's disease are less restrictive; studies can be prospective comparative studies and use registry data. As Leqembi received traditional approval, studies that support coverage of the drug can use registry data instead of being covered only in the case of an RCT.

Though the makers of Aduhelm no longer market the treatmen, and with Leqembi receiving full FDA approval, public focus on these medical products caused many to question FDA and CMS medical product review processes. This questioning has led to the changes seen in FDORA and increased focus on the CMS' role in spurring postmarket evidence generation for Medicare beneficiaries.

Safety

In many circumstances, RWD can provide information on long-term patient safety and effectiveness beyond initial trials. This evidence may be particularly valuable for cell and gene therapies that have immense promise for treating rare and genetic conditions, but also have little information available about their long-term effectiveness or potential long-term risks.[34] For example, CAR-T gene therapies, like Tecartus (brexucabtagene autoleucel), were granted accelerated approval because they fit the requirements and provided substantial evidence.[35] However, evidence generated from a retrospective analysis of RWD published after approval indicated that while the treatment was efficacious for the FDA indication, adverse events should be further examined.[36] Even when confirmatory evidence shows promise, it is critical to have as much information as possible on long-term patient progression for these treatments. In the case of CAR-T therapies, the FDA required several manufacturers to add a boxed warning to the products' label to indicate that some T-cell malignancies have infrequently occurred, which in some cases led to hospitalization and death.[37]

Furthermore, registries have played a significant part in driving evidence generation through CED, including regarding safety. For instance, in 2012, CMS elected to cover transcatheter aortic valve repair (TAVR) procedures, then transcatheter mitral valve repair (TMVR) in 2014, under CED. CMS also approved the Transcatheter Valve Therapy (TVT) registry to track patient safety and real-world outcomes related to the procedures.[38] In the TVT registry, patient-level data are submitted by participating hospitals to The Society of Thoracic Surgeons and American College of Cardiology Foundation's joint TVT registry. Registries like TVT allow for monitoring of safety and efficacy of new medical products and treatments and can help answer evidentiary questions around the patient, technology, and provider characteristics that can predict treatment success. CMS was able to lessen the provider and site requirements for both of these procedures in 2019 and 2020 because of the safety data collected in the TVT registry.[39, 40]

RWD/E within the Accelerated Approval Pathway

Although RCTs are the gold standard approach to measuring safety and efficacy, outcomes from RCTs may not reflect actual outcomes that might be observed in real-world settings. For example, RCTs can exclude populations that are more representative of the general population, such as Medicare beneficiaries that are often receiving multiple medications due to comorbidities. RWE can offer opportunities to address this issue within the accelerated approval pathway.

Accelerated approval treatments are often indicated for certain diseases with limited treatment options, including rare diseases and certain forms of cancer. As we highlight in a later section, RWD from rare disease patients within the FDA's Expanded Access Program (EAP) can support regulatory decision-making in certain contexts.[41, 42] RWD on the natural history of rare diseases can accompany data collected at pre-approval stages to help provide substantial evidence on product safety and efficacy. Similarly, within the scope of oncology, external control arms, a comparator built from data not collected as part of a trial, have been increasingly used to draw comparisons with medical products studied in single arm trials (i.e., with no internal comparison control arm).[43]

Likewise, confirmatory evidence generation in postmarket settings may benefit from research involving EHR, claims, or registry data and point-of-care trial approaches that integrate clinical research into clinical care to enable real-world randomized studies of approved medical products.[44] Once any treatment is approved for a new indication, especially products with well-established safety profiles from other indications, real-world patient outcomes can be studied in larger, real-world populations.

For example, the Pragmatica-Lung Cancer Treatment Trial mimics real-world conditions to confirm the effectiveness of a combination treatment (both of which have prior FDA approvals) versus traditional chemotherapy.[45, 46] Ultimately, stakeholders want to generate the best evidence possible for decision-making and, critically, for patients. RWD could be an avenue to advance study designs that better generate such evidence, especially over the long-term. For example, patient dropout from traditional trials can hinder the analysis and interpretation of the evidence it generates, and dropout or switching to other alternatives can be common in longer term studies.[47] This data loss is exacerbated in severe, fast-progressing diseases, which are frequently associated with the accelerated approval pathway.

Treatments receiving accelerated approval, however, will have greater uncertainty in their data. If the situation were otherwise, the treatment would likely advance along the traditional approval pathway. This same uncertainty in treatment safety and efficacy also might be true among payers following both accelerated and traditional approval. In both regulatory and payment scenarios, products evaluated under adequate and well-controlled settings with sufficient statistical power can be deemed relevant and reliable to understand treatment safety and efficacy. However, understanding treatment efficacy and safety in real-world settings would benefit from RWE studies that can further convince regulators and payers on broad product safety and effectiveness. We discuss this below through close examination of three distinct use cases.

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A Closer Look Across Three Distinct and Recent Use Cases

Use Case Selection

Workstream members prioritized use cases within the scope of rare disease and oncology treatments for review. Three treatments were selected for further discussion based on available information, temporal relevance (circa mid-2023), and ability to feasibly answer questions about initial and confirmatory evidence generation. Among the three treatments, we examined two instances where RWD/E was included to support initial approval; one where FDA considered RWE as part of the substantial evidence package, and the other where RWE was not considered helpful, and finally, a third instance where RWD/E was not used to support initial approval but could be considered within the scope of confirmatory evidence.[48] First, Elevidys (delandistrogene moxeparvovec-rokl), a rare disease gene therapy for Duchenne Muscular Dystrophy (DMD), was selected as a use case since it serves as a timely example of initial evidence generation from a treatment type that has received elevated attention from regulators and legislators.[49, 50, 51] Second, Vijoice (alpelisib) was selected since it recently leveraged data from a retrospective chart review study to gain initial accelerated approval. Alpelisib was initially developed in the oncology space and then repurposed for PIK3CA-Related Overgrowth Spectrum (PROS). Third, and finally, Keytruda (pembrolizumab) was selected to explore its potential to leverage RWD to generate confirmatory evidence, given that it is a product with multiple prior indications/approvals. We focused on the Merkel cell carcinoma indication for Keytruda.

Ultimately, stakeholders want to generate the best evidence possible for decision-making and, critically, for patients. RWD could be an avenue to advance study designs that better generate such evidence, especially over the long-term.

Payer Coverage Review

In September 2023, we used a commercial database to identify public and private payer coverage policies and examine coverage decisions for Elevidys, Vijoice, and Keytruda (for Merkel cell carcinoma indication) to determine coverage rationale for covering or not covering each drug.

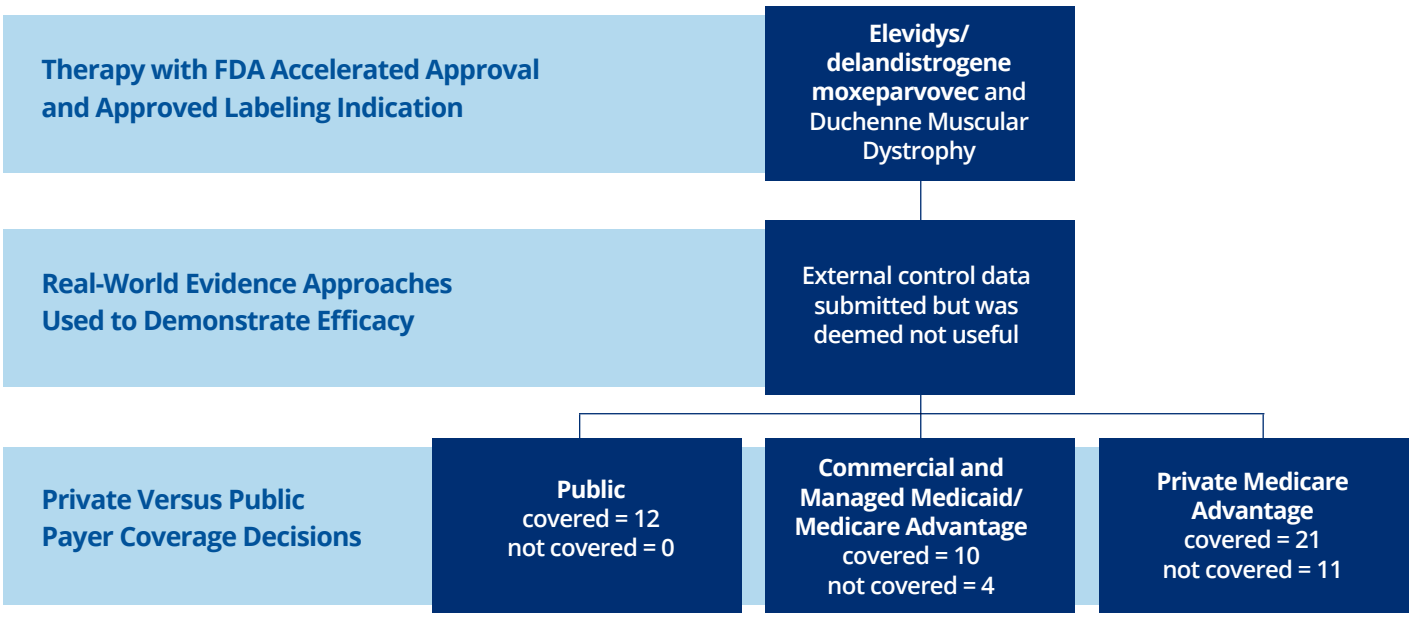
Elevidys	Gene therapy; rare disease	No prior indications	RWD/E submitted in initial approval application
Vijoice	Oncology	No prior indications	RWD/E considered within evidence package for accelerated approval
Keytruda	Oncology	Many prior indications	RWD/E could potentially generate confirmatory evidence

Use Case Assessment #1: Elevidys

Elevidys is an intravenous gene therapy for Duchenne muscular dystrophy gene therapy for DMD, which is a rare genetic condition that usually onsets in early childhood. The original biological license application (BLA) included three clinical studies involving children 4-7 years of age. These studies were split into two cohorts: 4-5-year-olds and 6-7-year-olds. Importantly, only one of the three studies was randomized, double-blinded, and placebo-controlled.[52] External control data from three separate studies were included in the BLA to facilitate interpretation of the two non-randomized trials. The FDA granted accelerated approval to Elevidys in June 2023, and it received widespread publicity as the first cell/gene therapy made available for DMD.[53] Additional interest emerged as a result of Center for Biologics Evaluation and Research (CBER) Director Peter Marks' previous comments, which expressed the desire for the FDA to advance patient access to cell/gene therapies.[54] The approval—applying to the younger patient cohort, not 6-7-year-olds—was based only on the randomized study. External control data was deemed "not helpful" in the Center Director's decisional memo because of high disease heterogeneity and the variation in supportive care.[55] This finding creates difficulty in confidently determining whether the study populations are sufficiently similar. Even though the randomized study was able to inform an approval decision, controversy remained given the lack of a pre-specified hypothesis (regarding patient ages) and efficacy interpretability. The small treatment effect size and subjective nature of the study's surrogate endpoints also casted doubt on efficacy.[56] Investigators evaluated treatment effects via the North Star Ambulatory Assessment (NSAA), a 17-item exam that tests mobility or ambulation. Since scoring is judged by providers and can be dependent on effort and immediate conditions, the subjective endpoint was difficult to confidently quantify. Still, Elevidys was granted accelerated approval with the NSAA identified as the primary endpoint to be studied in the Phase 3 EMBARK Trial in postmarketing requirements. Early results evaluated in the fall of 2023 indicated limited efficacy in patients; however, on June 20, 2024, FDA expanded Elevidys approval based on an assessment of secondary and exploratory endpoints.[57, 58]

Overall, the endpoint subjectivity, small treatment effect size, limited patient sample, and disease heterogeneity presented enough challenges that the additional concerns introduced by external controls were not well-positioned to be helpful. However, opportunities exist for RWD in cell/

Figure 1 | Elevidys Coverage Decisions



gene therapies, and even for DMD. The summary basis for action regarded patient-reported context as "compelling" and stated that "testimony by clinical investigators involved in the Applicant's studies, and videos of several study subjects, suggests that Elevidys may provide benefit to some patients."[59] If other biasing factors are mitigated, opportunities to include RWD in future BLAs persist.

In total, 74 percent of all policies reviewed (n= 58) covered Elevidys treatment for the accelerated approval indication. Less coverage was observed among commercial and Managed Medicaid/Medicare Advantage and private payers (71 percent, total n= 14; and 66 percent, total n= 32, respectively) versus public payers (100 percent coverage; total n= 12; see **Figure 1**). Given that the evidence from external control arm data was not convincing to regulators, it may that it was not convincing to payers as well. Therefore, cases such as this one show that it may be useful to discuss RWD choice selection during early study phases with regulators and payers.

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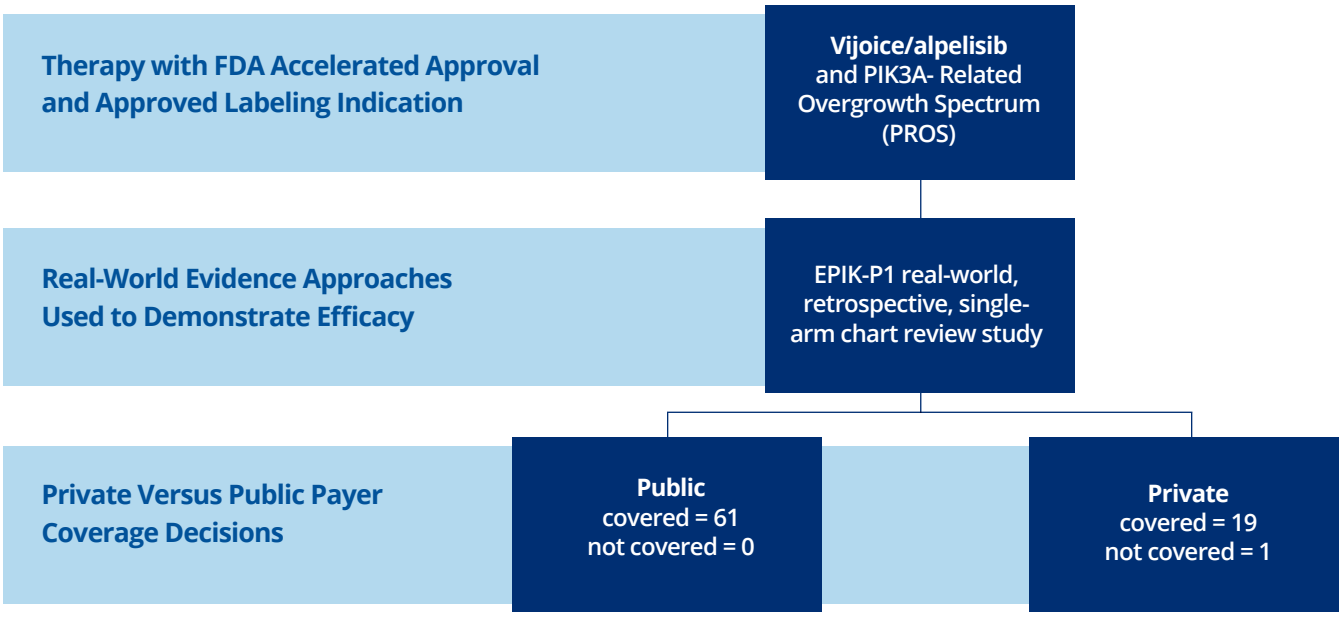
Use Case Assessment #2: Vijoice (alpelisib)

Alpelisib is a PI3K inhibitor that was initially granted full approval as Piqray to treat select patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer in combination with fulvestrant following progression on or after an endocrine-based regimen. In 2022, alpelisib, branded as Vijoice, was granted accelerated approval to treat patients aged 2 years and older with severe or life-threatening PIK3CA-related outcomes (PROs), an umbrella term for a rare PIK3CA-mutation condition with diverse clinical characteristics associated with cutaneous, vascular, musculoskeletal, and/or cerebral abnormalities, as well as overgrowth of tissue. Prior to the Vijoice accelerated approval, no approved pharmaceutical treatments to address the root causes of PROs existed.

Figure 2 | Vijoice Coverage Decisions



Vijoice's accelerated approval was based primarily on data from EPIK-P1, a single-arm retrospective chart review in 57 patients who were treated as part of an EAP, 37 of whom were evaluated for treatment efficacy. Per the FDA's approval summary, the acceptability of EPIK-P1 data was supported by the following attributes: use of a prospectively defined protocol for data collection and statistical analysis plan; use of blinded, independent, central review to assess patient imaging; and broad eligibility of patients participating in the EAP to reduce selection bias.[60] In addition, the EAP was designed with predefined eligibility criteria and included guidance for patient enrollment, treatment, and monitoring.

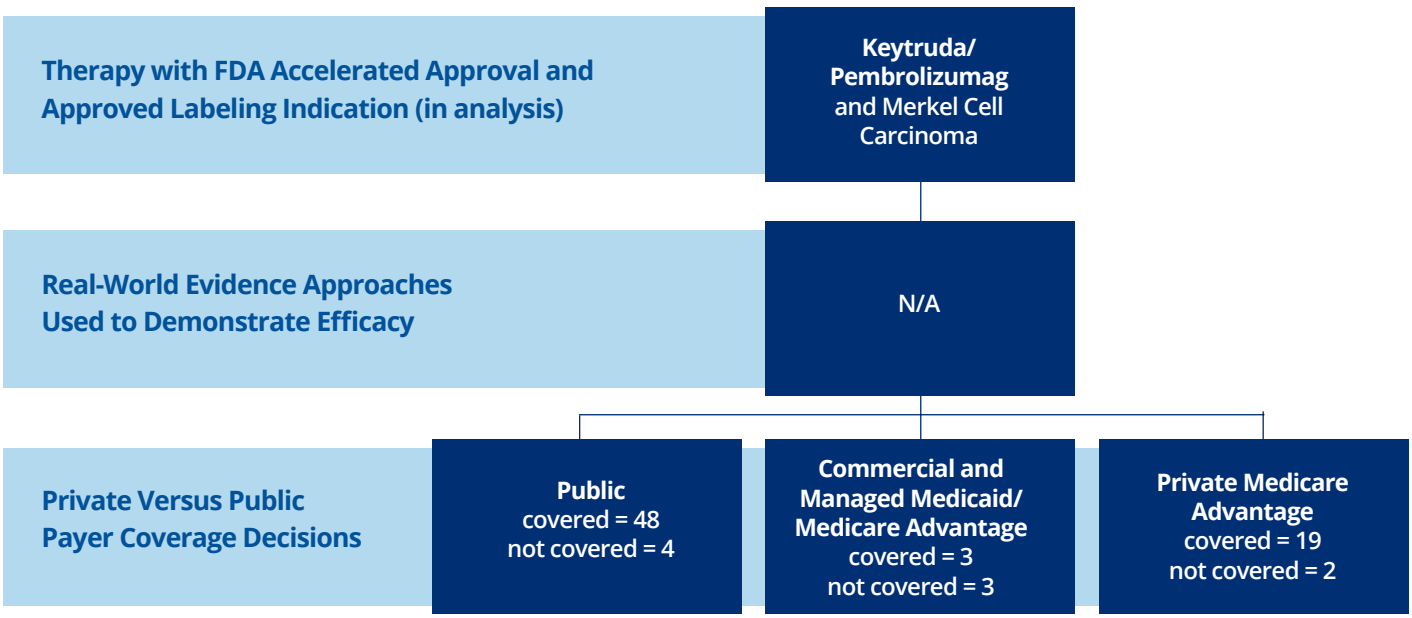
In total, 99 percent of all payer policies reviewed (n= 81) covered Vijoice treatment for the accelerated approval indication (see **Figure 2**). Although all public payer policies surveyed provided coverage (100 percent, total n= 61), 95 percent (total n= 20) of private payer policies surveyed covered Vijoice. No commercial and Managed Medicaid/Medicare Advantage policies were identified. Despite the FDA's approval decision, one (n= 1) private payer did not cover Vijoice, citing concerns with the overall quality of the chart-review data (e.g., patient population was small).[61] Vijoice is one example in which regulators may approve treatments based on RWE, but some regulators and some payers might perceive the quality of available RWE differently.

Use Case Assessment #3: Keytruda

Though not directly leveraging RWD/E in current applications, Keytruda represents an interesting case to explore hypothetical uses of RWD/E in the confirmatory setting. FDA initially approved Keytruda in 2014 under the accelerated approval process for the treatment of patients with advanced melanoma. Keytruda now has many approved indications.

Currently, two indications with ongoing accelerated approvals have confirmatory studies underway that are expected to be completed in 2024 and 2025. The Merkel Cell carcinoma indication was selected to explore payer coverage, as this indication's postmarketing requirements were projected to be completed sooner than the other indications. FDA converted the accelerated approval for the Merkel cell carcinoma indication to full approval in October 2023, after the payer policy analysis was completed.[62] Notably, the intent was not to determine

Figure 3 | Keytruda Coverage Decisions



new postmarketing requirements, but rather use agreed upon requirements as a basis for a hypothetical discussion about how such requirements might be approached by leveraging RWD in the future.

In total, 88 percent of all policies reviewed (n= 79) covered Keytruda (pembrolizumab--Merkel Cell carcinoma indication; see **Figure 3**). Coverage levels varied per payer type; although the greatest proportion of coverage was observed among public and private payers (92 percent, total n= 52; and 90 percent, total n= 21, respectively). Commercial and Managed Medicaid/Medicare Advantage provided the least level of coverage (50 percent out, total n= 6). Importantly, the nine policies that did not explicitly cover the Merkel Cell Carcinoma indication were last updated in 2020-21; FDA granted its accelerated approval in March 2020 and it is reasonably likely that more recent polices would cover this indication. In total, 100 percent of all policies updated after 2021 covered this indication. The apparent lack of prompt updates to payer policy speaks to a disconnect on accelerated approval drug coverage between regulators and payers. While we did not examine other indications, we can expect this to be consistent across its ongoing accelerated approval given the general coverage. Although Keytruda is a well-studied drug with several FDA reviews and labeling indications, potential exists to generate or leverage RWE to drive both accelerated approval decisions and potentially less varied levels of coverage across payer types.

Workgroup Considerations for Use Cases

The workstream explored key issues for each use case. Within the Eleidys discussion, the group considered if existing registries and EHR studies (such as those conducted by Parent Project Muscular Dystrophy) were close enough to be adapted for these purposes or whether a need exists for better fit-for-purpose approaches.[63, 64] Registries and patient generated health data (PGHD), that is health-related data created, recorded, or gathered by or from patients, or their family members/other caregivers, to help address a health concern, could be ideal for generating initial/confirmatory RWE for treatments like Elevidys.[65]

Key issues the workstream explored, as it related to Vijoice's regulatory submission and accelerated approval, were: 1) how to extend lessons from Vijoice, including how to effectively use data from EAPs, to other potential uses of initial approvals supported by RWD, 2) whether RWD is viable/helpful to obtain or generate confirmatory evidence efficiently, and 3) what barriers, real or perceived, might limit the value of RWE value as confirmatory evidence given that the initial approval already leveraged RWD.

The workstream acknowledged Keytruda's postmarketing requirements for its current accelerated approvals, yet selected to focus on the Merkel Cell carcinoma indication to explore payer coverage and discuss how RWD could be leveraged to generate confirmatory evidence.

Discussion

Our use case assessments show a continuous need to better understand data quality and fitness-for-purpose RWD to delineate the impact of RWE among regulator and payer decisions for drugs under the accelerated approval pathway. We observed, across three use cases involving 218 payer policies, that variation exists in payer coverage for therapies with accelerated approval, regardless of whether RWE served as initial evidence. Therefore, meeting fit-for-purpose data and data quality requirements and needs among regulators, payers, health care providers, and patients, along with opportunities to engage these stakeholders at early and mid-stage medical product development phases, might create efficiencies for generating confirmatory evidence and patient access to medical products within the accelerated approval pathway. We provide general considerations along this vein in our discussion below on real-word context in endpoint selection, generalizability, and representativeness.

Real-World Context in Endpoint Selection

Accelerated approval and payment decisions are context dependent, rendering it difficult to extrapolate recommendations from one use case to another, especially when considering the selection and use of endpoints. For example, the study evaluating Elevidys for DMD sought to measure ambulation using a subjective, performance-based measure (physician-evaluated North Star Ambulatory Assessment) and efficacy using a surrogate endpoint (expression of micro-dystrophin after 12 weeks).[66] Meanwhile, in the EPIK-P1 study for Vijoice, the primary endpoint analysis at Week 24 showed that 27 percent of patients achieved a confirmed response to treatment, objectively defined as 20 percent or greater reduction in the sum of PROS target lesion volume.[67] Subjective endpoints like Elevidys' can be difficult to interpret but are important to patients. Objective endpoints like Vijoice's can be easier to measure, but may not always directly translate to clear clinical or patient benefit. Given that both subjective and objective endpoints have different yet complementary strengths and limitations, as do surrogate and real-world endpoints, medical product developers should carefully identify or collaborate with patients to develop endpoints that are fit-for-purpose to support regulator and payer decision-making.

Sponsors may struggle to reach consensus around surrogate endpoint selection to measure clinical value and benefit. Real-world endpoints can be leveraged as one potential strategy to address this challenge. Moreover, payers may be more convinced by or confident in objective real-world endpoints, versus subjective and surrogate endpoints, when considering coverage. Thus, endpoint and measurement selection must consider reliability, validity, sensitivity to treatment effects, and align with data quality specifications to reflect real-world outcomes. For products with EAPs prior to approval, these programs may provide instructive information for the development of reliable and valid real-world endpoints post accelerated approval.

Generalizability and Representativeness

Generalizability and representativeness are important factors to consider when assessing clinical benefit and value. We observed in the case of Vijoice, that despite FDA accelerated approval, at least one payer had concerns with clinical value due to the perceived lack of generalizability because of the study's small patient population. **Therefore, to address concerns about generalizability, larger observational studies involving more representative cohorts can be conducted to measure causality in treatment effect of Vijoice and other similarly situated products under regulatory and payment consideration.** Studies involving diverse, real-world populations, like point-of-care and other pragmatic trial approaches, can be useful to produce generalizable confirmatory evidence.

Data Repositories and Registries

As noted above, data repositories, such as registries, can be a potential source of RWD to support clinical trials and generate confirmatory RWE on the clinical value of medical products with accelerated regulatory approval. For instance, the FDA's final guidance on "Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products" explains that registries can be used to select study participants for inclusion in an interventional study.[68] **Thus, registries can provide information needed to determine sample size, selection criteria, and study endpoints needed to power both initial and confirmatory evidence generation.** Also, and contrary to the outcome in the Elevidys use case, fit-for-purpose registries can serve as a compelling source of external control arm data for interventional trials. This finding was the case with Bruneura (cerlinponase alfa), which received approval for treating a relatively rare, debilitating form of pediatric Batten disease.[69, 70]

Medical product developers may consider using or building registries for the purpose of sourcing or storing fit-for-purpose RWE that is complete (e.g., contains internal comparator data), reflective of the patient journey (e.g., captures different exposures and events

that may affect or confound results), and available when an appropriate external comparison group is untenable. Registries, in fact, are scalable at both national and international levels, making them very resourceful for serving rare disease populations. In Europe, for example, data from nine countries populated the STRIDE Registry, which led to evidence that informed decisions on conditional approval of ataluren for DMD treatment.[71, 72] This example in Europe, alongside the case considerations presented for Elevidys, demonstrate opportunities for sponsors to work closely with regulators to understand whether registry data is fit-for-purpose to support accelerated or conditional, as well as full, approval decisions.

Registry development to collect postmarket outcomes for medical products has become more frequent in recent years. For example, the Center for International Blood and Marrow Transplant Research (CIBMTR) has enabled registry-based studies on Kymriah (tisagenlecleucel) and Yescarta (axicabtagene ciloleucel).[73, 74] Such registries could be a viable and valuable resource to help monitor long-term risks and benefits of cell and gene therapies, particularly where such information is difficult to collect in traditional trials. Additionally, registry-based monitoring could help ensure CMS and other payers have the most up-to-date and relevant information to make the more informed coverage decisions around the clinical value of medical products.

Registries provide opportunities to conduct retrospective, natural history studies, where registry data might serve as an external control arm. For example, Skyclarys (omaveloxolone) had orphan drug status and became the first treatment approved for Friedriech's ataxia in 2023, and it used natural history data to confirm effectiveness claims.[75, 76] Spinal muscular atrophy is another rare, neuromuscular disorder, and two of its treatments received orphan drug designation and fast track approval.[77] Evrysdi (risdiplam) and Spinraza (nusinersen) currently have multiple, registry-based, natural history studies ongoing to evaluate safety and efficacy in postmarketing settings.[78] In Germany, developers of Zolgensma (onasemnogene abeparvovec), were also required by the German Federal Joint Committee (G-BA) to collect registry data to better understand its clinical value.[79, 80] Where appropriate for a specific clinical and regulatory context (e.g., rare diseases where traditional trials may not be feasible), natural history data may provide a means of accelerating both initial approval and transition to full approval for accelerated approval products.

For either newly built or repurposed registries, it would be vital to ensure that patient registry data linked to EHRs is relevant and reliable through a direct evaluation or comparison trial based on current data collection initiatives.[81] For example, Parent Project Muscular Dystrophy (PPMD), a patient advocacy organization, manages a rare disease registry comprised of patient-reported data from several thousand patients (The Duchenne Registry) and combines this data with PPMD's Duchenne Outcomes Research Interchange as part of its EHR Study.[82, 83] PPMD's stated purpose of this effort is to help "clinicians improve and refine the standards of care, and help researchers learn more about Duchenne so treatments can be developed faster." Comparing two parallel yet different sources, such as The Duchenne Registry and PPMD's Duchenne Outcomes Research Interchange, can be useful to not only establish the plausibility and generalizability of study findings based on data observed within each source, but also establish proof of concept around efficiency in data linkage across multiple, patient-derived data sources and ability to generate fit-for-purpose data. Further work in this regard could help establish whether patient data linkage could assist in addressing data missingness issues observed when assessing long-term outcomes in rare disease populations and the reliability and fit-for-purpose nature of such data to support regulatory and payer decisions.

General data collection standards for data registries (e.g., demographics, comorbidities, details of diagnosis) and guidance on disease-specific elements that should be collected along with frequency of data collection would be beneficial to advance the field and practice of caring for rare disease patients. Recent FDA guidance on registries provides information specific

to sponsor utilization of new and existing registries for regulatory decision-making on safety or effectiveness.[84] Such standards also could include the documentation needed for data collection, integrity and traceability, along with data checking to ensure adequate data quality. **CMS could spur action on more robust registries by updating its legal framework to require registry designs that collect more complete comparator data.** Additional guidance from CMS could be helpful, as well as collaboration between CMS and manufacturers early in the medical product development life cycle. Guidance around useful registries or useful aspects of registries would also be helpful to address evidentiary gaps. Although, for many rare diseases, it is often difficult to find registries that contain data on the outcomes of interest, especially in the timeframe needed. Standardized registries, like the Rare Disease Cures Accelerator-Data and Analytics Platform, that collect data on many different rare diseases in one platform appear to be in development, which can augment existing registries.[85]

External Controls

External control arms have historically been used successfully to support regulatory decision-making.[86] However, external controls have seen inconsistent impact with accelerated approvals due to the risk of bias and confounding. This result includes bias and confounding due to difficulty in interpreting cases of heterogenous diseases, small patient populations, and treatments that have small effect sizes. All three of these factors contributed to why external comparison data did not impact the FDA's decision on the Elevidys accelerated approval. In recent years, many BLAs have been submitted to the FDA that include external comparison arms. Even in cases where accelerated approval was granted with external controls providing impactful context, such as Blincyto (blinatumomab) in 2014, the FDA routinely comments on the difficulty of matching heterogenous patient populations across trial groups and historical controls.[87] To evaluate blinatumomab, leveraging propensity score analysis was important to mitigate confounders between treatment and external control arms.[88]

External control arm data could be collected concurrently with a treatment arm to minimize challenges of matching to the two trial arms and the comparability of procedures and timing of outcome measurements.[89] However, important limitations exist in the context of rare diseases, where few eligible patients may be available and those that are will want to be in the trial. Therefore, future efforts should involve the development of methods to support using historical or concurrent external control data from other RWD sources, even where assessment timelines might not align, or uses of hybrid external control arms, where a small control arm of the trial is supplemented by external data to lessen the need for a larger sample size in the control arm.

While external controls may be a promising avenue, a consideration of case-by-case nuances for identifying a useful dataset comparator (i.e., an external dataset that is demonstrably relevant to serve as a control arm) is warranted. When randomization is not an option, the FDA may require a statistical demonstration of how the compared populations are sufficiently similar, and the population must be representative enough to support internal and external validity. The FDA has identified baseline characteristics for the population and the disease that must be considered, and they include, patient demographics (e.g., age, sex, race, geographic origin), disease characteristics (e.g., severity, duration), patient comorbidities, concurrent/past treatments, and intercurrent events.[90] Since patients with rare, severe diseases and limited treatment options may opt for new treatment options as they arise, external control arms may be best suited for conditions with shorter time frames to limit the number confounding intercurrent events. Likewise, time periods and index dates are priority interests for the FDA's evaluation of external control arms. Therefore, studies on treatments that can generate evidence over shorter time periods will likely have more success matching appropriate control arms.

Postmarket Point-of-care Trials

In addition to the approaches noted above, stakeholders also can consider point-of-care trials as a means to efficiently generate practical evidence in postmarket settings to confirm benefits and risks of a product granted accelerated approval.[91] Limits to traditional prospective, postmarket studies for many products exist after accelerated approval is granted because approved therapies can be prescribed outside of confirmatory trials, including in off-label use. Furthermore, some studies may use endpoints that require a significant amount of time to fully measure (e.g., overall survival). Though FDORA authority allows FDA to require confirmatory trials be underway at time of accelerated approval, the FDA and drug developers should consider the potential for these trials that could begin soon after approval is granted. Under favorable conditions, RWE-based approaches, like point-of-care trials or other pragmatic trial designs, may be appropriate to address the limitations of these more traditional, confirmatory trial approaches. For example, with a drug like Keytruda that is well understood, point-of-care trials initiated as a new accelerated approval is granted—rather than before—might be best suited for generating confirmatory evidence in a broader, real-world population, to not only confirm the existence of any benefit for a given indication but also provide practical evidence to inform care guidelines and payer decision-making. The Pragmatica-Lung trial, noted above, is one early indicator of both multi-stakeholder interest and potential directions these trials could take in the future. The FDA also has shown recent interest in support of these trials through the FDA's newly announced Center for Drug Evaluation and Research (CDER) Center for Clinical Trial Innovation (C3TI), which includes a demonstration program initiative for "streamlined trials embedded in clinical practice."[92]

Considerations for Private Payers

As CMS continues to explore strategies to address their postmarket evidence needs, private payers also should consider how they might support evidence generation that enables them to make decisions to improve patient care. For example, private payers might require CED-inspired data collection requirements for some accelerated approval therapies to ensure patient access while also confirming benefit for those patients. Additionally, value-based payment arrangements may have increasing value as new and expensive medical products enter the market still needing additional evidence generation to confirm benefits and risks.[93] Payers that take a more active role in setting evidence generation expectations can ensure that medical products are being used effectively to improve costs and outcomes. Such payer involvement might be particularly relevant for gene therapies that require long-term follow-up to fully determine benefits and risks but are also only paid for once. A combination of long-term data collection expectations and value-based payment arrangements, including outcomes-based agreements, that provide reimbursements to payers if therapies are less effective than expected may ensure more efficient use of cell and gene therapies while providing critical access to patients. For example, CMS's Cell and Gene Therapy Access Model is exploring outcomes-based agreements for the coverage of cell and gene therapies under Medicaid and will require data to inform decision-making on product effectiveness.[94] **As concerns about the affordability of new and expensive products continue to rise, payer involvement in evidence generation in postmarket settings will be critical.**

Conclusion

Though the potential of RWD for evidence is still relatively untapped, in appropriate circumstances, it can potentially serve as an important contributor to generate evidence for accelerated approval decisions in both initial and confirmatory evidence cases, as well as related payer coverage decisions. Many opportunities remain to align evidence generation capacity to address the shared needs of all stakeholders. The challenges of quickly determining the efficacy of therapies for unmet needs through accelerated approval pathways showcases the potential value of RWD to address not only regulatory questions, but also questions about coverage and how best to use new medical products in real-world populations. Like all uses of RWD, medical product sponsors considering the use of RWD to inform decision-making around accelerated approval products should ensure the population, treatment(s), outcomes and key covariates are measured in RWD in a way that is relevant, reliable, and fit-for-purpose. The considerations in this paper are intended to inform those efforts and chart potential paths for increased use of RWD sources as components of evidence generation

The challenges of quickly determining the efficacy of therapies for unmet needs through accelerated approval pathways showcases the potential value of RWD to address not only regulatory questions, but also questions about coverage and how best to use new medical products in real-world populations.

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APPENDIX A
RWE Collaborative Advisory Group

This paper was informed by the expert collaborators in the Duke-Margolis Real-World Evidence Collaborative Advisory Group. We thank the members of the Advisory Group, especially those from the 2023 cohort, for informing the development of this paper. The following list reflects the 2023 Advisory Group roster, which advised on the initial development of this workstream.

Listed 2023 member affiliations may not reflect current affiliations. For a current roster, the Duke-Margolis RWE Collaborative's Advisory Group, please visit the RWE Collaborative webpage.

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APPENDIX B
Accelerated Approvals and Coverage Decisions Workstream Roster

This paper was informed by monthly meetings of the 2023 RWE Collaborative workstream on accelerated approvals and coverage decisions. The following list represents workstream participants and their affiliations as of December 2023.

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APPENDIX C
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APPENDIX D
List of Coverage Policies and Determinations for Keytruda*

Plan ID	Plan Types	Covered (Y/N)
Public 1	Medicare Part D	Y
Public 2	Medicare Advantage,Medicare-Medicaid Dual-Eligibles	Y
Public 3	Medicare	Y
Public 4	Medicare	Y
Public 5	Medicare-Medicaid Dual-Eligibles	Y
Public 6	Medicare Part D	Y
Public 7	Medicare Advantage	Y
Public 8	Medicare-Medicaid Dual-Eligibles	Y
Public 9	Medicare	Y
Public 10	Medicare Advantage	Y
Public 11	Medicare Part D	Y
Public 12	Medicare-Medicaid Dual-Eligibles	Y
Public 13	Medicare Advantage	Y
Public 14	Medicare Advantage	Y
Public 15	Medicare Advantage	Y
Public 16	Medicare Advantage,Medicare-Medicaid Dual-Eligibles,Medicare Part D	Y
Public 17	Medicare	Y
Public 18	Medicare Advantage	Y
Public 19	Medicare Part D	Y
Public 20	Medicare Advantage,Medicare-Medicaid Dual-Eligibles	Y
Public 21	Medicare-Medicaid Dual-Eligibles	Y
Public 22	Medicare,Medicare-Medicaid Dual-Eligibles	Y
Public 23	Medicare Advantage	Y
Public 24	Federal Employer,Individual,International,Large Group,Medicare Advantage, Medicare-Medicaid Dual-Eligibles,Medicare Part D,Military/Tricare,Self Funded/ Employer Sponsored,Small Group	Merkel indication not specified
Public 25	Medicare-Medicaid Dual-Eligibles	Y
Public 26	Managed Medicaid	Y
Public 27	Medicare FFS	Merkel indication not specified
Public 28	Medicare Advantage	Y
Public 29	Medicare-Medicaid Dual-Eligibles	Y
Public 30	Medicare Advantage	Y
Public 31	Medicaid/CHIP	Y
Public 32	Medicaid FFS	Y
Public 33	Managed Medicaid	Y

Public 34	Commercial	Merkel indication not specified
Public 35	Medicaid FFS	Y
Public 36	Medicare	Y
Public 37	Medicaid/CHIP	Merkel indication not specified
Public 38	Medicaid/CHIP	Y
Public 39	Medicare Advantage,Medicare-Medicaid Dual-Eligibles	Y
Public 40	Public Employers	Y
Public 41	Medicaid/CHIP,Medicare-Medicaid Dual-Eligibles	Y
Public 42	Medicare Advanateg	Y
Public 43	Medicare Advantage,Medicare-Medicaid Dual-Eligibles	Y
Public 44	Medicare Advantage	Y
Public 45	Medicare-Medicaid Dual-Eligibles	Y
Public 46	Medicare Advantage,Medicare-Medicaid Dual-Eligibles	Y
Public 47	Individual,Medicaid FFS	Y
Public 48	Medicare	Y
Public 49	Medicare Advantage,Medicare-Medicaid Dual-Eligibles,Medicare Part D	Y
Public 50	Medicare Advantage,Medicare-Medicaid Dual-Eligibles	Y
Public 51	Medicare Part D	Y
Public 52	Medicare Advantage	Y
Private 1	Commercial	Y
Private 2	Commercial	Y
Private 3	Commercial	Y
Private 4	Commercial	Y
Private 5	Commercial	Y
Private 6	Commercial	Y
Private 7	Commercial	Y
Private 8	Commercial	Y
Private 9	Individual, Large Group	Merkel indication not specified
Private 10	Self Funded/Employer Sponsored	Y
Private 11	Commercial	Y
Private 12	Commercial	Y
Private 13	Individual	Merkel indication not specified
Private 14	Individual	Y
Private 15	Individual	Y
Private 16	Individual	Y
Private 17	Individual	Y

Private 18	Individual	Y
Private 19	Individual	Y
Private 20	Commercial	Y
Private 21	Commercial	Y
Commercial, Managed Medicaid 1	Individual, Managed Medicaid	Merkel indication not specified
Commercial, Managed Medicaid, Medicare Advantage 2	Commercial, Managed Medicaid, Medicare Advantage	Merkel indication not specified
Commercial and Managed Medicare 3	Commercial, Medicare	Merkel indication not specified
Commercial and Medicare Advantage 4	Commercial and Medicare Advantage	Y
Commercial and Managed Medicare 5	Commercial and Medicare Advantage	Y
Commercial and Managed Medicare 6	Commercial and Medicare Advantage	Y

*As of September 2023 based on publicly available data. Copies of coverage policies are available upon request.

APPENDIX E
List of Coverage Policies and Determinations for Vijoice

Plan ID	Plan Types	Covered (Y/N)
Public 1	Medicare	Y
Public 2	Medicare Advantage	Y
Public 3	Medicare Advantage	Y
Public 4	Medicare Advantage	Y
Public 5	Medicare-Medicaid Dual-Eligibles	Y
Public 6	Medicare-Medicaid Dual-Eligibles	Y
Public 7	Medicare,Medicare-Medicaid Dual-Eligibles	Y
Public 8	Medicare Advantage	Y
Public 9	Medicare Advantage	Y
Public 10	Medicare Advantage	Y
Public 11	Medicare Advantage,Medicare Part D	Y
Public 12	Medicare Part D	Y
Public 13	Medicare Advantage	Y
Public 14	Medicare Advantage,Medicare Part D	Y
Public 15	Medicare Part D	Y
Public 16	Medicaid/CHIP	Y
Public 17	Medicaid FFS	Y

Public 18	Medicare Advantage, Medicare-Medicaid Dual-Eligibles	Y
Public 19	Medicaid FFS	Y
Public 20	Medicaid FFS	Y
Public 21	Managed Medicaid, Medicare-Medicaid Dual-Eligibles	Y
Public 22	Medicaid FFS	Y
Public 23	Medicaid FFS	Y
Public 24	Medicare Advantage	Y
Public 25	Medicare Advantage	Y
Public 26	Medicaid FFS	Y
Public 27	Medicaid FFS	Y
Public 28	Medicare Advantage	Y
Public 29	Managed Medicaid	Y
Public 30	Medicare Advantage, Medicare-Medicaid Dual-Eligibles	Y
Public 31	Medicare Advantage	Y
Public 32	Medicare Advantage, Medicare Part D	Y
Public 33	Managed Medicaid	Y
Public 34	Medicaid/CHIP	Y
Public 35	Managed Medicaid	Y
Public 36	Managed Medicaid	Y
Public 37	Medicare Advantage	Y
Public 38	Medicaid/CHIP	Y
Public 39	Medicare Advantage	Y
Public 40	Medicare-Medicaid Dual-Eligibles	Y
Public 41	Medicare-Medicaid Dual-Eligibles	Y
Public 42	Medicare Advantage	Y
Public 43	Medicare-Medicaid Dual-Eligibles	Y
Public 44	Medicare-Medicaid Dual-Eligibles	Y
Public 45	Medicaid FFS	Y
Public 46	Medicare Part D	Y
Public 47	Medicaid/CHIP	Y
Public 48	Medicare Part D	Y
Public 49	Medicare-Medicaid Dual-Eligibles	Y
Public 50	Managed Medicaid	Y
Public 51	Managed Medicaid	Y
Public 52	Medicare-Medicaid Dual-Eligibles	Y
Public 53	Medicare-Medicaid Dual-Eligibles	Y
Public 54	Managed Medicaid	Y
Public 55	Managed Medicaid	Y

Public 56	Medicare Advantage,Medicare-Medicaid Dual-Eligibles	Y
Public 57	Medicare Advantage	Y
Public 58	Medicare Advantage,Medicare-Medicaid Dual-Eligibles	Y
Public 59	Medicare Advantage	Y
Public 60	Medicare Part D	Y
Public 61	Medicare Part D	Y
Private 1	Commercial	Y
Private 2	Commercial	Y
Private 3	Commercial	Y
Private 4	Commercial	Y
Private 5	Self Funded/Employer Sponsored	Y
Private 6	Individual	Y
Private 7	Commercial	Y
Private 8	Commercial	Y
Private 9	Commercial	Y
Private 10	Commercial	Y
Private 11	Individual,Large Group,Small Group	Y
Private 12	Commercial	Y
Private 13	Commercial	Y
Private 14	Commercial	Y
Private 15	Commercial	Y
Private 16	Public Employers	N
Private 17	Commercial	Y
Private 18	Commercial	Y
Private 19	Commercial	Y

*As of September 2023 based on publicly available data. Copies of coverage policies are available upon request.

APPENDIX F
List of Coverage Policies and Determinations for Elevidys*

Plan ID	Plan Types	Covered (Y/N)
Public 1	Medicare Advantage	Y
Public 2	Medicare-Medicaid Dual-Eligibles	y
Public 3	Managed Medicaid	Y
Public 4	Managed Medicaid	Y
Public 5	Managed Medicaid	Y
Public 6	Managed Medicaid	Y
Public 7	Managed Medicaid	Y
Public 8	Managed Medicaid	Y
Public 9	Managed Medicaid	Y
Public 10	Managed Medicaid	Y
Public 11	Managed Medicaid	Y
Public 12	Managed Medicaid	Y
Private 1	Commercial	Y
Private 2	Commercial	N
Private 3	Commercial	Y
Private 4	Commercial	N
Private 5	Commercial	N
Private 6	Commercial	N
Private 7	Commercial	N
Private 8	Commercial	N
Private 9	Commercial	Y
Private 10	Commercial	N
Private 11	Commercial	Y
Private 12	Commercial	Y
Private 13	Individual	Y
Private 14	Individual	Y
Private 15	Commercial	Y
Private 16	Individual	Y
Private 17	Commercial	Y
Private 18	Commercial	N
Private 19	Commercial	N
Private 20	Commercial	Y
Private 21	Commercial	Y
Private 22	Commercial	Y

Private 23	Commercial	Y
Private 24	Commercial	Y
Private 25	Commercial	Y
Private 26	Commercial	Y
Private 27	Commercial	N
Private 28	Commercial	N
Private 29	Commercial	Y
Private 30	Commercial	Y
Private 31	Commercial	Y
Private 32	Commercial	Y
Commercial and Managed Medicaid/ Medicare Advantage 1	Commercial, Managed Medicaid	Y
Commercial and Managed Medicaid/ Medicare Advantage 2	Commercial, Managed Medicaid	N
Commercial and Managed Medicaid/ Medicare Advantage 3	Commercial, Medicare Advantage	Y
Commercial and Managed Medicaid/ Medicare Advantage 4	Commercial, Medicare Advantage	N
Commercial and Managed Medicaid/ Medicare Advantage 5	Commercial, Managed Medicaid, Medicare Advantage	Y
Commercial and Managed Medicaid/ Medicare Advantage 6	Commercial, Managed Medicaid	Y
Commercial and Managed Medicaid/ Medicare Advantage 7	Commercial, Managed Medicaid	N
Commercial and Managed Medicaid/ Medicare Advantage 8	Commercial, Managed Medicaid, Medicare	Y
Commercial and Managed Medicaid/ Medicare Advantage 9	Commercial, Managed Medicaid, Medicare Advantage	N
Commercial and Managed Medicaid/ Medicare Advantage 10	Commercial, Managed Medicaid	Y
Commercial and Managed Medicaid/ Medicare Advantage 11	Commercial, Managed Medicaid	Y
Commercial and Managed Medicaid/ Medicare Advantage 12	Commercial, Managed Medicaid	Y
Commercial and Managed Medicaid/ Medicare Advantage 13	Commercial, Managed Medicaid	Y
Commercial and Managed Medicaid/ Medicare Advantage 14	Commercial, Managed Medicaid	Y

*As of September 2023 based on publicly available data. Copies of coverage policies are available upon request.