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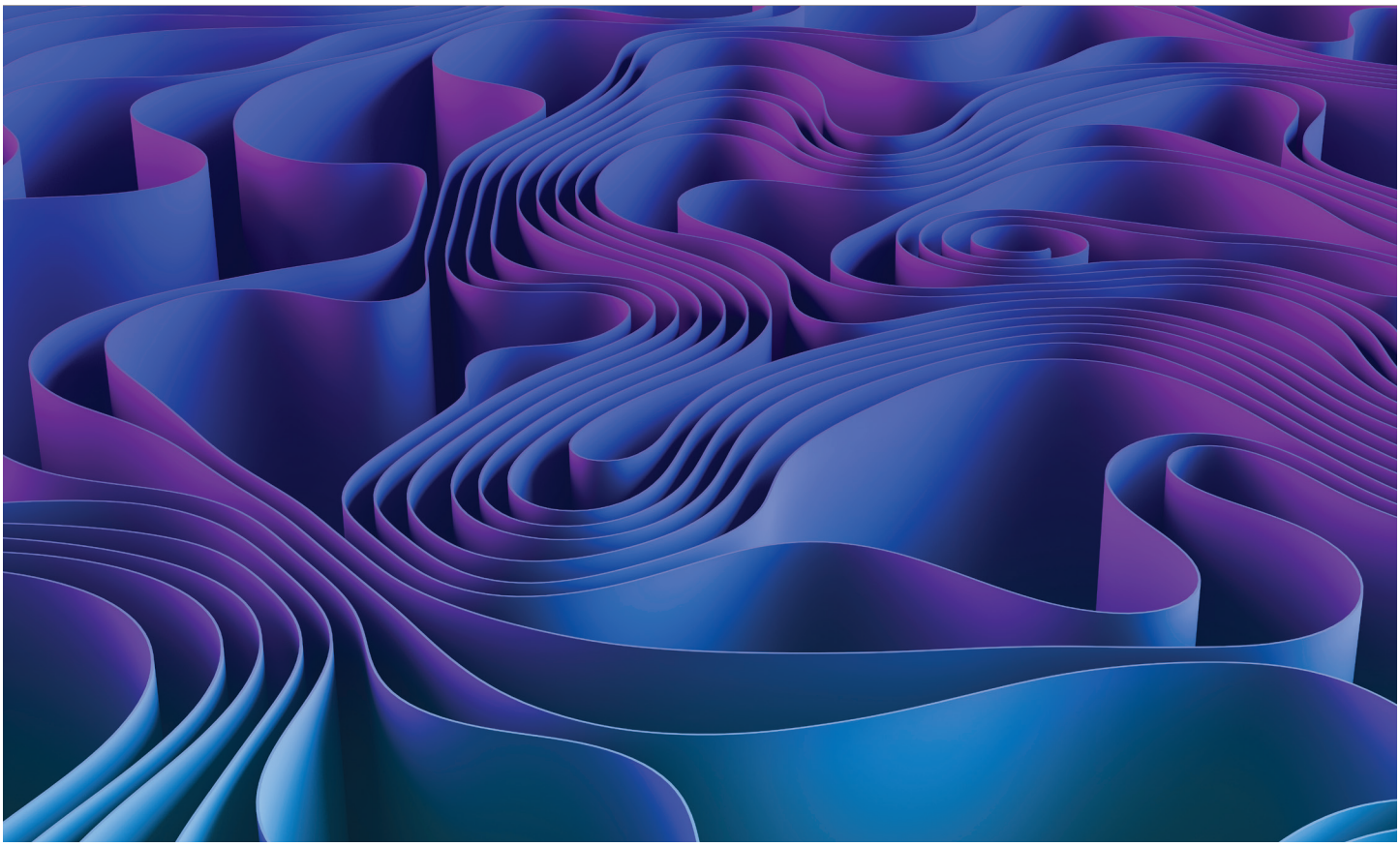


DESIGN LAB BRIEFING

Value-Based Contracts for Accelerated Approval Products

September 2023

CONFIDENTIAL

Tufts Medical Center Institute for Clinical Research and Health Policy Studies
Center for Biomedical System Design

The information contained in this briefing book is divided into three sections 1) Product Description, 2) Context/Background, and 3) Challenges to Address, with preliminary solutions. The product description will include development status, population effect size, market authorization, and other cure characteristics.

Target Area Group: Products that receive Accelerated Approval Program (AAP) market entry.

Design Lab Date: September 2023

Product: Astrotuminib (synthetic oncology case)

Key Questions: How can Value-Based Contracts (VBCs) help resolve the key challenges AAP-approved products present for patient/provider access, payer value assessments, and regulatory confirmatory evidence?

Executive Summary of Financing Challenge(s) and Proposed Solution(s): AAP-approved products use surrogate endpoints for clinical benefit and often have relatively small trials and shorter-term readouts. While the AAP approval grants commercial approval for a labelled indication, it also requires confirmatory clinical trials to be run, where a clinical benefit endpoint is investigated. The clinical evidence at time of launch is therefore uncertain and payers find it difficult to assess financial value for their coverage and reimbursement decisions. As a result, payers may restrict patient/provider access, seek price reductions, or even deny coverage entirely.

This case does not focus primarily on the structure of a Value-Based Contract (VBC). Rather, this case investigates whether VBCs can 1) Address the value uncertainties perceived by payers [enabling patient/provider access], 2) Inform the value-setting process [Payer Value Assessment (PVA)] itself, and 3) Contribute to the regulatory totality of evidence.

Breakout Group structured discussions will address the following areas:

Breakout groups 1&2: Patient/Provider Access Impact
Breakout groups 3&4: Payer Value Assessment (PVA) Impact
Breakout group 5: Contribution to Regulatory Totality of Evidence
Breakout group 6: PVA to Regulatory Interface

Astrotuminib product description

Our synthetic oncology case study will address "Astrorenoma", a malignant tumor of the kidney, affecting men and women equally, at a rate of approximately 1 in 30,000 people in the United States. Astrorenoma generally attacks a single kidney, has a propensity to spread to the other kidney, and later metastases primarily attacks the brain. Generally, patients with a diagnosis of Astrorenoma in a single kidney undergo a nephrectomy. If there is progression to the other kidney, double nephrectomy is standard of care with dialysis initiated.

Transplant eligibility could be as early as 2 years for patients where the disease has not spread to the second kidney. Thus, because both kidneys may be impacted and because Astrorenoma is unrelated to renal cell carcinoma and behaves differently, the current standard of care is removal of

the affected kidneys, starting dialysis and determining candidacy for transplant as indicated case by case. Close long-term follow-up for recurrent disease is essential.

Detection is commonly seen at 35-65 years of age. Early diagnosis is ideal, however most patients progress to bilateral disease and frank hematuria prior to confirmation by biopsy. In early stages, it presents as micro-hematuria which often goes undetected unless discovered incidentally. Even then, micro-hematuria is often disregarded if less than 10 cells per high-power field (hpf), delaying diagnosis. It has been challenging to identify targeted diagnostics for Astrorenoma and liquid tumor assays have been unsuccessful in identifying patients early in disease progression.

Treatment with Astrotuminib

Astrotuminib is a daily, oral small molecule that was awarded orphan drug status and granted Accelerated Approval. It targets the "Metaphor Pathway", specifically targeting tumor growth factors and is intended as a first-line treatment. Patients need to be monitored closely for any increase in tumor number or size. After surgery, patients are placed on long-term dialysis for those with unilateral nephrectomies and a poorly functioning remaining kidney, and always for bilateral nephrectomies. Patients taking Astrotuminib and lacking a functional kidney may typically become eligible for transplant after 2-5 years of observation for recurrence in other organs. Note that in the USA, the typical waiting time for a kidney transplant is more than 5 years. Patients may start accruing wait time with the start of dialysis.

For eligible patients, Astrotuminib treatment is recommended even when there is disease progression of tumors in both kidneys. Treatment with Astrotuminib is based on provider recommendation after discussion of treatment options with patients. Patients who are candidates for kidney transplant prior to starting Astrotuminib treatment should be on transplant eligibility lists in the event that the progression of Astrorenoma is not adequately managed by the treatment.

	Astrotuminib for Astrorenoma
Condition	• Malignant tumor of the kidney, unrelated to renal cell carcinoma • Propensity for occurring in both kidneys or early metastasis • Late metastasis to brain primarily • Current standard of care removal of the affected kidneys, starting dialysis & determining candidacy for transplant as indicated case by case
Population	• Onset at 35-65 years old, gender agnostic • Commercial insurer population • Prevalence in this population is 1 in 30,000
Product	• Daily, oral small molecule targeting the "Metaphor Pathway" • Approved on an accelerated basis • Used as first-line treatment
Clinical Evidence	• 40-55 years old with involvement of a single kidney; no metastasis • No history of heart disease • Responses split between dramatic responders (30% sub-population) with 24-month PFS and non-responders (70%) • Possibility of preventing life-long dialysis or transplant
Label	• Any patient with Astrorenoma with no metastasis • Any age • Involvement of both kidneys
Payer Segmentation, Coverage & VBC	• Commercial population (majority of patients in commercial insurance, including ACA) • Price set at $240K/year, $20K/month, in use as first-line therapy • The VBC would track discontinuation at <24 months and provides a pro-rata performance rebate of total net spend (100% if discontinued in months 1-3, with linear reduction to 0% if discontinued in month 24).

Clinical Evidence of Benefits and Harms
Early trials in patients aged 40-55, with involvement of a single kidney, no metastatic disease, and no history of heart disease have been promising. Results split between dramatic responders (30% subpopulation) with Progression Free Survival (PFS) at 24-months and non-responders (70%) of the small population treated to date, with no clear identifying characteristics or biomarkers predictively distinguishing responders from non-responders. However, the possibility of preventing life-long dialysis or transplant has spurred early release and plans for capturing Real-World Evidence (RWE) for Astrorenoma patients. It is expected that Astrorenoma will be the first of multiple indications for this tumor-agnostic drug, Astrotuminib. Therapy has less toxicity than the current standard of care, allowing for an earlier return to work.

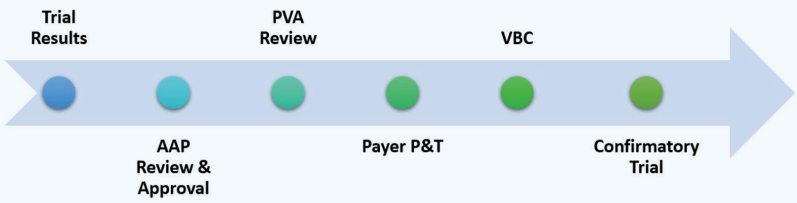
Based on the above evidence, Astrotuminib was awarded orphan drug status and granted Accelerated Approval for first-line treatment of non-metastatic Astrorenoma (without regard to age or number of kidneys involved). A confirmatory trial of Astrotuminib is already underway, with 5-year overall survival dialysis-free as the primary endpoint.

Payer Segmentation, Coverage, and Value-Based Contract (VBC)
The VBC tracks discontinuation at <24 months and provides a pro-rata performance rebate of total net spend (100% if discontinued in months 1-3, with linear reduction to 0% if discontinued in month 24). The VBC parameters would be agreed to by both developers and private payers, with some differences in populations versus the clinical evidence available at time of launch.

The commercial population, which includes the majority of patients in commercial insurance, including ACA, would have a price set at $240K/year, $20K/month, in use as first-line therapy. VBC data would be available in real time so that payments reflect specific patient outcomes, and the accumulated picture over time will inform developers and payers about actual per patient costs. Such information is especially useful when early diagnosis is a challenge, and where markers to identify responders/non-responders are not possible.

While the cost of Astrotuminib is higher than the $100K average annual costs associated with dialysis in the US, it is comparable to other immune-oncology treatments and the $250K price tag for a single kidney transplant, excluding the ongoing cost of long-term immunosuppression treatment of approximately $10-14K per year.

Original Process: Data Generation for Accelerated Approval Program Products



AAP: *Accelerated Approval Program*
P&T: *Pharmacy & Therapeutics*
PVA: *Payer Value Assessment*
VBC: *Value-Based Contract*

This image depicts the original process for data generation as a linear or consecutive process of data generation. Each stakeholder works to collect evidence related to a new medicine at a discrete point in time. Currently, Payer Value Assessments (PVAs) in the US are considered by payers before P&T decisions are made, but unlikely to share the PVA outside of the payer institution. It is not yet common for VBC data to be shared widely.

The accelerated approval program & recent updates

In 1992, the U.S. FDA initiated an Accelerated Approval Program (AAP) to address concerns that new medicines for diseases without adequate therapies were not reaching patients quickly enough. Since that time, the FDA's Center for Drug Evaluation and Research (CDER) has approved 278 new medicines via the AAP.[1] The pace of AAP approvals has increased over time, with a quarter of these approvals (70 drugs) granted between 2020-2021.

Through the AAP, medicines that have shown promise to advance care are allowed to go to market with data limited to surrogate endpoints, and an agreement that confirmatory trials would be conducted after market entry to confirm clinical benefit. The confirmatory trials have been a consistent feature of the AAP agreement between CDER and manufactures.

Unfortunately, 1/3 of all AAP-approved medicines (104 drugs) have not completed the confirmatory trials in the agreed upon timeframes. According to the Office of Inspector General report estimates,[2] Medicare and Medicaid spent more than $18 billion for AAP-approved drugs with incomplete confirmatory trials between 2018-2020.

There are many reasons why confirmatory trials are so difficult to complete, including limited incentives for patients to join the trials and insufficient resource allocation by manufacturers (or transfer of ownership of a drug).[3]

In response, the FDA has initiated specific changes to the AAP in December of 2022 under the Consolidated Appropriations Act, including:

1. A mandate that confirmatory trials are underway prior to AAP approval decisions.
2. A more streamlined process to take drugs off the market if clinical benefit is not proven.

[1]U.S Dept. of Health and Human Services, Office of Inspector General, Data Snapshot. "Delays in Confirmatory Trials for Drug Applications Granted FDA's Accelerated Approval Raise Concerns" September 2022 OEI-01-21-00401.
[2]https://www.fiercehealthcare.com/payers/fdas-califf-calls-insurers-help-providers-participate-critical-clinical-drug-trials (Accessed online March 23, 2023).
[3]Kaltenboeck, A., et al, "Strengthening the Accelerated Approval Pathway: An Analysis of Potential Policy Reforms and Their Impact on Uncertainty, Access Innovation and Costs," Institute for Clinical and Economic Review White Paper, April 26, 2021. (Accessed online March 23, 2023).

Motivation and context/background

Value-Based Contracts as Evidence Generation Opportunities

At the time of market authorization and especially for products that receive Accelerated Approval, key stakeholders, including payers, providers, regulators, patients, and Payer Value Assessment (PVA) departments, are making decisions based on registrational clinical trial safety and efficacy data that typically do not reflect the real-world outcomes of the patients receiving the product. While the Accelerated Approval Program (AAP) was initiated to ensure early patient access to products demonstrating evidence of efficacy, investigations have shown that the initial indications of benefit are often left unproven over time, prompting payers and providers to have concerns about these medicines that may lead to limited access for patients.

With AAP-approved products, the FDA has agreed that surrogate endpoints in oncology are stable predictors of clinical benefit*, recognizing that cancer patients face life-threatening needs. The FDA guidance has been updated to ensure that developers design and initiate confirmatory clinical trials a priori to Accelerated Approval to allow for clear post-marketing data development that is efficiently produced and will verify clinical benefit.

Despite the FDA's procedural advancements, the data available at the launch of AAP products leaves stakeholders with questions regarding the full value these products will bring to patients. Some patients will choose the AAP product per their personal benefit/risk judgment and access, while others will select the current standard of care. For payers, the initial internal PVA process would have to be based on the initial, surrogate data available at launch to determine to what extent to offer coverage for patients at the significant cost of the therapy.

For providers and patients, the FDA has endorsed the use of a treatment for patients' unmet need. Faced with a serious condition, patients and their providers may be recep-

*See FDA News Release, March 25, 2023, "FDA Issues Draft Guidance Aimed at Improving Oncology Clinical trials for Accelerated Approval," https://www.fda.gov/news-events/press-announcements/fda-issues-draft-guidance-aimed-improving-oncology-clinical-trials-accelerated-approval. Accessed Jun 6, 2023.

tive to monitoring their personal response to the new product to develop data that may improve understanding of the therapy's effectiveness.

For developers, the Accelerated Approval Program provides the possibility for patients with an unmet need to gain earlier market access to a new and innovative treatment. Often, AAP-approved treatments address the needs of a relatively small patient population, so developers appreciate that the early approval will allow them to earn possible near- and mid-term financial gains (offset in the initial years by market launch and education costs). Prior to launch, developers commit upfront development costs and are required by the FDA to initiate the confirmatory trials before receiving approval.

What is a Payer Value Assessment in the USA?

In the United States, Health Technology Assessments (HTAs) are not controlled or adjudicated at the federal government level. While there are regional collaborations that assess the value of new medicines and devices, there is a consistent aversion to creating a system where a medicine's scientific value is translated into a direct economic value determination. At the same time, data analytics have progressed to the point where health outcomes from a medical intervention in real world settings can be understood.

Payer organizations have consistent access to data about health treatment interventions for their patient populations. They are able to use their data to assess the value of the medicines, vaccines, medical devices, and treatment protocols that they provide for their patient populations. Yet, there is no one standard value assessment process that is followed consistently across payer organizations. While value is a ubiquitous part of the payer decision-making process, the process itself is more informal and fragmented when compared to an HTA system in other advanced nations.

For major payer organizations, value assessments can be a strategic analytic process used to assess the scientific value of a new intervention, specifically regarding the payer's patient population. Payer Value Assessments (PVAs) use publicly available data on a new medicine to look at the safety and efficacy profile of that product. In addition, where payers and providers are better able to track health outcomes, there is heightened interest to apply that knowledge to effectively and efficiently use new medicines and vaccines to meet patients' needs.

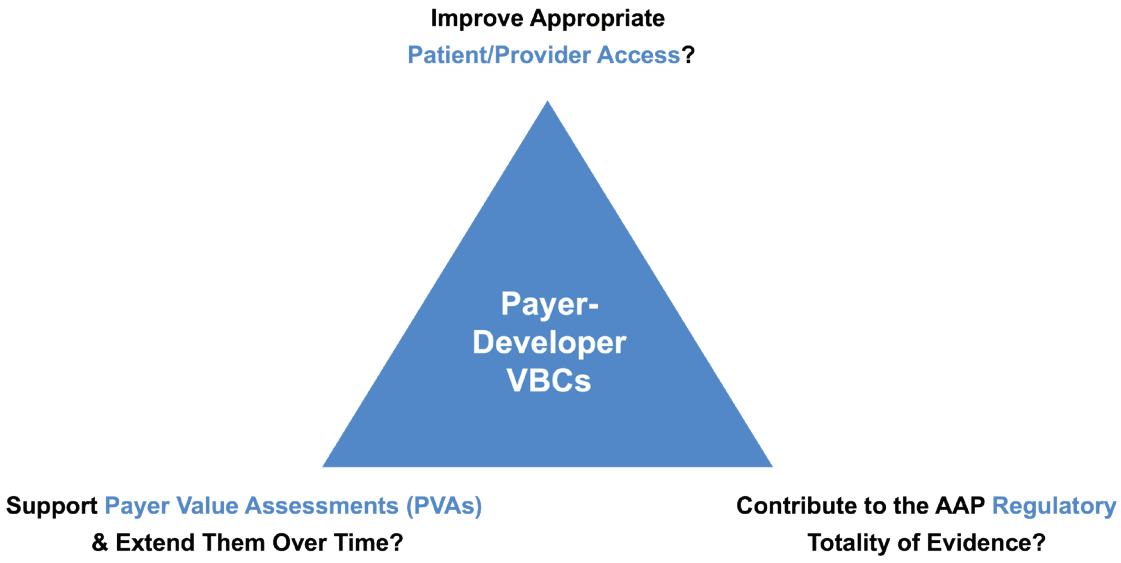
Especially when a product comes to market early, such as via the Accelerated Approval Program (AAP), an early PVA would have to rely on available data. In such a scenario, the PVA could provide an early assessment, with an understanding that as more data became available, payer decisions could be revisited. In this scenario, the "fit for purpose" data that could be generated from a VBC would likely be useful to the PVA process and subsequent payer decisions regarding treatment pathways and patient access to the AAP-approved product.

With payers taking the lead on both the VBCs and the PVAs, they have the opportunity to incorporate VBC and other private data sources, as well as publicly available data in periodic PVA reviews. At such times, payers would have the benefit of VBC data and other internal financial data to assess the overall cost of care and the impact of the AAP-approved medicine. They would also be able to scan public data sources to better understand old and new competitors, any Regulatory updates (e.g., label changes), or data on utilization rates and other costs of care. Periodic PVA reviews could provide shorter-term, realistic assessments of new products on the market, providing payers, providers, and patients up-to-date, data-driven value assessments.

The PVA process is unlikely to influence policy at the national level in the US on par with EU, UK, Canadian, or Australian HTA procedures. At the same time, the ability to reassess PVA recommendations as new data is available could become a timely advantage for patient care.

As a result, developers must seek returns on these investments, allowing them to continue to invest in research by reaching as many patients in need of treatment as quickly as possible. With the Accelerated Approval in hand, the available scientific evidence has supported the developer's confidence in their own product.

In this Design Lab, we will investigate how Value-Based Contracts (VBCs) can provide data on AAP-approved medicines that mitigates inherent uncertainties in patient value. We will explore how the VBC data might influence both the initial and subsequent coverage decisions. The Real-World Data (RWD) collected through the VBCs can confirm that patients receive products that help them, and also establish net payments that correlate with the value they bring. Because VBC terms usually extend for no more than 24 months, it is reasonable to assume that multiple 'rounds' of VBCs will occur before the confirmatory trial and FDA review is completed. Subsequent coverage policies and VBCs may therefore change, according to what is learned about the product's performance from the prior VBCs.



In this case study, we will explore whether the data developed from VBCs can support PVA deliberations, contribute to the regulatory totality of evidence, and inform patient/provider therapy selection. Such data may therefore build support either for maintaining (or expanding) patient/provider access or for increased caution (or restrictions) to using these new medicines.

The breakout group discussions for this case study are centered around three key questions exploring the following topics in more depth:

Question 1: Can VBC outcomes data improve appropriate patient/provider access of Accelerated Approval medicines?

Astrorenoma is a life-threatening disease that is hard to diagnose early enough to save patients' kidneys. Astrotuminib has been granted an Accelerated Approval as an orphan drug to treat Astrorenoma, based on early trial data but responders and non-responders are difficult to differentiate prior to drug use. Those who do respond (30%) see dramatic improvement, with progression-free survival at 24 months. Patients facing this disease are eager for new treatments, but

payers are understandably concerned that if they pay for Astrotuminib for all patients, knowing that not all will respond, the costs will outweigh the value provided.

We will examine whether VBCs can impact appropriate patient/provider access during the gap between accelerated approval and confirmatory trial evidence review. The AAP authorizes access for small patient populations that have a high unmet need for treatment. Yet, these conditions themselves create challenges for developing a timely and robust data package. In this breakout group discussion, we will explore whether the data generated by VBCs can:

- Inform the use of AAP-approved products by understanding the outcomes in RW context.
- Address coverage and reimbursement uncertainty for patients outside the clinical inclusion/exclusion criteria, but within the labeled indication.
- Reduce Medicaid and legislative desire to restrict AAP-approved drug access.
- Improve patient care directly by using evidence in the care setting.

Question 2: Can VBC outcomes data support PVAs over time?

Astrotuminib will come to market when the data available is limited, and before confirmatory trials are complete. In general, the Payer Value Assessment (PVA) process relies on the data available from clinical trials. However, in this case, Astrotuminib will not have a robust data portfolio upon which the initial PVA review would be able to produce a long-lasting report on the product. It is presumed that a VBC helps provide initial coverage for Astrotuminib by partially addressing payer uncertainties regarding value.

In this case, we will examine whether VBCs can generate outcomes data that could support subsequent PVA recommendations. We will explore how PVA approaches, outputs, and timing (real time and iterative) might change to incorporate the VBC data in the Astrotuminib case. We will explore how the data generated in VBCs can:

- Encourage methodological changes in the PVA process that a) recognize patient heterogeneity and b) shift from audit-based to prospective reviews.
- Encourage earlier PVA processes so that they can influence the endpoints of confirmatory trials and provide assessments that are more helpful to stakeholders.
- Prompt a shift to a system of more iterative PVA assessments that take place early, and more often, in response to new data generated.
- Explore how subsequent VBC rounds might evolve to address Payer Value Assessments.

Question 3: Can VBC outcomes data contribute to the AAP regulatory totality of evidence?

Astrotuminib will come to market with an indication that suggests improvement versus standard of care for patients suffering from Astrorenoma. In line with the updated process for AAP-approved products, the developer will have initiated a confirmatory trial as part of the approval process for this orphan cancer product. Therefore, the endpoints for the confirmatory trial will have been agreed upon at the time of launch. However, the confirmatory trial will take years to conduct and review. With shorter term horizons and an easily collected endpoint, VBCs will produce data about Astrotuminib performance in real-world settings.

We will examine whether VBCs using available clinical outcomes reporting can contribute to the totality of evidence, particularly in the case of AAP-approved medicines. In this breakout group discussion, we will explore how VBC-generated data can:

- Highlight the value of VBC-generated outcomes data.
- Enhance integrated evidence development plans by including VBC-generated outcomes data.
- Encourage patient-centric endpoint selection.
- Contribute to the data provided for label extension uses.

Challenges that value-based contracts address (elucidation & preliminary solutions)

Patient/Provider Access

The Accelerated Approval Program (AAP) was initiated to enable early patient access to therapies addressing a serious unmet medical need. These products are coming to market early without the full evidence of clinical benefit, leading some payers to resist covering AAP-approved medicines, and limiting patient access. As stated above, investigations have shown that the assumed benefit is often left unproven, despite the high price tag for these medicines. A process originally put in place to expand access to care may in fact impede patient and provider access because evidence of value is lacking.

The FDA has moved to ensure that the post-marketing confirmatory trials are underway at the time of granting Accelerated Approval and that there is a clear program to take medicines off the market that do not prove clinical benefit. Yet patients and providers don't want to wait, and they may not have to: It is possible that more controlled payment contracts—those structured to measure and reward value—will lessen the uncertainty around value earlier for payers, encouraging coverage for patients, and reimbursement for providers.

Topics for breakout discussions:

- In the short-term, the structure and use of a VBC could improve coverage for patients because payers would be more confident that they will be paying for a defined value benefit.
    - Could Astrotuminib VBC patient discontinuation outcomes data increase confidence regarding the coverage for patients meeting the FDA labeled indication but falling outside the supporting clinical trial inclusion and exclusion criteria, such as co-morbidities, age, severity, etc.?

- As VBC data becomes more broadly used, Astrotuminib VBC patient discontinuation outcomes data could refine care regimens within both labeled indication and clinical trial populations.
    - Could VBC data refine the patient populations treated as more outcomes are reported?

- VBCs have the potential to transform the infrastructure of patient outcomes reporting and the sharing of VBC-generated data.
    - What institutional or systemic changes would have to occur to support such a transformation? How could private payer VBC data be shared in the new system?

- In the mid-term, ongoing VBC data generation could be leveraged to balance clinical management with patient/provider access.
    - With a VBC in place, could payers actually change utilization management, either with step therapy approaches or restrictions based on the RWD they obtain from the VBC?

- In a perpetual learning environment, second- and third- generation VBC data could be managed to mitigate the patient burden related to reporting processes.
    - Could VBCs between developers and payers leverage patient-reported outcomes data?

Payer Value Assessment (PVA) Implications

While Health Technology Assessments are not a 'fourth hurdle" to market in the US, PVAs and Pharmacy & Therapeutic (P&T) committees combine to impact payer coverage decisions and patient access and pricing negotiations/decisions. For AAP-approved products where data is limited at launch, the PVA processes would benefit from additional RWD, especially where variations in response to a treatment are documented.

The data generated in VBCs can potentially reset the balance between uncertainty and access for AAP-approved medicines. The development and use of value evidence creates an opportunity to apply a real-world context to AAP-approved products. The VBC terms also ensure that patients have received the value that the VBC has measured and both parties are satisfied that payments reflect that value. VBCs can resolve uncertainty post facto with ongoing data generation.

For this case study, our challenge is to consider how VBC outcomes data might impact the PVA process. If VBCs are generating data to confirm the value, what opportunity can be developed to incorporate VBC data into future PVA reviews? Are the value measures in a VBC more relevant to the patient experience than the evidence from confirmatory trials and the early trials that currently inform the PVA review? For example, are Progression-Free Survival (PFS) or Overall Survival (OS) measures as relevant for patient Quality of Life (QoL) as discontinuation might be (i.e., discontinuation identifies patients that cannot tolerate the medicine, thus more immediately measuring patient benefit)?

Topics for breakout discussions:

- As VBCs endeavor to clarify value, there would be less need to debate the uncertainty of the 'projected value' and level of existing evidence for AAP-approved products, requiring a shift of PVA methods to focus on the outcome metrics. For example, personalized reimbursement would recognize patient heterogeneity, allowing for variation in the value assessment and in payments.
    - For Astrotuminib with VBCs using a patient discontinuation outcome metric, how might PVA processes connect to other stakeholders and their decisions?

- VBCs are structured to provide ongoing evidence, thus leading PVA processes into iterative assessment cycles as new evidence is compiled.
    - For Astrotuminib with VBCs using a patient discontinuation outcome metric, what might be the impacts on initial assessments, and then future adjustments?

- PVA departments would require procedural changes if they were to accept the ongoing generation of VBC data.
    - How might AAP-approved products shift how value is defined and measured?
    - Will PVAs be able to reconsider their own value assessment process and adapt?
    - Will PVA decision-makers have an impact on second- and third-generation VBC design?

- VBC data can benefit additional stakeholders, but the ability to navigate contract privacy concerns and the implications of more transparency with VBC data (e.g., sharing with the FDA for AAP-approved products) needs to be explored.
    - While the VBC structures have become more transparent, how would developers react to transparency re: outcomes? How might payers react?
    - How might VBC developers and payers embrace more transparency of their data?

Regulatory Totality of Evidence

CMS and other payers have proposed to limit payments, restrict patient-covered populations or delay access to AAP-approved medicines out of concern that the clinical benefit is unproven. Adding to these challenges for small population conditions, regulatory confirmatory trial data may be structured as a pragmatic trial based on a voluntary observational registry of treated patients, rather than as an RCT with a standard of care control arm. This may be necessary due to recruitment and ethical challenges once the drug was on the market for example. At the same time, there remains a need for additional evidence of value. Particularly in such cases, VBC data with their inclusion of all treated patients in the VBC population may provide important evidence, faster.

For Astrotuminib, the 5-year overall survival trial will likely require 8 or more years to recruit, complete, analyze and publish. Given the 30% expected benefit population after 24 months, the 5-year overall survival dialysis-free endpoint will require a much larger initially treated population than the prior trials to generate sufficient events.

As AAP-approved products reach the market, VBCs in and of themselves encourage appropriate patient/provider access for the population included in the VBC, because payers contract to pay for medicines when they live up to the contracted value assessment. VBCs also provide that data in an efficient, timely manner, albeit with privacy agreements in place related to contract terms and the patient data developed. Nonetheless, it is feasible to assert that timely VBC-generated data could be used to satisfy other data requirements, as part of a totality of evidence required for regulatory assessments. The FDA has not issued specific guidance regarding how it will incorporate VBC real-world clinical data into the ongoing totality of evidence for a product. Clinical data from VBCs will likely qualify for mandatory reporting to the FDA.

Can such uses of this data be explored, while upholding the utility of the VBC data generation process for its original purpose?

Topics for breakout discussions:

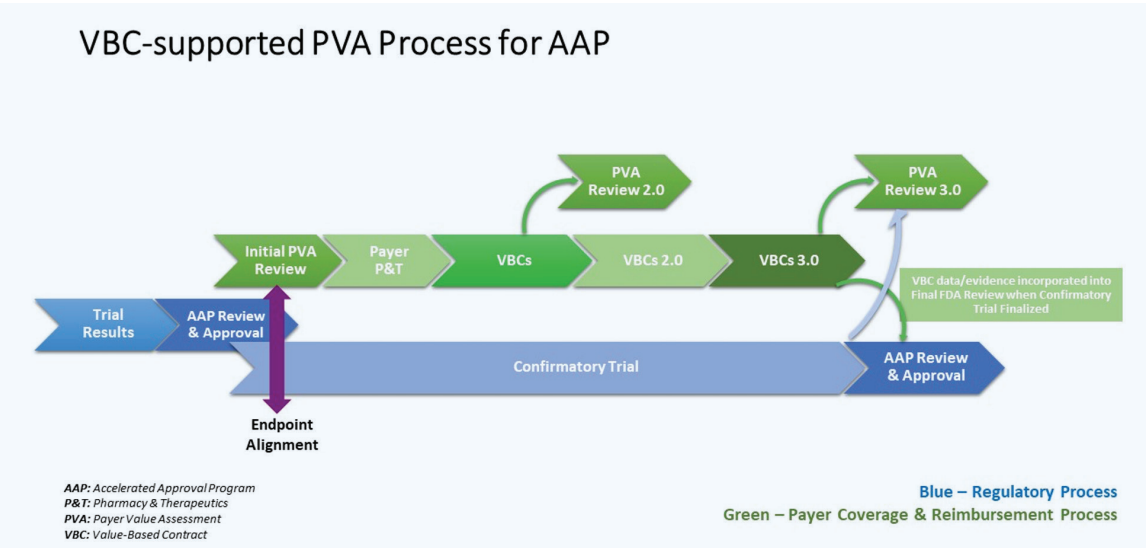
- For Astrotuminib with VBCs using a patient discontinuation outcome metric with associated claims information about the patients, what might be learned, if anything, that could contribute to "the totality of evidence"?

    - How would such structures differ between payer types (i.e., integrated delivery networks [IDNs] with internal visibility vs. smaller payers with timing delays)?

- Who might use Astrotuminib VBC discontinuation data and for what purpose? Assume that the VBC data will be available years prior to the confirmatory trial read-outs.
    - What stakeholders would have to be involved and in what capacity?
    - How can VBC-generated data satisfy their original contracted goals, while also contributing to the regulatory totality of evidence?

- VBC data can benefit additional stakeholders, but the ability to navigate contract privacy concerns and the implications of more transparency with VBC data (e.g., sharing with the FDA for AAP-approved products) needs to be explored.
    - While the VBC structures have become more transparent, how would developers react to transparency re: outcomes? How might payers react?

- VBC-generated outcomes data can be brought to regulatory evidence discussions but may require meta-analysis across VBC results.
    - What structural changes might be required to support multi-VBC, multi-institution studies?



This image depicts more integrative and collaborative data generation processes, where the data from Value-Based Contracts is systematically incorporated into the totality of evidence for AAP-approved products. The timing and number of PVA reviews for a product would change in this scenario, as would the transparency of VBC-generated data. Endpoint alignment between the PVA and Confirmatory Trial development would help to align both processes.

Appendix A: Value-based contracts review

Value-Based Contracts (VBCs) between payers and developers provide a structure where both parties agree on specific definitions of value and invest in methods to measure that value. Payments are tied to the specific health outcomes, ensuring that patient health is central to the contract terms. VBCs require tools in place to define and track health benefits (e.g., Electronic Health Records, claims data, patient-reported outcomes, etc.) that are efficient and effective so that the VBC is not cumbersome, nor a significant added expense.

Initiated in 2016, the NEWDIGS FoCUS consortium has investigated new, innovative financing and reimbursement models in the United States that will ensure patient access and establish sustainable financing solutions that work across stakeholder groups. Over the past 7 years, the FoCUS work has contributed to our understanding of how multiple stakeholders (payers, providers, patient advocacy organization, pharmaceutical developers, academics, and others) can reach new levels of collaboration and success when key dimensions of risk are addressed from multiple stakeholder perspectives.

While no one VBC can resolve all financing risks, FoCUS Design Lab workshops consolidated a list of the highest potential solutions. These precision financing solutions are utilized based upon a payer's assessment of the specific therapy and their organizational needs. Table 1 below outlines 8 high potential solutions that can improve patient access and address financial sustainability, with a focus on the specific risks that are addressed with each tool (payment timing, performance, and actuarial risk).

In addition to analyzing current individual financing tools, the FoCUS program proposed a new service solution to payers who are not able to build internal capabilities to manage durable gene and cell therapies. The Orphan Reinsurer and Benefit Manager (ORBM) combines the risk-bearing of reinsurers with the therapy contracting capabilities of pharmacy benefit managers, the provider network-building and medical management capabilities of insurers, and perhaps a specialty pharmacy distribution capability. This new service solution would be able to address performance, payment timing and actuarial risks, as well as executional risk. ORBM organizations can help facilitate access to durable, curative therapies by using precision financing solutions.

Please see the FoCUS toolkit for more information:
Toolkit Overview: Precision Financing Solutions | NEWDIGS (tuftsmedicalcenter.org)

Table 1: FoCUS Precision Financing Solutions Summary

Precision Financing Solution	Performance Risk	Partial Risk Mitigation
Milestone-based Contracts	Upfront payments, developers obligated to pay refunds if patient performance milestones/outcomes are not met. Timing: <1 year	
Multi-year Milestone-based Contracts	Upfront payments, developers obligated to pay refunds if patient performance milestones/outcomes are not met. Timing: >1 year. Longer contracts fit better when a therapy's value is demonstrated over a long time period. More complicated tracking procedures are required.	
Performance-based Annuities	Upfront payments for part of the price of therapy, with commitment to periodic payments once performance milestones/outcomes are met. Timing: >1 year.	Partially mitigates actuarial risk. Smoothes payment timing
Warranty	A developer would provide an insurance product that reimburses payers for other drug /medical costs if a product does not provide expected outcomes. Coverage would be on a named patient basis. Timing: >1 year.	
	Payment Timing	
Payment over Time/ Installment Financing	Payment for a treatment over multiple years, not in one upfront payment. Timing: requires payers to be able to sign contracts for periods >1 year.	Partially mitigates actuarial risk
	Actuarial Risk	
Subscription	Provides a fixed fee for either a target level or unlimited supply of a treatment during a period of time, limiting actuarial uncertainty for the payer.	Manages total budgetary costs
Reinsurance/Stop Loss insurance	Agreements where insurance companies have insurance to reduce the impact of unexpected high costs for a patient or group of patients. *Stop Loss insurance* is a product that provides protection against unpredictable costs for a patient above a threshold. These products are multi-year contracts, in response to durable therapies.	
Risk Pools	Where federal or state programs cover insurance products in which a premium is set and paid for coverage of a defined treatment for a group, to create cost predictability	

For this AAP case study, the FoCUS work provides a strong foundation from which VBCs can be investigated for their contribution to medicines that reach the market via AAP. VBCs in this case study focus on those between payers and developers, where some of the challenges are the same: to ensure patient access to new medicines and to provide sustainable financial solutions. In addition, the AAP Case Study will also explore how VBCs can support PVA decisions and contribute to the regulatory totality of evidence.

With these objectives in mind, we will assume that VBCs can enhance the success of AAP-approved medicines. Our September 2023 Design Lab will dig deeper to explore what parameters of a VBC would be essential to meet the needs of stakeholders involved in AAP-approved products, noting that 1) AAP-approved medicines will no longer come to market without a confirmatory trial initiated at time of approval; and 2) Payers are not willing to pay for AAP-approved medicines that come to market with a high price tag and limited evidence.

Paying for Drugs that Work: The Accelerating Clinical Evidence Model

The Secretary has selected three new models for testing by the Innovation Center the Accelerating Clinical Evidence Model. The Model would adjust Medicare Part B payment amounts for Accelerated Approval Program (AAP) drugs to give manufacturers an incentive to expedite and complete confirmatory clinical trials. Working in consultation with FDA, CMS could consider various approaches to adjust payments to the provider for AAP drugs, seeking to balance incentives for developing novel treatments with potential harms of delayed confirmatory clinical trials. Any adjustments would be structured in a manner that attempts to avoid penalizing physicians or beneficiaries for choosing (or avoiding) an accelerated approval treatment. By incentivizing timely confirmatory trial completion, CMS could enable improved access to post-market safety and efficacy data.

Beneficiary Population: Medicare fee-for-service (FFS) beneficiaries. Model Participants: Mandatory participation for applicable Medicare Part B fee-for-service providers.

Test Question: Do targeted adjustments on payments for AAP drugs accelerate confirmatory trial completion, provide timely information on the safety and effectiveness of AAP drugs on the market, facilitate earlier withdrawals of AAP drugs when appropriate, and reduce Medicare spending on drugs that do not have confirmed clinical benefit? (Secretary Xavier Becerra, 2023).

Resource:
https://asgct.org/publications/news/february-2023/hhs-secretary-announces-cgt-access-model. Accessed online May 18, 2023.

Appendix B: PVA & HTA— how do these institutions compare?

In the context of the PIVOT Design Lab, we have introduced a term unique to the value assessment environment in the United States, namely, the Payer Value Assessment (PVA). In the U.S. market, the government does not have the authority to conduct health technology assessments with the intention of determining the economic value of a new medicine, vaccine, or medical device. Where government Health Technology Assessment Agencies have been organized in the U.K., Canada, Europe, Latin America, and Asia (esp. Australia, and more recently South Korea, China, India, and Japan), the United States has been determined not to interfere with the market's ability to set the value of new medicines, vaccines, and medical devices. At the same time, U.S. payers have the sophistication to develop internal value assessments on the full range of services that they provide for patients.

These PVA processes produce information that is proprietary to the payer institution, which is both a strength and a weakness. PVA assessments allow payers to analyze new treatments with direct reference to how their patient populations would be impacted using a new health intervention. While the results of these assessments may never be shared publicly, the PVA can contribute to the internal evidence of a product's value and can be used in internal decision-making. Unlike the public HTA process, a PVA might not allow data to be shared externally, limiting its broader influence.

It is unclear how the PVA process is organized within payer institutions, but there is potential for these assessments to be long-lasting. The strength of the PVA group, where their research is conducted and with what resources they have available; these remain the decisions that vary across private payer institutions with competing internal demands. At the same time, payers are able to reassess a new medical intervention as data is generated. With a 'PVA 2.0' or 'PVA 3.0' feasible, these assessments would be more robust as more data become available and the utility of their conclusions thus more integrated into how payers allocate resources.

In our Design Lab, we are assessing how AAP-approved products' value might be better understood if data generated from Value-Based Contracts (VBCs) can be utilized more broadly. In this context, VBC data could become a strong support in the development of first and second-generation PVAs, in addition to public data such as clinical trial readouts, Regulatory label updates, data on old or new competitor treatments. With a more robust and iterative PVA process in place and VBC data incorporated into these assessments, payers and developers, providers and patients could expect to have progressively updated understandings of the new treatment's value, prior to the finalization of confirmatory trials.

U.S. Context	Health Technology Assessment (ICER)	Payer Value Assessment
Scope	Recommended to disaggregate clinical and economic assessments of value, without the mandatory inclusion of a cost effectiveness assessment	Private payer organizations have discretion re: how the PVA is used for internal decision-making, including whether or not a cost effectiveness assessment is part of the PVA, and/or what the PVA would cover (e.g., not just medicines, but treatment practices/physician services).
Objectives	To ensure scientific excellence in the application of new medical treatment interventions, including an aggregation of societal values. To set the quality of technology assessments across individual organizations.	To support the institution's decision-making, toward effective and efficient use of payer resources across all patients and patient care objectives.
Advisory Role	Advisory only	Advisory (at institution's discretion)

Resources

1. Strengthening the Accelerated Approval Program_ICER White Paper_April 2021.pdf
2. HHS Secretary Responds to the President's Executive Order on Drug Prices | CMS
3. Lowering Prescription Drug Costs for Americans, Response to President Biden's Executive Order (cms.gov)
4. A Report in Response to the Executive Order on Lowering Prescription Drug Costs for Americans Frequently Asked Questions (cms.gov)
5. Immuno-Oncology Medicines: Policy Implications and Economic Considerations (nih.gov)
6. The Cost of Transplant Immunosuppressant Therapy: Is This Sustainable? (nih.gov)