Limited Data Does Not Preclude Payer Coverage—Humanitarian Device Exemptions: A Case Study

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Prepared by:
Lakshman Ramamurthy PhD
Carrie Bullock MPH
Will Zellweger
Virna Dapic PhD
Avalere Health LLC

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Executive Summary

Medical devices and related innovations play an important part in meeting the needs of patients, requiring processes to ensure the safety, quality and availability of technologies to patients. The U.S. Food and Drug Administration (FDA) determines which devices are marketed while public healthcare programs, such as Medicare, and commercial health plans determine how these devices will get reimbursed. The combination of these two factors affects patient access to new, innovative products.

In this study, we examine whether and how the evidence considered during the FDA approval process affects coverage for devices. This paper considers divergent approval pathways—namely Humanitarian Device Exemptions (HDEs) and Premarket Approval (PMA)—with widely varying clinical evidence requirements, and evaluates how differences in the evidence packages associated with these two device pathways result in similarities and/or differences in reimbursement.

We surveyed 10 HDEs, from a total of 54 approved to date by the FDA since the program was initiated by the Food Drug and Cosmetic Act in 1990. We limited our selection by choosing devices for which payer policies were publicly available and in doing attempted to cover a diversity of therapeutic indications. We also studied three PMA devices approved in the recent past (within five years), including those that had been particularly novel or in the news. For the coverage survey and medical director interviews, we chose the five largest commercial payers based on total enrollment. We also reviewed publicly available Medicare coverage decisions, and surveyed a sample of Medicaid state policies for HDE devices.

Contrary to conventional wisdom, we found that a higher evidentiary burden for FDA approval does not consistently correspond to more robust coverage. Likewise, our analysis also demonstrates that devices that receive marketing authorization with limited data are able to receive payer coverage for the specific populations that are indicated.

Our study further reveals that payer behavior is not monolithic and the process for coverage is distinct between public and private payers. For example, the process for public payers to open and implement a formal coverage policy is generally lengthier, more transparent (e.g., mandated public comment process) and faces greater political/stakeholder scrutiny. Private payers, on the other hand, initiate and maintain more formal coverage policies for medical items and services than Medicare and Medicaid. In addition, coverage among private payers is often divergent.

Finally, our research shows that payers generally considered FDA's approval notice when making coverage decisions. However, in the case of private payers, it only contributed a fraction of the rationale for the decision, with other data playing an equally important role, such as additional clinical trials and opinions provided by professional societies/organizations. We also found that in some cases, the unmet need and the severity of the condition treated by a particular device overrode the absence of robust data used for FDA approval, with unmet clinical need contributing significantly to payer coverage decision making.

Correspondence regarding contents in this paper may be addressed to lramamurthy@avalere.com

Introduction to Regulation and Reimbursement of Medical Devices

Evidence Requirements for FDA Approval Vary Based on Regulatory Approval Pathway

Medical devices are classified based on the risk the device poses to patients. The risks range from Class I to Class III. The lowest risk devices are in Class I and are mostly exempt from any requirements prior to marketing within the U.S. Examples of Class I devices include arm slings, latex examination gloves and most hearing aids.

A majority of medical devices fall into the Class II category and manufacturers of such devices are required to notify FDA prior to marketing those devices via a "510(k) submission." The 510(k) application allows the manufacturer to demonstrate that the device is "substantially equivalent" in terms of the intended use and safety and effectiveness to a medical device already legally marketed ("predicate") in the U.S. Examples of such devices include X-ray machines, dialysis machines, fetal monitors and glucose monitors.

Class III is reserved for devices deemed high-risk products and are subjected to a pre-market approval (PMA) procedure analogous to that for new drugs. By statute, the PMA process is reserved for medical devices that "support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury".[1,2] Class III devices require FDA approval usually based on clinical experience before the products can be marketed. PMAs are the most involved and expensive process that a device manufacturer typically files.

In addition to 510(k) and PMA regulatory pathways, a manufacturer also can pursue the humanitarian device exemption (HDE) pathway. An HDE pathway is designed for a device intended to treat or diagnose a disease or condition that afflicts fewer than 4,000 individuals in the U.S. per year. HDEs are reviewed to ensure that they pose no safety concerns or any unreasonable risks and that their probable benefits outweigh the risks.

The evidence to support a PMA is usually gathered in the context of a clinical trial, which includes a randomized controlled trial and a statistically robust sample size. This varies from the requirements for an HDE, where sample size may be limited by the lack of adequate numbers of patients, particularly in rare or infrequent conditions. The requirements for the HDE and PMA approval pathways are summarized in Table 1.

[1] 21 C.F.R Part 814.

[2] 21 C.F.R Part 814.

Table 1: Requirements for the HDE and PMA approval pathways

REQUIREMENTS	HDE	PMA
Standard	Safety and probable benefit	Safety and effectiveness
Population	Rare (4,000 U.S. patients/year)	General
Clinical study design	Clinical data not absolutely required but helpful	Large, often Randomized Controlled Trials (RCTs)
IRB approval after market	Yes	No
Selling price	Limited profit allowed	Market Value
Review time frame, days	75	180

Source: FDA.gov

PMA and HDE Devices Have Different Requirements

Along with differences in the evidentiary threshold, PMAs and HDEs have different pre- and postmarket requirements. Applicant must show that there is no other way that the HDE device could be brought to market and that a comparable device to meet the relevant clinical need is unavailable. Additionally, the use of HDEs must first be reviewed by an IRB at the facility where it will be used.

FDA has the authority to require sponsors to perform a post-approval study (or studies) at the time of approval of a premarket approval (PMA), humanitarian device exemption (HDE), or product development protocol (PDP) application to help assure continued safety and effectiveness (or continued probable benefit, in the case of an HDE) of the approved device. Post-approval studies allow FDA to evaluate device performance and scan for potential problems once the device is used more widely; this information is sometimes difficult to obtain in a focused clinical trial. Examples of PMAs, some of which have required post-approval studies, include implantable cardiovascular defibrillators, implantable middle ear devices, and more recently some tests for screening genetic mutations prior to delivering cancer chemotherapy.

Reimbursement of Medical Devices Differs Among Public and Private Payers

The health insurance marketplace in the U.S. consists of commercial and government payers, also referred to as private and public payers, respectively. Government payers include Medicare and Medicaid fee-for-service programs. Public and private payers determine reimbursement for medical technologies and services by developing policies that delineate whether or not and for whom the device will be covered, and how much the provider will be compensated by the payer for the item or service. Both public payers and private payers create and publish formal coverage policies.

To be covered by the Center for Medicare & Medicaid Services (CMS), products generally must be approved by FDA, fall into one of the statutorily defined "benefit categories," and be "reasonable and necessary" for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member.[3] To meet the "reasonable and necessary" standard, a product or service must improve health outcomes, be safe and effective, and must not be deemed experimental or investigational. The reasonable and necessary provisions are not defined explicitly in regulation and remain at the discretion of the Medicare program. For Medicare in particular, FDA-approved devices with therapeutic indications are presumed to meet this definition unless directly addressed through a Local Coverage Determination (LCD) or National Coverage Determination (NCD).

In contrast, private payers tend to create and rely on more established, formal coverage policies. This reliance may be the result of additional resources, and a more cost/profit conscious environment. In the absence of a formal coverage policy by a private payer, FDA-approved devices are typically considered non-covered. Requests for coverage or payment for medical devices are typically evaluated on a case-by-case basis.

It should also be noted that public payers are often subjected to more requirements to develop their coverage policies in an open and transparent manner. For example, Medicare's national and local coverage policies must undergo opportunities for public comment and are open to more political scrutiny given the nature of publicly funded programs.

Research Methodology—Survey of FDA Evidence Requirement and Payer Coverage of Medical Devices

Device Selection for the Study

To explore if any of the factors considered during FDA approval played a role in subsequent coverage decisions, we conducted an analysis of the evidence used to support FDA approval for a number of medical devices that were approved via differential regulatory approval pathways—namely Humanitarian Device Exemptions (HDE) and Premarket Approval (PMA).

As of January 2014, 58 medical devices (Figure 1) have sought and obtained approval through FDA's Humanitarian Use Device (HUD)/HDE pathway.[4] We selected 10 medical devices approved by FDA through the HDE pathway and these are listed in Table 2 (Appendix). In selecting these devices, we sought to include diverse therapeutic indications affecting both adult and pediatric patients—namely, cardiovascular, neurological, orthopedic and restorative, and pulmonary.

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[3] 42 U.S.C. § 139y(a)(1)(A)

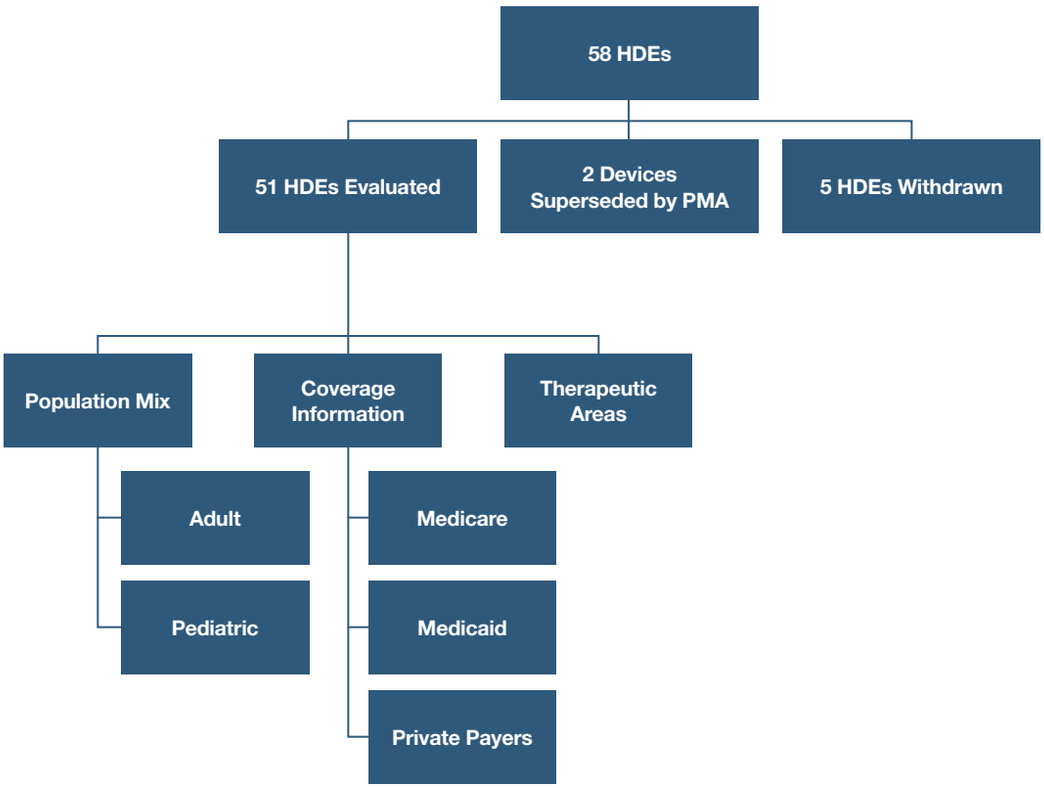
[4] Medical Devices, U.S. Food and Drug Administration. "Listing of CDRH Humanitarian Device Exemptions." Last accessed January 29, 2014. http://www.fda.gov/medicaldevices/productsandmedicalprocedures/deviceapprovalsandclearances/hdeapprovals/ucm161827.htm.

To gain a better understanding of the evidence manufacturers must obtain to demonstrate the effectiveness of their device, our research further included three PMA devices, listed in Table 3 (Appendix) to use in comparison for the regulatory approval requirements and coverage considerations. PMA devices, as mentioned above, have the most stringent approval requirements. The three devices were selected based on the criteria similar to HDEs.

Limitations on Device Selection for the Study

Our research consisted of a review of the clinical information submitted to FDA, and thus was limited to devices with available clinical study data. Similarly, we selected devices for which we were able to obtain at least some detailed private and/or public coverage policies. Finally, we also considered during our selection any "high-profile" devices, as evidenced by the media coverage and the recognition of these devices in the healthcare market. The small number of devices itself was a limitation for the study and should be borne in mind when interpreting this analysis.

Figure 1: Evaluation Process for 10 HDEs



Analysis of Regulatory Decisions

To study the regulatory approval decision for each HDE device, we reviewed FDA's Summary of Safety and Probable Benefit (SSPB) document, and where available, additional information used to inform FDA about the device. In the cases of PMAs, we looked at the Summary of Safety and Effectiveness Data (SSED). Specifically, we focused our research on the types of clinical and analytical studies performed to assess device performance and included in the submission to FDA for approval consideration. Also considered were the sample size (i.e., the number of subjects studied, number of clinical sites, statistical rigor and clinical endpoints considered in the design of studies). This was evaluated in the context of how much overall data was submitted to the Agency, including device description, performance and any software-related information.

Analysis of Coverage Policies—Commercial Payer and FFS Medicare and Medicaid

We studied existing coverage policies for the selected medical devices, both HDE and PMA devices, and focused on the five largest U.S. commercial payers, as determined by total enrollment. We also researched the coverage policies of the selected medical devices for fee-for-service (FFS) Medicare, both national and local, and three state FFS Medicaid programs. The three state FFS Medicaid programs selected were the most likely to have publicly available coverage information based on prior experience. Table 4 (Appendix) describes the commercial payers and FFS Medicaid payers selected for analysis.

We searched for relevant payer coverage polices through publicly available policy indexes and keyword search engines on commercial and public payer websites, searching by device name and approved indication(s). All located and relevant coverage policies were documented and reviewed.

Payer Interviews

We conducted interviews with medical directors[5] from three commercial payers to gain a more thorough understanding of the coverage decision-making process for medical devices, including for those approved by the HDE pathway. Specifically, we were interested in the process private payers use to develop and update coverage policies on devices and the evidence evaluated to inform these policies.

[5] Interviewed medical directors were solicited by Avalere and selected, in part, based on existing relationships and/or prior interview experience with Avalere or based on their expertise on select therapeutic areas. Interview questions were provided in advance and interviews lasted between 50 and 75 minutes. Per agreement with interviewees, interviewee identification, plan name, and all plan details, were blinded and will remain confidential. Interviewees were paid an honorarium for their participation in the project.

Findings

Regulatory Evidentiary Threshold Varies for PMA and HDEs with Limited Impact on Payer Behavior

As mentioned earlier in the paper, devices approved through the PMA pathway fall into the highest risk class, Class III. The evidentiary threshold for the PMA approval process is more significant than it is for the HDE devices. In Table 1 (Appendix), we outline the requirements for the two approval pathways.

The 10 HDE devices we selected provided preclinical, animal and clinical study data to FDA for review. Clinical studies, the main focus of the evidentiary review, conducted with the HDEs enrolled significantly smaller number of patients than studies associated with a PMA application. While some of the clinical studies for HDE devices were randomized, others were not due to the small number of patients with the condition. They varied depending on the prevalence of the condition, and availability of subjects for the study.

For devices approved through the PMA pathway, FDA often required post-approval studies. While HDE approved devices generally are not subject to post-approval studies, an exception is AbioCor Implantable Replacement Heart, which was subject to a post-approval study requirement.

Considering the size of clinical trials for HDE devices and a lack of a requirement that the sponsor show clinical effectiveness of such device, we hypothesized that the HDEs may come to market with less evidence than payers typically require for coverage determinations. However, given their small targeted patient populations, we also recognized that these devices may be less likely to come under intense payer scrutiny. To study that closely, we selected four out of the 10 HDE devices to evaluate how private payers viewed the information presented to FDA and how it influenced their behavior. We selected the subset of devices based on the public availability of detailed coverage policies, as we wanted to closely evaluate what evidence was considered. The following four were selected: 1) Melody Transcatheter Pulmonary Valve, 2) Abiocor's Implantable Replacement Heart, 3) NeuRx's DPS Diaphragm Pacing System, and 4) Activa Dystonia Therapy. Coverage policies from five private payers were reviewed (see Table 4 (Appendix) for the list of private payers).

Closer Examination of How Payers Viewed Regulatory Evidence for HDEs

Our research showed that payers generally considered FDA's approval notice when making coverage decisions. However, in the case of private payers, it only contributed a fraction of the rationale for the decision, with other data playing an equally important role, such as additional clinical trials, and opinions provided by professional societies/organizations. Our research also showed that in some cases the unmet need and the severity of the condition overrode the absence of robust FDA information.

Figure 2: Coverage Policies for Individual HDE Devices as Considered by Various Commercial Payers

2a. Melody Transcatheter Pulmonary Valve (TPV)

AET	· Considers coverage of TPV implantation using FDA-approved devices (e.g.. Melody TPV), when used in patients with condition for which it was approved by the FDA
CI	· Cigna covers TPV implantation as medically necessary when used in accordance with the FDA HDE requirements · Use for other indications is considered experimental and thus not covered
WLP	· TPV implantation is considered medically necessary when the conditions for which the device has been approved are met · If the conditions are not met, use is considered investigational and medically unnecessary
HUM	· Eligibility for TVP replacement requires review by a medical director · Eligibility requirements are same as the indication for which it was granted approval under FDA
UNH	· United Health does not cover the device because there is insufficient evidence for long-term efficacy and durability, regardless of the fact that the device is FDA approved

AET= Aetna; CI=Cigna; WLP=WellPoint/Anthem; HUM=Humana; UNH=UnitedHealthcare

2b. Abiocor Implantable Replacement Heart

AET	· Aetna does not have specific policy for the implantable replacement heart; however, the use of total artificial heart (e.g. ABIOCOR Total Artificial heart) is considered investigational and experimental because the safety and effectiveness has not been established
CI	· Cigna covers the AbioCor Implantable Replacement Heart as medically necessary as destination therapy when performed in accordance with the FDAs HDE requirements · Use for other indications is considered experimental
WLP	· The AbioCor Implantable Replacement Heart System is considered investigational and not medically necessary for all indications
HUM	· Humana has no specific policy for the HDE device, however it does covers AbioCor Total Artificial Heart for specific indications
UNH	· The device is unproven as an alternative to heart transplantation because there is a limited evidence available. Well-designed studies are needed.

AET= Aetna; CI=Cigna; WLP=WellPoint/Anthem; HUM=Humana; UNH=UnitedHealthcare

2c. NeuRx DPS Diaphragm Pacing System

AET	· Aetna considers the device medically necessary for three indications including ALS in patients who have stimulatable diaphragms and are experiencing chronic hypoventilation (same as approved by the FDA)
CI	· Cigna covers the device for ALS when provided in accordance with the HDE specification of the FDA approval
WLP	· Diaphragm stimulation with an FDA approved diaphragm pacing system is considered medically necessary for ALS when criteria outlined in the FDA approval order are met
HUM	· Humana considers coverage of the device if all of the criteria outlined in the FDA's approval order are met
UNH	· No information is available

AET= Aetna; CI=Cigna; WLP=WellPoint/Anthem; HUM=Humana; UNH=UnitedHealthcare

2d. Activa Dystonia Therapy

AET	· Aetna considers DBS medically necessary durable medical equipment when used in accordance with the FDA approved indication
CI	· Cigna covers DBS as medically necessary when used in accordance wit the HDE specification of the FDA approval
WLP	· WellPoint covers DBS as medically necessary when used in accordance wit the HDE specification of the FDA approval
HUM	· Humana covers the device when used in accordance with the HDE specifications of the FDA approval
UNH	· United Health covers DBS as medically necessary when used in accordance with the HDE specification of the FDA approval

AET= Aetna; CI=Cigna; WLP=WellPoint/Anthem; HUM=Humana; UNH=UnitedHealthcare

Detailed Review of Coverage Policies Reveal Specific Themes

Our review of public and private coverage policies for HDE and PMA devices revealed several central themes that may inform how reimbursement is impacted for medical devices—regardless of the regulatory pathway for approval, and the evidence requirement thereof:

(1) Most medical devices are covered or non-covered through formal private payer coverage policies and typically public payers do not maintain coverage policies for most medical devices;

(2) Payers value unmet needs and the total available evidence more than which pathway a device uses to reach the market;

(3) Medical devices approved by FDA, even those approved via a PMA, are not guaranteed medical coverage by commercial payers; and

(4) Additional factors beyond the availability and quality of clinical evidence that may influence the likelihood of positive commercial coverage include medical similarity to PMA-approved devices.

Each of these broad themes was further complemented and supported by additional takeaways derived from the in-person interviews with commercial medical directors.

Theme 1: Most medical devices are covered or non-covered through formal private payer coverage policies and typically public payers do not maintain coverage policies for HDE-approved medical devices

The majority of medical devices are covered or non-covered through a formal coverage policy in the commercial market. Within the scope of this study—the HDE researched universe (defined as the selected 10 HDE devices across the 5 selected commercial payers), coverage was defined 84% of the time by a formal coverage policy. That is, of the possible 50 coverage policies, 42 policies were identified and found to be active. All of HDE pathway approved medical devices researched were either covered or non-covered by formal coverage policies by at least two private payers, while 60% of the targeted HDE devices were covered or non-covered by a medical policy for all five of the private payers researched. Tables 5 and 6 (Appendix) summarize the outcomes of coverage decisions for HDE- and PMA-approved devices respectively.

During one-on-one interviews, medical directors of various commercial payers who are responsible for setting coverage policies noted that medical device coverage policies, regardless of FDA approval pathway (i.e., HDE or PMA),[6] are triggered in response to a number of events—namely, in response to a provider request, issuance of an FDA

[6] Premarket Approval (PMA), 510k or Humanitarian Use Device/Humanitarian Device Exemption (HUD/HDE)

approval, the device in question being the subject of a major publication (usually negatively), and/or concerns over fraud or abuse. Furthermore, commercial payer medical directors affirmed that, absent a formal coverage policy, a particular device—whether approved through an HDE or PMA pathway—would not be considered a covered benefit and will be evaluated on a case-by-case basis. In other words, a medical device is by default considered non-covered if no specific coverage policy exists.

Based on the research of the selected medical devices, public payers, in contrast, do not appear to maintain coverage policies for the majority of medical devices approved through the HDE pathway. In contrast to the prevalence of formal coverage policies for HDE approved devices by private payers, among public payers Heartsbreath[7] was identified as the only HDE approved medical device for which Medicare maintains an explicit, product-specific NCD. The NCD "determined that the evidence does not adequately define the technical characteristics of the test nor demonstrate that Heartsbreath testing to predict heart transplant rejection improves health outcomes."

Table 6 (Appendix) summarizes the private and public payer coverage policies, where applicable, for the 10 selected HDE approved devices targeted for this paper.

Theme 2: Payers value unmet needs and the total available evidence more than which pathway a device uses to reach the market

According to interviewed commercial medical directors, the evidentiary threshold for coverage does not differ for HDE-approved medical devices during coverage consideration. Specifically, there are no special evidentiary parameters or exceptions to coverage requirements for HDE devices by virtue of their FDA approval pathway. However, interviewees added that the coverage evidentiary threshold may be lower for devices treating patients with limited to no options, particularly for life-threatening diseases. This is in part the result of payers evaluating such devices relative to the current standard of care (SOC). HDE-approved devices by definition treat smaller, underserved patient populations, therefore private payers may make positive coverage determinations based on more limited available data, relative to the data they would require to support positive coverage of a PMA-approved device that is intended for a larger patient population with several treatment options (e.g. Bronchial Thermoplasty). This is supported by the various positive coverage decisions for the specific HDE devices studied by various commercial payers (Figure 2).

[7] Centers for Medicare & Medicaid Services, Medicare Coverage Database, *National Coverage Determination (NCD) for Heartsbreath Test for Heart Transplant Rejection (260.10)*. http://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=325&ncdver=1&NCAId=217&NcaName=Heartsbreath+Test+for+Heart+Transplant+Rejection&IsPopup=y&bc=AAAAAAAACAAAAA%3D%3D& (publication number 100-3).

Although FDA may consider a potentially lower evidentiary threshold for approval of HDE devices that treat small patient populations with little to no available treatment options, private payers do require some level of clinical utility data. As a result, private payers may non-cover HDE devices that have only limited, small, short-term or feasibility-focused clinical utility data available. Over the course of the secondary research, at least three HDE devices were found in which some of the active coverage policies explicitly directed non-coverage, citing limited, small and short-term or feasibility focused clinical data as at least one of the reasons for non-coverage or being classified as experimental, etc. These devices included:

- Argus II Retinal Prosthesis System
  - *"Currently, there is insufficient evidence that the use of artificial retina devices result in improved vision. Available data are limited to small, short-term, feasibility studies."* – Aetna[8]
- ABIOCOR Total Artificial heart
  - *"The AbioCor heart may eventually be an attractive option as destination therapy in appropriately selected individuals, because the system is totally implantable requiring no percutaneous line attachments, and initial data regarding the technical functioning of the device appears encouraging. However, additional clinical studies are needed with larger numbers of individuals to enable further analysis of outcomes including QOL issues, survival, and adverse complications."* – WellPoint[9]
  - *"There is limited evidence that the AbioCor TAH, as a permanent replacement for the failing heart, improves survival. Well-designed studies are needed to establish the safety and efficacy of this device."* – UnitedHealthcare[10]
- IntraBronchial Valve
  - *"Aetna considers bronchoscopic lung volume reduction procedures experimental and investigational because of insufficient evidence of their effectiveness…"* – Aetna[11]

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[8] Aetna, "Clinical Policy Bulletin: Wound Care" Number: 0244, Replaces CPB 331, http://www.aetna.com/cpb/medical/data/200_299/0244.html (Effective: 05/28/1998).

[9] Anthem, "Mechanical Circulatory Assist Devices (Ventricular Assist Devices, Percutaneous Ventricular Assist Devices and Artificial Hearts)", Policy # TRANS.00014, http://www.anthem.com/medicalpolicies/policies/mp_pw_a053826.htm (Current Effective Date: 10/08/2013).

[10] UnitedHealthcare, "TOTAL ARTIFICIAL HEART", Policy Number: 2013T0384K, https://www.unitedhealthcareonline.com/ccmcontent/ProviderII/UHC/en-US/Assets/ProviderStaticFiles/ProviderStaticFilesPdf/Tools%20and%20Resources/Policies%20and%20Protocols/Medical%20Policies/Medical%20Policies/Total_Artificial_Heart.pdf (Effective Date: 09/01/2013).

[11] Aetna, "Clinical Policy Bulletin: Lung Volume Reduction Surgery" Number: 0160, http://www.aetna.com/cpb/medical/data/100_199/0160.html (Effective: 05/19/1997).

It bears mentioning that ABIOCOR was covered by several of the large commercial payers studied but was non-covered by one of them, as they found that this was unproven as a replacement for heart transplantation and that evidence available was insufficient to prove otherwise. This highlights a flexible standard when one considers how commercial payers evaluate evidence and determine whether a device is "medically necessary." This theme was further reinforced by input from interviewed medical directors who confirmed that a lack of data demonstrating effectiveness versus SOC, particularly in the long-run, could hurt a device's chances of gaining or maintaining positive coverage.

Theme 3: Private payer coverage under medical policy for devices approved through PMA is not guaranteed

The study also revealed that commercial coverage of medical devices approved by FDA under PMAs, the most comprehensive pathway for agency approval, is not guaranteed. Two of the three PMA-approved medical devices assessed were explicitly non-covered by some payers, those being:

- Arctic Front Cryocatheter received FDA approval through the PMA process on December 17, 2010, intended to destroy (ablate) abnormal heart tissue to treat drug refractory paroxysmal atrial fibrillation (PAF), an intermittent abnormal heartbeat in the upper chambers of the heart that cannot be treated with medicines[12]
  - *"Cigna does not cover any other method of transcatheter ablation of the pulmonary veins for the treatment of atrial fibrillation, including but not limited to cryoablation/cryoballoon ablation, because it is considered experimental, investigational or unproven."* – Cigna
  - *"Cryoablation: Evidence in the peer-reviewed literature suggests that transcatheter cryoablation/cryoballoon ablation of the pulmonary veins is technically feasible and may be effective for the treatment of a subset of patients with AF. Generally the studies are limited by small sample size and short-term follow-up. Additional well designed trials with long-term follow-up are needed before a definitive assessment can be made of the safety and efficacy of transcatheter cryoablation/cryoballoon ablation compared to radiofrequency ablation or antiarrhythmic drug therapies."* – Cigna[13]

[12] U.S. Food and Drug Administration, *Arctic Front® Cardiac CryoAblation Catheter - P100010*. Device Approvals and Clearances. Approval Date: December 17, 2010 http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm240093.htm

[13] Cigna Medical Coverage Policy, "Transcatherter Ablation of Arrhythmogenic Foci in the Pulmonary Veins for the Treatment of Atrial Fibrillation" Coverage Policy Number: 0469, https://cignaforhcp.cigna.com/public/content/pdf/coveragePolicies/medical/mm_0469_coveragepositioncriteria_transcatheter_ablation_arrhythmogenic_foci.pdf (Effective: 12/15/2013).

- Alair Bronchial Thermoplasty received FDA approval through the PMA process on April 27, 2010, indicated for the treatment of severe persistent asthma in patients 18 years and older whose asthma is not well-controlled with inhaled corticosteroids and long-acting beta-agonist medicines[14]
  - *"Bronchial thermoplasty is unproven for treating asthma. Additional large-scale sham treatment trials are needed to eliminate the potential for placebo effect and draw definitive conclusions that the long-term improvements in asthma control seen with bronchial thermoplasty outweigh the increased short-term risk of adverse events and hospitalizations."* – UnitedHealthcare[15]
  - *"Aetna considers bronchial thermoplasty experimental and investigational for the treatment of asthma and other indications (e.g., chronic obstructive pulmonary disease) because its effectiveness has not been established… In summary, although available data are promising, more research is needed to ascertain what role, if any, BT should play in the treatment of patients with asthma."* – Aetna

During the interviews, commercial medical directors emphasized that payers expect devices to be better, safer or cheaper relative to other treatment options, as demonstrated through outcomes data, in order to be covered. For this reason, even medical devices approved through the more rigorous PMA pathway may face payer scrutiny, particularly when other viable treatment options exist that are of the same or lesser cost. Studies that are sufficient for approval through PMA may or may not support the evidentiary threshold of payers despite more stringent FDA requirements.

Theme 4: Additional factors beyond the availability and quality of clinical evidence may influence the likelihood of positive commercial coverage, including medical similarity to PMA approved devices

Commercial payers were generally less inclined to cover another novel device if there were already existing modalities, particularly in cases where the novel device did not demonstrate significant clinical outcomes over existing ones. However in the cases of HDEs, we found that existence of proven technologies may have helped in payer awareness and familiarity with a novel device—particularly if HDE has a restricted indication of use for a small population with a clinically unmet need

[14] U.S. Food and Drug Administration, *Asthmatx, Inc. Alair Bronchial Thermoplasty System - P080032*. Device Approvals and Clearances. Approval Date: April 27, 2010 http://www.fda.gov/medicaldevices/productsandmedicalprocedures/deviceapprovalsandclearances/recently-approveddevices/ucm212594.htm

[15] UnitedHealthcare, "BRONCHIAL THERMOPLASTY", Policy Number: 2013T0542G, https://www.unitedhealthcareonline.com/ccmcontent/ProviderII/UHC/en-US/Assets/ProviderStaticFiles/ProviderStaticFilesPdf/Tools%20and%20Resources/Policies%20and%20Protocols/Medical%20Policies/Medical%20Policies/bronchial_thermoplasty.pdf (Effective Date: 10/01/2013).

While it cannot be concluded that medical similarity to an approved and related device is a driving factor in the coverage decision process, three of the five payer private polices we analyzed covered HDEs that are "medically similar" to a PMA approved device(s).

Under this scenario, being medically similar may have improved the probability or at least not precluded coverage of a novel HDE because payers were likely to: (1) have an understanding of device/indication utilization within the payer's coverage population; (2) have a preexisting comfort/familiarity with the device (or type of device) safety profile; and (3) be comfortable and/or understand the types of relevant outcomes data. These HDE devices included:

- Melody Transcatheter Pulmonary Valve, compared to Transcatheter Aortic Value Implantation (i.e., TAVR)
- Osteogenic Protein-1 (OP-1) Implant, compared to INFUSE Bone Graft (Bone Morphogenic Protein-2)
- Berlin Heart EXCOR Pediatric VAD, compared to various adult ventricular assist devices
- Activa Dystonia Therapy, compared to Activa Tremor Control System, Activa Parkinson's Control Therapy, and other similar deep brain stimulation (DBS) devices

Conclusion

In summary, when device manufacturers are seeking FDA approval, they should be cognizant of the differences in payer evidence requirements for positive coverage of their technologies. These differences can include quality of clinical data, size and types of data (e.g., outcomes focused, comparative effectiveness, if any supplied, etc.) being generated. In addition, they should be aware of unmet need.

This will help increase the likelihood of timely coverage by commercial payers, which require some level of clinical data upon which to base coverage decisions regardless of the FDA approval pathway. Such data, while likely above the requirement for seeking FDA approval, nevertheless improve the overall data package and concomitantly the device's prospects for positive coverage during payer consideration. In this context, it is helpful to understand that the higher FDA evidentiary standard required for PMA approval of a device, if lacking utility and outcomes data, does not guarantee favorable coverage, while the lower relative FDA evidentiary standard for HDE approval does not necessarily preclude coverage as long as utility is clearly identified and demonstrated.

While FDA approval is necessary, it is not sufficient for payer coverage, which varies widely and depends on demonstrated health outcomes and, at times, meeting an unmet medical need, both of which are intricately linked. In the event of an unmet need, the

evidentiary bar set by payers may be lower, or if the disease/condition that is being treated is particularly exigent. Therefore, there is not a clear and obvious proportional relationship between the extent of evidence gathered for FDA approval via the PMA or HDE pathway and likely coverage for that device.

It is clear, however, that devices that demonstrate ability to alleviate pain, or reduce the drastic burden of disease, and to some extent also lead to overall positive outcomes or lead to a positive prognosis, have a better chance of being covered than those devices which perform robustly, yet fail to show any perceptible unmet clinical benefit. This is independent of the extent of the regulatory hurdle cleared by the device prior to a payer coverage decision process.

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Appendix

Table 2: HDE Pathway Approved Medical Devices

	HDE	Label Indication	Population (Adult/Pediatric)	Issued
1	Argus II Retinal Prosthesis System[17]	Intended for patients aged 25 years and older with bare or no light perception vision caused by advanced retinitis pigmentosa	Adult	2/13/2013
2	Melody Transcatheter Pulmonary Valve[18]	Indicated for use as an adjunct to surgery in the management of pediatric and adult patients with dysfunctional prosthetic Right Ventricular Outflow Tract (RVOT) conduit	Both	1/25/2010
3	Heartsbreath[19]	For use as an aid in the diagnosis of grade 3 heart transplant rejection in patients who have received heart transplants within the preceding year	Adult	2/24/2004
4	NeuRx DPS, Diaphragm Pacing System[20]	Indicated for use in amyotrophic lateral sclerosis (ALS) patients with a stimulatable diaphragm	Adult	9/28/2011
5	INFUSE Bone Graft (Bone Morphogenic Protein-2)[21]	For use as an alternative to autograph in recalcitrant long bone nonunions where use of autograph is unfeasible and alternative treatments have failed	Adult	10/17/2001
6	Epicel[22]	Indicated for use in patients who have deep dermal or full thickness burns comprising a total body surface area of greater than or equal to 30%	Adult	8/27/2007
7	Berlin Heart EXCOR Pediatric Ventricular Assist[23]	Indicated to provide mechanical circulatory support as a bridge to cardiac transplantation	Pediatric	12/16/2011
8	AbioCor Implantable Replacement Heart[24]	Indicated for use in severe biventricular end stage heart disease patients	Adult	9/5/2006
9	Activa Dystonia[25]	For unilateral or bilateral stimulation of the internal globus pallidus (GPi) or the subthalamic nucleus (STN) to aid in the management of chronic, intractable primary dystonia, including generalized and/or segmental dystonia, hemidystonia, and cervical dystonia (torticollis) in patients seven years of age or above	Both	4/15/2003
10	IBV Valve System[26]	Indicated to control prolonged air leaks of the lung	Adult	9/24/2008

Source: FDA.gov

[17] http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm343162.htm
[18] http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm199258.htm
[19] http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm081213.htm
[20] http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm278684.htm
[21] http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm081154.htm
[22] http://www.accessdata.fda.gov/cdrh_docs/pdf/H990002a.pdf
[23] http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm302715.htm
[24] http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm077536.htm
[25] http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm082535.htm
[26] http://www.fda.gov/newsevents/newsroom/pressannouncements/2008/ucm116970.htm

Table 3: PMA Pathway Approved Medical Devices

	HDE	Label Indication	Population (Adult/Pediatric)	Issued
1	Arctic Front Cryocatheter[27]	Intended to destroy (ablate) abnormal heart tissue to treat drug refractory paroxysmal atrial fibrillation (PAF), an intermittent abnormal heartbeat in the upper chambers of the heart that cannot be treated with medication	Both	12/17/2010
2	Alair Bronchial Thermoplasty[28]	Indicated for the treatment of severe persistent asthma in patients 18 years and older whose asthma is not well-controlled with inhaled corticosteroids and long-acting beta-agonists	Adult	4/24/2010
3	SAPIEN Transcatheter Health Valve[29]	Indicated for transfemoral delivery in patients with severe symptomatic native aortic valve stenosis who have been determined by a cardiac surgeon to be inoperable for open aortic valve replacement and in whom existing co-morbidities would not preclude the expected benefit from correction of the aortic stenosis	Adult	11/2/11

Source: FDA.gov

Table 4: Selected Payers

	Commercial Payer	Approx. Covered Lives
1	United Healthcare	36 million
2	WellPoint/Anthem	31 million
3	Aetna	18 million
4	Cigna	13 million
5	Humana	9 million
	FFS Medicaid (State)	**-**
1	North Carolina	-
2	Florida	-
3	Texas	-

Enrollment Source: Atlantic Information Services 2013 Directory of Health Plans

Note: As Medicaid is administered and managed at the state level, centralized enrollment numbers are not released by the Centers for Medicare & Medicaid Services (CMS) or a similar national level organization

[27] http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm240093.htm
[28] http://www.fda.gov/medicaldevices/productsandmedicalprocedures/deviceapprovalsandclearances/recently-approveddevices/ucm212594.htm
[29] http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm280840.htm

Table 5: Outcomes of Coverage Decisions for HDE-approved Devices

HDE Approved Device	AET	CI	WLP	UNH	HUM
Argus II Retinal Prosthesis System	✗	/	✗	/	/
Melody Transcatheter Pulmonary Valve	✓	✓	✓	✗	✓
Heartsbreath	✗	✗	✗	✗	✗
NeuRx DPS, Diaphragm Pacing System	✓	✓	✓	/	✓
OP-1 Putty	✓	✗	✓	✗	✓
Epicel	✓	✓	✗	/	✗
Berlin Heart EXCOR Pediatric Ventricular Assist	✓	✓	✓	/	✓
Abiocor Implantable Replacement Heart	✗	✓	✗	✗	✓
Activa Dystonia	✓	✓	✓	✓	✓
IBV Valve System	✗	/	✗	/	/

AET = Aetna; CI = Cigna; WLP = WellPoint/Anthem; UNH = UnitedHealthcare; HUM = Humana

✓ = Covered; ✗ = Non-covered; / = No coverage policy

Table 6: Outcomes of Coverage Decisions for PMA-approved Devices

PMA Approved Device	AET	CI	WLP	UNH	HUM
Arctic Front Cryocatheter	/	✗	/	/	/
Alair Bronchial Thermoplasty	✗	/	/	✗	✗
SAPIEN Transcatheter Heart Valve	✓	✓	✓	✓	✓

AET = Aetna; CI = Cigna; WLP = WellPoint/Anthem; UNH = UnitedHealthcare; HUM = Humana

✓ = Covered; ✗ = Non-covered; / = No coverage policy

Table 7: Variation among coverage policy availability for public and private payers

HDE Approved Device	Medicare FFS	AET	CI	WLP	UNH	HUM	NC Medicaid	FL Medicaid	TX Medicaid
Argus II Retinal Prosthesis System	✗	✓	✗	✓	✗	✗	✗	✗	✗
Melody Transcatheter Pulmonary Valve	✗	✓	✓	✓	✓	✓	✗	✗	✗
Heartsbreath	✓	✓	✓	✓	✓	✓	✗	✗	✗
NeuRx DPS, Diaphragm Pacing System	✗	✓	✓	✓	✗	✓	✗	✗	✗
OP-1 Putty	✗	✓	✓	✓	✓	✓	✗	✗	✗
Epicel	✓	✓	✓	✓	✗	✓	✓	✗	✗
Berlin Heart EXCOR Pediatric Ventricular Assist	✓	✓	✓	✓	✗	✓	✗	✗	✗
Abiocor Implantable Replacement Heart	✗	✓	✓	✓	✓	✓	✗	✗	✗
Activa Dystonia	✗	✓	✓	✓	✓	✓	✗	✗	✗
IBV Valve System	✗	✓	✗	✓	✗	✗	✗	✗	✗

✓ Coverage policy exists; ✗ = No coverage policy exists

FFS = Fee for service; AET = Aetna; CI = Cigna; WLP = WellPoint/Anthem; UNH = UnitedHealthcare; HUM = Humana

Note: Skin substitutes (e.g. Epicel) are generally defined through local coverage determinations (LCDs). Separately, Medicare's NCD for artificial hearts and related devices covers ventricular assist devices (VADs) broadly, and does not specify coverage or non-coverage for the Berlin Heart EXCOR Pediatric Ventricular Assist device by name

The information on coverage policies was current as of December 2013.

About Us

Avalere is a vibrant community of innovative thinkers dedicated to solving the challenges of the healthcare system. We deliver a comprehensive perspective, compelling substance, and creative solutions to help you make better business decisions. We partner with stakeholders from across healthcare to help improve care delivery through better data, insights, and strategies. For more information, please contact Reggie Williams at RWilliams@avalerehealth.net. You can also visit us at www.**avalerehealth**.net. We look forward to working with you.

Contact Us

Avalere Health
1350 Connecticut Ave, NW Suite 900
Washington, DC 20036
202.207.1300 | Fax 202.467.4455
www.**avalerehealth**.net