EXECUTIVE SUMMARY

The Duke-Margolis Institute for Health Policy (Duke-Margolis) and the Heart Valve Collaboratory (HVC) jointly facilitated a Roundtable Series that demonstrates the value and opportunity of multistakeholder engagement to inform post-market evidence generation strategies to support coverage, patient access, and technology uptake. In particular, this Roundtable Series facilitated discussions of the coverage and evidence needs of emerging tricuspid valve intervention (TVI) devices and procedures. Stakeholders identified evidentiary gaps and outcome measures that would likely drive post-market data collection requirements to support Medicare coverage. Stakeholders also identified opportunities to improve data collection strategies, including using innovative real-world data collection methods to address challenges with provider burden, data quality, and completion. Finally, the series underscored the need to clarify expectations from payers and other key stakeholders to drive alignment on post-market evidence generation strategies.

Patient access to novel technologies involves a series of major policy decisions, including regulatory approval, payer coverage determinations, and physician adoption. In some cases, evidentiary gaps at the time of regulatory approval may lead to delays in coverage, as well as patient and provider adoption. The Centers for Medicare & Medicaid Services (CMS) issues Medicare coverage for products and services for which sufficient evidence exists to support “reasonable and necessary” use for Medicare beneficiaries. Current CMS initiatives to improve Medicare coverage processes for novel technologies aim to minimize the time between regulatory approval and Medicare coverage, and establish a timely, transparent, and predictable process with early, multistakeholder engagement to identify post-market evidence needs to support sustained patient access and better outcomes. Recent policy developments support these efforts, such as through the proposed Transitional Coverage for Emerging Technologies (TCET) Medicare coverage pathway and proposed guidance documents: updated Coverage with Evidence Development (CED)) guidance, guidance on National Coverage Analysis Evidence Reviews, and Clinical Endpoints Guidance: Knee Osteoarthritis.

The Roundtable series illustrates how early, multistakeholder engagement can help inform CMS and private-sector action to identify and advance the development for Medicare coverage and effective technology uptake in areas of innovation that may benefit from shared actions to address common challenges, including not only greater clarity about evidence needs and how to meet them efficiently, and steps to improve the infrastructure for developing such evidence in a way that makes post-market evidence development less costly, faster, and more relevant to stakeholder needs. This report describes the processes and outputs of early engagement to support coverage for TVI procedures, which can be applied to other novel technologies that may require post-market evidence generation to support Medicare coverage and sustained patient access.
INTRODUCTION

Tricuspid regurgitation (TR) is a valvular disorder that occurs when the tricuspid valve fails to completely close during right ventricular contraction, leading to a backward flow of blood from the right ventricle into the right atrium through the tricuspid valve. An estimated 2.5 million people in the U.S. have at least a moderate degree of TR, with rates increasing with age. Tricuspid regurgitation can cause a number of symptoms that interfere with patient quality of life (QoL), including fatigue, heart rhythm abnormalities, shortness of breath, and edema. When left untreated, TR can cause weakening of the right ventricle and lead to right-sided heart failure. Diuretics and other medical therapies can help manage TR symptoms. Due to operative risks, surgery is only recommended in cases of severe TR in which patients are undergoing a left-sided valve surgery. A need exists for a treatment alternative for patients with severe TR with symptoms that persist despite medical therapy, in a manner that presents fewer risks than open heart surgery. A number of transcatheter tricuspid valve intervention (TVI) devices have been evaluated in clinical trials, potentially reaching U.S. Food and Drug Administration (FDA) regulatory authorization between 2024-2025.

While FDA authorization for these emerging TVI devices is pending, discussions continue around the need for more predictable and timely coverage for innovative technologies and the importance of post-market evidence generation in certain cases to inform long-term coverage. In response to this technological and policy landscape, between September 2021 and August 2022, Duke-Margolis, in collaboration with the HVC, facilitated a series of four Coverage and Evidence Roundtables to discuss post-market evidentiary needs for novel TVI technologies, specifically evidence strategies to support access through long-term Medicare coverage. This report reflects the discussions and findings from the Roundtables, which covered three key topics: identifying post-market evidence generation needs based
on areas of clinical uncertainty, identifying promising post-market evidence generation strategies, and identifying implementation considerations for efficient real-world data (RWD) collection.

BACKGROUND

Burden of Disease and Treatment Options for Tricuspid Regurgitation

Tricuspid regurgitation has two main etiologies: primary and secondary. Primary TR etiology occurs in 10 percent of diagnosed cases and is due to valve defects caused by congenital factors, infection, or injury to the valve, most frequently from pacemaker leads. Secondary TR, the most common, often arises as a result of existing disease, most commonly left-sided heart failure, pulmonary hypertension, mitral valve stenosis or regurgitation, ventricular dysfunction, or atrial enlargement. In the U.S., the prevalence of moderate to severe TR is an estimated 2.5 million.

Patients with TR become symptomatic in late stages of the disease and often present with dyspnea, fatigue, edema, and elevated venous pressure. Clinical practice guidelines recommend diuretics and other medical therapies to manage symptoms. Surgery is most commonly performed as a secondary procedure for patients with severe TR undergoing concomitant left-sided valve surgery or coronary artery bypass graft. Guidelines recommend that surgery for isolated TR may be considered, but the effectiveness of the procedure may not be well-established.

Emerging Tricuspid Valve Interventions

Given the high prevalence and poor prognosis of the condition, a need exists for earlier diagnosis and treatment for TR. Experience in transcatheter approaches for other valvular repair and replacement devices and improvements in imaging techniques have generated an interest in the development of similar treatment approaches to treat TR, which aim to replicate surgical intervention techniques. They present a new, minimally invasive treatment option for patients that are at high risk for surgical interventions or those that would otherwise not be treated until later in their disease stage with varied forms of medical treatment to ease their symptoms. Currently, there are three TVI devices under consideration for patient access; two transcatheter repair devices and one transcatheter replacement device. Two pivotal studies have reached primary endpoint completion at the time of publication this report.

Transcatheter valve procedures are complex, require precise imaging, and rely on surrogate measures to define procedure success. Given the relatively recent applications of these approaches on the tricuspid valve, factors that drive procedural success and clinical improvement have not yet been defined. Many clinical uncertainties exist regarding accurate diagnosis, patient selection, imaging techniques, procedural outcomes, device selection, and ideal clinical outcomes. These uncertainties are inherent in the development of new treatments and drive expanding clinical evidence and product development. Continued evidence generation within and beyond clinical trial settings will address many of these uncertainties and inform patient selection and clinical decision-making.
Pathway to Medicare Coverage

Patient access to these new TVI procedures strongly depends on Medicare coverage, as the average age of patients studied in the ongoing trials range between 77 and 78.7. CMS determines whether or not a novel technology is covered by Medicare based on an assessment on whether it is “reasonable and necessary,” which is defined as (1) safe and effective, (2) not experimental or investigational, and (3) appropriate for use in Medicare beneficiaries. A novel technology is considered “appropriate” if it is furnished according to the medical practice standards for the diagnosis or treatment of a condition, in a setting of care that can meet patient needs by a qualified provider, whether a product meets medical needs of the patient, and whether the product is as least as beneficial as existing alternatives. Occasionally, when a novel technology is being evaluated for national coverage and lacks sufficient evidence to substantiate the “reasonable and necessary,” determination, CMS has used the CED program to provide product access for Medicare beneficiaries under conditions of additional evidence collection.

Multiple pathways to Medicare coverage exist, including national coverage determinations, local coverage determinations, and existing payment systems. A coverage framework for transcatheter valve procedures has been in place since 2012 with the Medicare National Coverage Decision (NCD) for transcatheter aortic valve replacement (TAVR). A similar coverage policy was established for transcatheter edge-to-edge repair (TEER) procedures to treat mitral regurgitation in 2014. Given the similarities in technology, it is likely that TVI procedures may have a similar coverage framework as the other transcatheter valve procedures. In this case, following a favorable FDA determination, CMS will initiate a national coverage analysis (NCA), which could define coverage for the product class. As part of the NCA, CMS may evaluate whether TVI procedures can improve health outcomes for Medicare beneficiaries, if health improvements are long-term, and if there is available evidence to identify characteristics of patients, providers, and sites that can reliably predict overall benefit or harm from TVI procedures. In order to evaluate these evidentiary questions, CMS may rely on pivotal clinical trial data, specialty society consensus statements, as well as evidence from published peer-reviewed literature. Given the novelty of the emerging TR treatments, even with well-designed premarket randomized trials sufficient to determine safety and effectiveness, additional evidence questions may remain that also relate to benefits and risks for particular groups of Medicare beneficiaries. For example, there may be uncertainty around the provider, patient, and site criteria that increase the likelihood of treatment success, as well as the clinical endpoints that would most impact long-term health outcomes for Medicare beneficiaries. Therefore, it is plausible that CMS’s assessment for “reasonable and necessary” Medicare coverage, may result in a CED framework, similar to TAVR and TEER. The areas of clinical uncertainty for TVI procedures include diagnosis of TR, patient selection, imaging technique, procedural outcomes, and ideal clinical outcomes, which will impact Medicare’s evidence assessment. These uncertainties may inform the outcomes of interest that CMS includes in a potential CED policy.

For both TAVR and TEER, the STS/ACC Transcatheter Valve Therapy (TVT) Registry was used to satisfy CED requirements. The TVT Registry retains a modular design that facilitates data collection modules for different disease areas. Currently, there are modules for aortic, mitral, and tricuspid valve procedures. As a CMS-approved CED study for both TAVR and TEER, the TVT registry has captured data on all commercial valve procedures in the U.S. It has been the data infrastructure for numerous FDA
required post approval studies (PAS) and has informed product label expansions and clinical practice guidelines. Importantly, data from the registry was used to inform expanded facility and operator coverage criteria for both TAVR and TEER coverage reconsiderations.19, 20

Opportunities to Improve the Coverage Process
The Medicare coverage process includes determining safeguards that will increase the likelihood of improved health outcomes from using a novel technology. This determination is a balance between patient access to technologies and appropriateness of care. Because the coverage process begins after FDA approval, it can impact overall time to patient access. The policy goal of the Medicare coverage process is to demonstrate the value of novel technologies. There are opportunities for Medicare to reach this policy goal more efficiently by:

- Minimizing time between FDA approval and coverage determinations;
- Establishing a transparent, timely, and predictable process to establish coverage; and
- Clarifying evidence goals and effective ways to develop this evidence through early stakeholder engagement.

Minimizing time between FDA approval and Medicare coverage allows patients to access technologies faster and allows the health care system to see the benefits from the technology faster. A transparent, timely, and predictable process to coverage can establish certainty for both manufacturers and CMS on the time and resources required to establish coverage and develop a post-market data collection infrastructure when needed. Early engagement between stakeholders—such as CMS, other payers, providers, and patients—can help manufacturers identify evidence gaps that are meaningful to stakeholders and incorporate them into their clinical study plans. Early engagement also can set expectations for evidence generation milestones, which can provide further clarity for manufacturers as they develop a study plan. For example, if CMS identifies demonstrating clinical benefit as an evidence threshold for novel TVI devices (for which the endpoints for effectiveness are currently based on surrogate measures without validated clinical benefits), manufacturers could design a fit-for-purpose (FFP) study. Finally, early engagement facilitates earlier development of a data collection infrastructure, if needed, which can benefit from collaboration across manufacturers and the clinical community, as well as FDA, CMS and other payers.

Some of these opportunities to improve the coverage process are captured in the recent proposal for the Transitional Coverage for Emerging Technologies (TCET) pathway, an expedited coverage pathway for certain devices with breakthrough designation.22 The proposed pathway is designed to reduce uncertainty by evaluating technologies early, encourage evidence development to address evidentiary gaps, and facilitate early, predictable, and safe beneficiary access to new technologies through a defined sequence of activities. Per the proposal published in the Federal Register on June 27, 2023, CMS will engage with manufacturers that opt-in to the TCET pathway one year ahead of anticipated FDA authorization, during which time CMS will:
• conduct an evidence preview to review the strengths and weaknesses of the technology and identify any evidentiary gaps;
• assign a preliminary benefit category determination; and
• facilitate engagement between FDA, manufacturers, and the Agency for Healthcare Research and Quality (AHRQ).

The proposed TCET pathway is designed to expedite the NCD process such that coverage could be established within six months of FDA authorization at the earliest. During the TCET coverage period, manufacturers would generate any additional evidence to support evidence gaps identified by CMS in support of a coverage reconsideration.

Simultaneously with TCET, CMS released three additional proposed guidance documents designed to modernize Medicare coverage pathways—updated guidance for Coverage with Evidence Development (CED), guidance on CMS National Coverage Analysis Evidence Reviews, and Clinical Endpoints Guidance: Knee Osteoarthritis.

• The CED guidance document is an updated list of criteria for CED studies that allows for real-world evidence (RWE) generation and data gathering in patients’ usual sites of care.23
• The NCA Evidence Review guidance document details how CMS evaluates clinical evidence to determine the strengths and weaknesses of a product to support coverage decisions and reconsiderations.24
• The Knee Osteoarthrosis Clinical Endpoint Guidance document illustrates the methodology that CMS uses to identify clinically meaningful endpoints.25 In turn, these endpoints could be suitable FFP CED studies to support coverage.

While these guidance documents complement the TCET proposal, they are not mutually exclusive, suggesting that process for identifying clinically meaningful outcomes through stakeholder engagement could be applied to other coverage pathways that employ CED. When viewed comprehensively, they show a path forward for modernizing Medicare coverage processes by providing insight into the types of evidence and outcomes that CMS wants to review for coverage determinations, as well as study design and considerations for making FFP studies more rigorous.

Much of the proposal for TCET is focused on the operational process by which CMS will engage with manufacturers to align on evidence needs for a coordinated evidence generation strategy to ensure patient access to a technology within a pre-specified timeframe.26 However, opportunity exists for broader, early stakeholder engagement to inform the development of clinically meaningful endpoints for truly novel technologies for which there is little existing literature or evidence on benefits and risks, and for identifying key actions extending beyond a particular product for improving the efficiency, time, and quality of needed post-market evidence development. Early, multistakeholder engagement can further inform the types of data sources that may best support these endpoints, as well as how to efficiently generate such evidence in a way that reduces burden to manufacturers, clinicians, and patients. In particular, there may be a role for broader stakeholder engagement within the processes that CMS has outlined in the guidance document for Clinically Meaningful Endpoints—in terms of the outcomes of interest, appropriate data sources, and data collection methodologies—which can then inform the development of post-market studies to collect data on those endpoints. This could support further actions to enhance relevant evidence development, such as by CMS as part of their quality
improvement and data interoperability initiatives, and by stakeholders through identifying key opportunities for improving existing registries to address emerging evidence needs. Identifying such multistakeholder opportunities to improve post-market evidence generation could provide a path for better support, resources, and collaboration to achieve this goal.

Given the technological landscape of emerging TVI procedures nearing FDA determinations, and the evolving policy landscape of a potential new Medicare coverage pathway, Duke-Margolis convened the Coverage and Evidence Roundtables to illustrate the value of early multistakeholder engagement that could be part of a coverage assessment process for TVI procedures and other novel technologies. This report provides an analysis of the Roundtable discussions held between September 2021 and August 2022\(^1\) on the outstanding evidence needs for emerging TVI devices based on ongoing, pivotal clinical studies and the post-market data collection strategies that can address them in order to ensure long-term coverage, and thus, patient access.

These discussions were designed to illustrate what early stakeholder engagement could look like before FDA authorization to inform clinical endpoints most relevant to support coverage. This engagement strategy could be employed for technologies that are expected to have evidentiary gaps at the time of FDA authorization that could result in a coverage assessment. Some of these technologies could be eligible for TCET, Parallel Review, or rely on CED as a condition for coverage.

For instance, early engagement could help clarify outcomes of interest and data collection strategies would allow for earlier development of an evidence generation plan, which would allow for a more seamless transition from pivotal trial phases. For products under the TCET pathway specifically, early engagement, perhaps even prior to TCET application (currently proposed at 1 year prior to expected FDA authorization) could lead to earlier development of the Evidence Development Plan, which, once finalized, triggers the formal coverage assessment.

Early engagement across stakeholders that impact the development and growth of a therapeutic space (e.g., manufacturers, clinicians, trialists, academic researchers, FDA, CMS, payers, etc.) could allow CMS to reflect evidence needs by stakeholder in Clinical Endpoints Guidance documents that, in turn, inform innovators and product developers on key evidence needs that can support both coverage and market adoption.

Finally, given the updated CED guidance document and forthcoming FFP studies guidance document, there are further opportunities to use novel RWD collection methods for CED studies. Early engagement across stakeholders that drive post-market data collection efforts could help CMS inform guidance on the types of infrastructures and data collection strategies that could answer different types of evidence

\(^{1}\) The Coverage and Evidence Roundtable series concluded before the primary endpoint completion of the TRILUMINATE and TRISCEND II pivotal studies. The analysis presented thus does not consider the impact of pivotal study results. The Pivotal Trial Results section of this report includes a brief analysis of the potential impact of the results of the two studies.
Earlier engagement and guidance on this issue would help manufacturers and others supporting post-market data collection efficiently develop study designs, thus streamlining the transition between the pivotal trial phase and commercial phase for novel technologies. Table 1 illustrates a basic framework for considering the type of early engagement that may be most appropriate given evidentiary questions in a therapeutic area.

**Table 1: Framework for Type of Early Engagement**

<table>
<thead>
<tr>
<th>Types of Evidentiary Questions</th>
<th>Relevant Stakeholders</th>
<th>How Stakeholders can help Streamline Coverage Processes</th>
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| Disease pathway is not fully understood; clinical guidelines are unclear for a product or procedure. | - CMS  
- Manufacturers  
- Providers  
- Researchers  
- Specialty Societies | Stakeholders can identify potential evidentiary gaps and endpoints to fill gaps in the absence of peer-reviewed literature. Could also be helpful to inform development of Clinical CMS Endpoint Guidance Documents. |
| Are improvements in quality of life associated with direct clinical benefits? | - CMS  
- FDA  
- Manufacturers  
- Specialty Societies  
- Researchers  
- RWD experts | Stakeholders can inform data collection efforts that can support validation of relevant endpoints. |
| Is there sufficient evidence to inform provider’s clinical decision-making? | - CMS  
- Manufacturers  
- Providers  
- Specialty Societies | Stakeholders can inform clinical evidence development pre and post-FDA authorization by identifying the level of evidence that would encourage technology uptake by providers. |
| Evidentiary questions span multiple upcoming products developed by multiple manufacturers. | - CMS  
- FDA  
- Manufacturers  
- RWD experts | Stakeholders can inform evidence collection in post-market settings for the procedure class. |
| Safety in Medicare populations. | - CMS  
- FDA  
- Manufacturers  
- RWD experts | These cases may not require complex post-market studies and may be appropriately answered through claims or EHR data. |

The process outlined in this report of identifying appropriate outcomes of interest, discussing potential data sources and RWD collection methods for building evidence, and identifying when and how to use
existing or develop new data infrastructures, can help plan for post-market data collection for different products. This planning will in turn make the CMS coverage processes for novel technologies more transparent and predictable, allowing for sponsors to more quickly develop post-market studies when needed and facilitate timelier patient access.

**Coverage and Evidence Roundtables on Emerging TVI Technologies**

Between September 2021 and August 2022, Duke-Margolis, in collaboration with the HVC, facilitated a series of four Coverage and Evidence Roundtables to discuss post-market evidentiary needs for novel TVI procedures, specifically evidence strategies to support access through long-term Medicare coverage. This series took place with multiple manufacturers involved in the tricuspid valve intervention space, multiple pivotal trials ongoing, and before the TRILUMINATE and TRISCEND II pivotal trial results were published. Duke-Margolis invited a broad group of stakeholders to participate in roundtable discussions, which are summarized below, to ensure a variety of perspectives. Attendees included clinicians, researchers, FDA, CMS, device manufacturers, and digital health technology developers with an expertise in RWE.

**POST-MARKET DATA COLLECTION CONSIDERATIONS**

*Pivotal Trial Designs*

Table 2 includes publicly available information about the pivotal studies that were evaluated in the Roundtables prior to when results were published. These include: procedure type, study design, inclusion and exclusion criteria, and the primary and secondary safety and effectiveness endpoints. Many of the safety endpoints and measures of effectiveness are similar across the clinical studies. Primary measures across all studies include heart failure hospitalization, all-cause mortality, and quality of life. Secondary measures across all studies include TR grade severity reduction, all-cause mortality, and quality of life.

During the Roundtables, several key issues were raised as significant evidence gaps that would likely impact post-market evidence generation needs. First, key effectiveness endpoints for all trials, such as TR grade reduction and right ventricular end diastolic volume (RVEDV), are echocardiographic measures that may be correlated to clinical outcomes. However, there are no standard imaging techniques or guidance on how to capture such echocardiographic measures. Further, different echocardiographic core laboratories may interpret such measures differently, which may in turn impact assessments of effectiveness. A need exists for standardized techniques to capture and interpret echocardiographic measures. Further, there is a need for more evidence to establish whether improvements in echocardiographic measures are indeed indicative of a meaningful clinical benefit.

Second, all three pivotal trials include patient quality of life (QoL) through the Kansas City Cardiomyopathy Questionnaire (KCCQ) as a part of the primary outcome. The KCCQ is a patient reported outcome (PRO) tool that captures patients’ perceptions of the frequency and severity of their symptoms, how these symptoms have impacted their activities, and how their symptoms and activities
Table 2: Pivotal Trial Designs for Tricuspid Valve Intervention Devices

<table>
<thead>
<tr>
<th>Pivotal Trial</th>
<th>Study Design</th>
<th>Key Inclusion Criteria</th>
<th>Primary Endpoints</th>
<th>Secondary Endpoints</th>
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<tr>
<td>TRILUMINATE Pivotal Trial (Estimated Enrollment = 1500) Transcatheter Valve Repair System Clinical Trial ID: NCT0390414728</td>
<td>• Randomized; Parallel Assignment • Active comparator: randomized cohort of device group vs. medical therapy control group • Experimental single arm: Subjects in which it is believed TR will not otherwise be reduced to moderate or less severity receive device</td>
<td>• Symptomatic, severe or greater TR despite Optimal Medical Therapy (OMT) • Intermediate or greater risk of mortality with tricuspid valve surgery • NYHA Class II-IVa</td>
<td>Hierarchical composite of number of participants with: • All-cause mortality or number of participants with tricuspid valve surgery • Rate of heart failure hospitalizations • Assessment of QOL improvement using KCCQ (1 year)</td>
<td>• Change in TR grade from severe to moderate or less (30 days) • Freedom from Major Adverse Events (MAEs) after procedure attempt (30 days) • Change in KCCQ Score (1 year) • Change in 6 Minute Walk Test (1 year)</td>
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<tr>
<td>TRISCEND II Pivotal Trial (Estimated Enrollment = 1070) Transcatheter Valve Replacement System Clinical Trial ID: NCT0448206212, 29</td>
<td>• Randomized; Parallel Assignment • Experimental: Device System + OMT • Active Comparator: OMT • Experimental: Single-Arm Registry of Device System + OMT in patients not eligible for randomization</td>
<td>• Symptomatic TR despite medical therapy • TR graded severe or greater • Heart team determines appropriate for procedure</td>
<td>TR Grade reduction and composite endpoint of KCCQ, NYHA, 6 min walk test (6 months – effectiveness endpoints) • Rate of MAEs (30 days – safety endpoint) • Composite endpoint that includes All-cause mortality; RVAD implantation or heart transplant; Tricuspid valve intervention; Heart failure hospitalizations; KCCQ; NYHA; 6 min walk test (1 year)</td>
<td>Composite endpoint that includes: • Reduction in TR grade • Change in QOL from baseline • Death and heart failure hospitalization • All-cause hospitalization • All-cause mortality • Change in RVEDV index (1 year)</td>
</tr>
<tr>
<td>CLASP II TR Pivotal Trial (Estimated Enrollment = 870) Transcatheter Valve Repair System Clinical Trial ID: NCT0409714530</td>
<td>• Randomized; Parallel Assignment • Experimental: Device System + OMT • Active Comparator: OMT • Experimental: Single-Arm Registry of Device system with OMT in patients not eligible for randomization</td>
<td>• Symptoms or signs of TR, or prior heart failure hospitalization due to TR despite medical therapy • Severe or greater TR • Intermediate or greater risk of mortality with tricuspid valve surgery • NYHA Class II-IVa or heart failure hospitalization in prior year</td>
<td>Composite endpoint that includes: • All-cause mortality • RVAD implantation or heart transplant • Tricuspid valve intervention • Heart failure hospitalizations • Quality of Life (QoL) improvement measured by KCCQ (2 years)</td>
<td>• MAEs (30 days) • 1 grade reduction in TR severity • Change in KCCQ score • Death and heart failure hospitalizations • All-cause hospitalization • RVEDV change (all 1 year) • All-cause mortality (1 &amp; 2 years) • Reduction in TR grade (Intraprocedural, post-implantation)</td>
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are impacting their QoL. The KCCQ has been a standard PRO tool for patients with left-sided heart failure. However, it is not yet validated for right-sided heart failure, which is a characteristic of patients with TR that are evaluated in these studies. Measures that are validated or qualified by the FDA are seen as reliable for interpreting efficacy and for standardized interpretation of study results. Further evidence to establish how changes in echocardiographic measures, such as TR grade, translate to
clinical benefit and efforts to validate the KCCQ for right-sided heart failure will be important for showing how TVI procedures can provide meaningful benefit to patients.

Given the novelty of the procedures, stakeholders discussed how the growing body of evidence would impact the evidence gaps and change how effectiveness can be measured. Stakeholders identified multiple considerations—technology, patient, and operator—that could impact the types of RWD to collect as the technology becomes more established.

Technology Considerations
As seen in Table 1, there are two different types of TVI procedures evaluated in pivotal trials: tricuspid valve repair and tricuspid valve replacement. The tricuspid valve repair devices are designed to coapt or approximate the tricuspid valve leaflets to reduce the orifice area of the tricuspid valve in order to minimize the regurgitant blood flow. The tricuspid replacement device implants a valve apparatus made from bovine tissue. Although the intent of the intervention is the same (to reduce TR grade), the mechanism of action is different, and thus there will be some key differences in how to evaluate the safety and effectiveness of the treatment, both in the short-term and long-term. As a result, there may be evidence questions on the appropriateness of treatment type that need to be addressed either through the clinical studies or RWE. For example, a tricuspid valve replacement may have interactions with implanted conduction systems, which can exacerbate existing atrial fibrillation and right ventricular dysfunction, which may in turn result in progressive TR.

Another example of technological factors to consider is device durability. Device durability can impact durability of the treatment and treatment effects. Long term data on the device durability can inform appropriateness of the treatment type for different patient characteristics and preferences. The durability of replacement valves, such as replacement aortic valves, has been evaluated at length in the TVT registry as it can impact the need for additional interventions to address adverse events, like paravalvular leaks. Device type also can impact the need for adjunctive medical therapy. Patients that undergo tricuspid valve replacements may require the use of antithrombotic therapy to mitigate blood clotting risks, which may have its own set of adverse outcomes. As evidence accumulates, medical understanding of how repair and replacement devices will impact different patients and how reducing TR grade affects patient health outcomes also will lead to updates on adjunctive medical therapy guidance for TVI procedures. Multistakeholder collaboration to share long-term data on patient outcomes can help track long-term patient outcomes longitudinally, even if patients change providers, sites, or payers.

Patient Considerations
Stakeholders in the Roundtable highlighted impact of etiology on outcomes as a significant area of clinical uncertainty. Etiology impacts patient prognosis with intervention, as well as their symptoms and overall QoL. The evolving understanding of how different etiologies affect patient symptoms, quality of life, and functional status will impact the outcomes of interest for different patient populations over time. With the accumulation of RWE, providers will be able to consider how different outcome measures might be better suited for different types of patients, especially regarding safety and reduction of patient symptoms based on etiology. Similarly, RWE on outcomes from TVI procedures
performed in patients who may have comorbidities or competing disease will be important for determining patient characteristics that can predict treatment success. Data collection on patient subgroups can impact future clinical guidelines for which patients should receive TVI procedures as well as the most appropriate device type.

Operator Considerations
Finally, with new interventions there will be a learning curve as providers determine how to identify patients, perform the procedures, and integrate them into their practice. Studies from the TVT registry on the learning curves for both TAVR and TEER suggest that as providers gain more experience with the procedure, there are marked improvements in procedure time and outcomes, particularly rehospitalizations, durability, and 30-day mortality rates.\textsuperscript{38, 39} A similar learning curve for TVI procedures will like occur as operators and sites gain experience with the devices.

Operator experience also may address some of the challenges with imaging techniques that are used to both diagnose and inform procedure success. As described earlier, imaging techniques are critical for many of the effectiveness measures, such as TR grade change and RVEDV. Fundamentally, imaging techniques are challenging because they involve viewing three valve leaflets in a 2-dimensional plane.\textsuperscript{40} Although transthoracic echocardiographic (TTE) imaging techniques are commonly used for diagnosing TR, transesophageal echocardiography can be used when TTE images are unclear.\textsuperscript{41} Additional methods, such as Doppler imaging or cardiac magnetic resonance (CMR) imaging, may be necessary to quantify TR severity and RV function.\textsuperscript{42, 43} These challenges with imaging, diagnosis of TR, and measuring its severity makes establishing baselines for peri- and post-procedure endpoints difficult, as well as determining which patients may most benefit from TVI procedures. \textit{As imaging techniques improve with time and diagnosis becomes less challenging, imaging may play a larger role in the outcomes of interest or better inform ideal timing for TVI procedures.}

Infrastructures to Support Data Collection
The evidence gaps and outcomes of interest described were identified as fundamental for providers to understand the clinical impact of these emerging therapies. While ongoing trials have captured several clinical measures that can support device approval, additional RWD collection likely will be necessary to address these evidence gaps for providers, researchers, payers, patients, and other stakeholders who wish to understand more about the impact of these new treatment options. Improvements in RWD collection also will support long-term surveillance efforts for FDA and Medicare requirements. Post-market evidence generation requirements, as well as key outcomes of interest identified by stakeholders, will inform the type of data collection infrastructure that is used to address them.

Given the inherent similarities between TVI procedures and existing valvular interventions, it is likely that, at the onset, the same data collection infrastructure may likely be leveraged to address post-market data collection requirements. For both TAVR and TEER, the TVT registry was used to satisfy FDA PAS requirements. The TVT registry is also the only CED study CMS approved for both TAVR and TEER. Thus, it is likely that TVT registry will play a large role in data collection for TVIs, particularly as the registry already has a module for tricuspid valve treatment.\textsuperscript{44} However, CMS has evaluated a broader set
of sources to support Medicare coverage for both procedures, including U.S.-based and international registries (as analyzed in peer-reviewed literature) and Medicare claims data. Learnings from the impact of data collection efforts for both TAVR and TEER can inform more efficient data collection approaches for TVI devices.

The TVT registry has been a cornerstone in the data infrastructure for all valve interventions. The vast experience with the registry points to areas where additional forms of data collection can contribute to a more comprehensive assessment of patient health. For example, QoL life data is particularly relevant to TVI procedures as they are the primary measures of effectiveness in pivotal trials. The data completeness rates for QoL data in the TVT registry are low, dropping to nearly 50 percent completion one year following an intervention. This completion rate is partially because QoL data, like the KCCQ, are not regularly collected in routine care and may create an extra demand on provider time. Opportunity exists to evaluate additional innovative data collection methods that can capture QoL data in a way that does not add to provider burden.

Another source of data that have been used to support Medicare coverage is Medicare claims data. Claims data allows payers to evaluate how a provider classified a particular visit, and the tests, treatments, or interventions that the patient received. This type of data can show patient interactions with health systems over time, and can be helpful for determining how many patients had adverse events after an intervention, or for determining how many are classified under a particular diagnosis-related group. Claims data represent units of service that are the basis for payment to providers. Consequently, substantial data from a patient visit is not captured in a medical claim as they are not separately paid. For example, PROs are not captured in claims data. Much of these data is still captured in electronic health records (EHRs), which are a very useful data source, though only accessible to providers, health systems, and patients. EHRs include notes about patient clinical visits, which offer deeper insight into patient symptoms, different treatment plans discussed by patient and provider, and information about comorbidities or other aspects of patient quality of life. Table 3 summarizes how different data sources can address different evidence questions, as well as considerations for collecting endpoints of interest.

Table 3: Key Outcomes of Interest that May Impact Post-Market Evidence Generation Needs for Tricuspid Valve Intervention Procedures

<table>
<thead>
<tr>
<th>Types of Endpoints</th>
<th>Considerations for Collecting Endpoints</th>
<th>Examples of Data Sources</th>
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<tr>
<td>Echocardiographic (TR grade reduction, right ventricular end diastolic volume)</td>
<td>This data can inform the development of standardized techniques to capture and interpret echocardiographic measures</td>
<td>• EHR data</td>
</tr>
<tr>
<td></td>
<td>There is a need for more evidence to establish whether improvements in echocardiographic measures are associated with a direct clinical benefit.</td>
<td>• TVT Registry\textsuperscript{21}</td>
</tr>
<tr>
<td></td>
<td>Operator experience with imaging techniques will likely improve over time</td>
<td></td>
</tr>
</tbody>
</table>
**Device Durability**
This data can inform appropriateness of the treatment type for different patient characteristics and preferences
Durability claims require long-term longitudinal data collection

<table>
<thead>
<tr>
<th>CMS Claims</th>
<th>TVT Registry</th>
</tr>
</thead>
</table>

**Quality of Life and Functional Capacity**
There is a need to validate the use of KCCQ in patients with right-sided heart failure
This type of data has low rates of completion in the TVT registry

<table>
<thead>
<tr>
<th>Direct from patient generated data</th>
<th>TVT Registry</th>
</tr>
</thead>
</table>

**Safety and efficacy in subgroups**
*Effect of comorbidities or competing disease, etiology, RV dysfunction*
This data will be important for determining patient characteristics that can predict treatment success and health outcomes
There is a need to understand how repair or replacement devices may interact with other implanted cardiovascular and valvular devices

<table>
<thead>
<tr>
<th>Point of Care Trials</th>
<th>TVT Registry</th>
</tr>
</thead>
</table>

**Safety in Medicare beneficiaries**
*Mortality, heart failure hospitalizations*
This data may be most easily accessible through administrative claims or electronic health record data

<table>
<thead>
<tr>
<th>CMS Claims</th>
<th>EHR data</th>
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Novel Data Collection Approaches
A core objective of the Roundtables was to evaluate more efficient forms of data collection. Stakeholders evaluated opportunities to improve existing data collection approaches as well as consider novel approaches that could address current challenges and limitations from existing infrastructures. As detailed below, these opportunities include mechanisms to improve the depth of data already being collected and new data sources that can contribute to a more complete assessment of patient health. Different evidence questions may be efficiently addressed via different data collection techniques. The options below represent different approaches that can be used in combination to address evidence gaps. A multi-modal or multi-pronged data collection approach, consisting of one or more of the methods described below, can build upon existing infrastructures, reduce provider burden, encourage broader participation, support FFP study designs, and encourage the development of standard, validated approaches for data collection to meet CMS requirements for Medicare coverage. Given the novelty of the treatments and the therapeutic space, the TVT registry will continue to have a prominent role to reduce subjective elements in treatment measures, endpoints, or variation in their interpretation.

**Data Automation**
Data completeness associated with provider burden of data collection was one of the key issues raised with the TVT registry. One solution to address this issue is automated data entry, whereby specialized software could automate the process of uploading patient records from EHRs into registries. Data automation would require registries to work with third-party software vendors to create programs capable of recognizing keywords and pulling the necessary data into a registry case report form. It likely would require integration with natural language processing to help bring unstructured data together into a usable format. Data automation also could facilitate point-of-care (POC) trials, a type of pragmatic
trial where the trial infrastructure is integrated with EHR systems for enrollment, randomization, and data collection. The intent of POC trials is to reach patients where they receive routine care, providing a seamless patient experience between research and care. A POC trial is characterized by fully integrated care and research workflows focused on streamlined data collection, which can dramatically reduce provider burden to meet data collection requirements.46 These types of trials can be particularly useful to evaluate outcomes and risks for specific patient sub-populations, such as those with right ventricular dysfunction and torrential TR.

Data Linkages
Linking data involves bringing together data from different sources to create a more complete view of patient health. This data linkage helps to mitigate some of the time and financial challenges of collecting primary data. Data linking often uses either rules-based or probabilistic matching methods to link patients across data sources and create longitudinal data sets.47 To protect patient privacy, tokenization can be employed when linking data sources. Tokenization is a process of de-identifying personal patient data and giving individual patients encrypted “tokens” that can match patient data across numerous sources. Tokenization is one method to view patient data without using unique patient identifiers.48 This allows researchers to draw conclusions through individual-level data without breaching patient privacy laws.

Linking different data sources together may increase data completeness to create a more comprehensive picture of patient health, especially if paired with tokenization methods to get around unique patient identifiers to draw conclusions from patient-level data. Potential data sources that could be helpful for understanding how TVI devices perform in real-world settings may include registries, the National Death Index, EHRs, and claims data. Although linking patient-level data would help provide a more complete picture of patient health without overburdening providers, current interoperability issues often prevent linkage across different systems set up by different software companies. Differences in data quality across systems and locations may lead to issues with data interpretation. Although the share of care sites that are integrating interoperability standards is increasing (with 6 in 10 hospitals engaging in key aspects of electronically sharing health information in 2021), this percentage varies depending on location and size.49

Differential Data Collection
As detailed above, under CED framework, any TVI procedure will need to be captured in a clinical study approved by CMS for Medicare coverage. The TVT registry has been the CED study for TAVR and TEER, and thus all hospitals offering TAVR and TEER therapy to Medicare patients are enrolled in this registry and comply with the data collection requirements. As this has proven to be cumbersome for many sites, efforts are ongoing to reduce the number of data fields in the TVT registry case report forms.44 One potential solution to address data quality and completeness for TVI procedures is to apply differential data collection to a network of sites based on their clinical and data reporting capabilities to ensure that critical evidence questions can be addressed. Early stakeholder engagement could inform the development of a registry that involves identifying sites that can collect in-depth data. This effort can be accompanied by a modest, less burdensome requirement that is FFP with a core set of data elements that could be collected by a broader range of providers to address CED questions with straightforward
data needs. Provided the data collection in the specified networks of sites can prove generalizability, both sets of data could support CED requirements by addressing different evidence gaps relevant to Medicare beneficiaries. The resulting data would include richer and more complex data with the development of outcome measures that are feasible and reliable in routine practice. This approach could address CED goals faster with less burdensome disruptions to patient access.

**Direct from Patient Data Collection**

Patient-generated data from digital health technologies could capture patient health data outside of health care settings. Patient generated QoL data, for example, would remove some burden from providers and their teams to collect data outside of routine care, as well as help address drop offs in patient follow-up. For instance, researchers could collect certain functional capacity data, such as the six-minute walk test, directly from patients through devices equipped with actigraphy, such as smartwatches. Patients also could directly answer QoL questionnaires through mobile applications. Keeping patients involved in their own data collection could increase data completeness without increasing provider burden.

Gathering data directly from patients outside the health care setting presents some implementation challenges. First and foremost, this form of data collection would require patients’ informed consent, which is not currently required for the TVT registry and other forms of passive data capture, such as claims and EHRs. Second, patients differ in physical and cognitive status, and some patients may be more able to correctly use digital wearables or use apps to accurately respond to patient surveys. Finally, some patients may be more willing than others to be open about their health status, symptoms, and QoL on virtual systems, affecting overall data quality. Home visits to work with patients on data collection and forms of renumeration may help to increase patient willingness to actively and openly participate in these methods of data collection, which may improve both data quality and data completeness.

**PIVOTAL TRIAL RESULTS**

On March 4, 2023, the primary endpoint results from the TRILUMINATE clinical study, evaluating tricuspid valve repair, were published. The primary endpoint, a hierarchical composite of all-cause mortality or tricuspid valve surgery, hospitalization for heart failure, and KCCQ change at year follow-up, had a win ratio of 1.48 (95 percent confidence interval, 1.06 to 2.13; P=0.2), favoring the treatment group. The difference between trial arms was driven primarily by the improvement in KCCQ score for the treatment group, as there were no demonstrated differences between trial arms in all-cause mortality or heart failure hospitalization. The results for the hierarchical secondary endpoints, also evaluated at year one follow up, included 98.3 percent freedom from major adverse events (P<0.001), increase of KCCQ by a mean of 12.3±1.8 points in the treatment group and 0.6±1.8 points in the control group (P<0.001), and six-minute walk distance change of −8.1±10.5 m in the treatment group and −25.2±10.3 m in the control group (P = 0.25).
On October 26, 2023, the primary endpoint results from the TRISCEND II study, evaluating tricuspid valve replacement, were presented. The primary safety endpoint, rate of major adverse events at 30-day follow-up was 27.4 percent. The primary effectiveness endpoint, evaluated at six months follow-up, showed significant reductions of TR grade in the treatment arm, with 98.8 percent of patients with mild or moderate TR compared to 21.6 percent in the arm with medical therapy alone (P<0.001), and significant improvements of QoL and functional outcomes for the treatment arm (P<0.001), with a hierarchical composite that showed 21.5 point increase in KCCQ, 90 percent of patients in NYHA I/II, and a 10.6 increase in six-minute walk distance.

Direct comparison between the two studies is not possible given the differences in devices, patient inclusion criteria, and follow-up timeframes. However, the primary and secondary endpoint analyses of these trials do offer valuable information, including the association of echocardiographic endpoints, like TR reduction to improvements in QoL as measured by KCCQ. These results also raise important questions, for example: is TR merely a manifestation of underlying conditions, such that its correction does not impact prognosis, or will there be evidence of prognostic improvement over the long-term following sustained TR reduction? Are there patient characteristics that could impact prognostic and symptomatic improvements? Finally, despite improved KCCQ scores across both studies, the differing results in the changes in six-minute walk distances between both studies emphasizes the identified stakeholder questions around patient selection and treatment appropriateness, given the differences in surgical risk.

Preliminary results from both trials underscore the original premise of this Roundtable series: additional clinical studies and RWE will be needed to substantiate the clinical benefit of TVI procedures, including long-term health outcomes. Stakeholders can capitalize on existing data sources, such as the TVT registry, claims, and EHR data, integrating data linkage strategies to create a holistic picture of patient health over time. Given the promising results on KCCQ improvement for both procedures, novel data collection methods, such as direct from patient data collection to capture QoL outcomes, may be necessary to supplement registry-based data collection. As these interventions become more widespread, having this infrastructure in place will also help track the provider, technology, and patient considerations that might predict treatment success. Furthermore, long-term data collection will be critical to evaluate the clinical impact of these measures, which may not be apparent at the six month and one year follow up of the respective pivotal studies.

POLICY IMPLICATIONS

The TVI devices are approaching FDA determinations at a time of broader discussions to modernize Medicare coverage processes and the role of RWD collection strategies to support more timely and efficient Medicare coverage. A growing number of potentially disruptive novel technologies are reaching FDA determinations with limited evidence on long-term health outcomes for Medicare beneficiaries. While they may have sufficient evidence to inform FDA’s risk-benefit assessment in their determination of “safety and effectiveness” for regulatory approval, they may not have sufficient evidence to substantiate Medicare’s “reasonable and necessary” determination for Medicare coverage. This
possibility is often due to the fact that clinical trial populations may not be representative of the diverse real-world Medicare population, and that protocol-driven guidance on patient criteria and the procedure may not be representative of real-world practice. As demonstrated in this series, TVI procedures have substantial areas of clinical uncertainty. RWE generation can address these areas of uncertainty, thereby informing the value of the technology. Additionally, RWE generation over time can help support the validation of endpoints for novel therapeutic areas, such as TVI procedures.

*Streamlining Medicare Coverage Processes*

The proposed CED and Clinical Endpoints Knee Osteoarthritis guidance documents are important steps in ongoing efforts to streamline Medicare coverage processes by clarifying both the types of health outcomes of interest to CMS and the criteria for study designs that can produce the evidence needed to support Medicare coverage. For truly novel therapies, for which there is sparse existing evidence, early stakeholder engagement can help inform CMS on the key outcomes of interest and the methods to generate that data.

This roundtable series demonstrates the value of early engagement to identify evidentiary gaps for truly novel technologies and plan for post-market infrastructures and studies to fill these gaps. For novel therapeutic areas like TVI procedures, there may not be substantive literature to inform clinical endpoints guidance as described in the knee osteoarthritis guidance document. In these cases, early multistakeholder engagement, such as this described series of Roundtables, could help CMS determine appropriate outcomes of interest. As in this Roundtable series, CMS could consider engaging with providers, patient groups, researchers, FDA, manufacturers, and health technology companies when developing further guidance on clinical endpoints for novel therapeutic disease areas. Accordingly, early multistakeholder engagement can inform a post-market evidence generation plan for both the outcomes of interest and the ideal data infrastructure that can meet updated CED study criteria. As noted in this series, traditional registry approaches, secondary uses of RWE, and even POC trials are appropriate data collection techniques for different outcomes of interest. CMS can utilize this type of early engagement to inform feedback or guidance on data sources and CED study designs that could be best suited to answer evidentiary questions.

Finally, the early, multistakeholder engagement, as demonstrated in this Roundtable series, also could be applied for emerging therapies that could be eligible for the proposed TCET pathway. The TCET pathway proposal specifies that CMS will engage with manufacturers, FDA, and AHRQ to align evidentiary gaps and a corresponding evidence development plan. Other stakeholder groups, including clinicians, patient advocacy organizations, and specialty societies are invited to provide public comment on ensuing proposals for evidence generation. For truly novel technologies, this type of broader stakeholder feedback may be most effective much earlier in the process for determining clinical outcomes of interest.

**CONCLUSION**
During the Duke-Margolis and HVC Roundtable series, key stakeholders that will likely drive the development of the TVI therapeutic space identified evidence gaps and the data collection strategies that could be used in real-world settings to address them. As the emerging technologies near regulatory determinations, these discussions could inform how to meet post-market evidence generation requirements, particularly to inform Medicare coverage.

This Roundtable series demonstrated how early multistakeholder engagement can help inform coverage and evidence needs for novel technologies, particularly those that may have limited evidence at the time of regulatory authorization and necessitate Medicare coverage assessments. Early engagement could further streamline proposed Medicare coverage processes and ensure timelier patient access to novel medical technologies.
AUTHORS

Beena Bhuiyan Khan, M.Sc., Research Director at Duke-Margolis Institute for Health Policy
Hannah Graunke, MPP, Senior Policy Analyst at Duke-Margolis Institute for Health Policy
Mark McClellan, MD, PhD, Director of Duke-Margolis Institute for Health Policy

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DISCLOSURES

Beena Bhuiyan Khan is a former employee of Abbott and Boston Scientific and a shareholder of the respective parent companies. Mark B. McClellan, MD, PhD, is an independent director on the boards of Johnson & Johnson, Cigna, Alignment Healthcare, and PrognomIQ; co-chairs the Guiding Committee for the Health Care Payment Learning and Action Network; and receives fees for serving as an advisor for Arsenal Capital Partners, Blackstone Life Sciences, and MITRE.

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The Heart Valve Collaboratory is a collaborative, multi-disciplinary, patient-centered community of stakeholders addressing complex problems and embracing innovation to help patients with heart valve disease achieve their fullest potential for health.

For more information, visit healthpolicy.duke.edu and heartvalvecollaboratory.org

For more information about this Report, please contact: Beena Bhuiyan Khan at beena.bk@duke.edu
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