Use of endpoint adjudication to improve the quality and validity of endpoint assessment for medical device development and post marketing evaluation: Rationale and best practices. A report from the cardiac safety research consortium

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This white paper provides a summary of presentations, discussions and conclusions of a Thinktank entitled "The Role of Endpoint Adjudication in Medical Device Clinical Trials". The think tank was cosponsored by the Cardiac Safety Research Committee, MDEpiNet and the US Food and Drug Administration (FDA) and was convened at the FDA's White Oak headquarters on March 11, 2016. Attention was focused on tailoring best practices for evaluation of endpoints in medical device clinical trials, practical issues in endpoint adjudication of therapeutic, diagnostic, biomarker and drug-device combinations, and the role of adjudication in regulatory and reimbursement issues throughout the device lifecycle. Attendees included representatives from medical device companies, the FDA, Centers for Medicare and Medicaid Services (CMS), end point adjudication specialist groups, clinical research organizations, and active, academically based adjudicators. The manuscript presents recommendations from the think tank regarding (1) rationale for when adjudication is appropriate, (2) best practices establishment and operation of a medical device adjudication committee and (3) the role of endpoint adjudication for post market evaluation in the emerging era of real world evidence. (Am Heart J 2017;190:76-85.)

During both pre-approval testing and post- approval surveillance, medical devices require evaluation to assess whether they provide safe and effective treatment. There are a number of parameters that can be used to assess the impact of a device on disease progression, but clinical endpoints that measure the effect on morbidity and mortality represent the highest standard for patients, providers, and regulatory authorities. Assessment of these endpoints requires a process that provides high quality data, which are reviewed with appropriate expertise and limited bias. Although study investigators are ultimately responsible for data submission and identifying potential endpoints, there is inherent bias among these individuals that may cause over- or under-reporting of events. Ascertainment of clinical endpoint events may also vary among investigators based on local practice or other factors. Independent and consistent adjudication of events using uniformly applied endpoint definitions and processes for endpoint reporting enhances freedom from bias and the interpretability of study results. This paper reviews the rationale and operational processes of independent clinical events committees (CEC) as a method to improve the quality and validity of endpoint assessment (See Figure).

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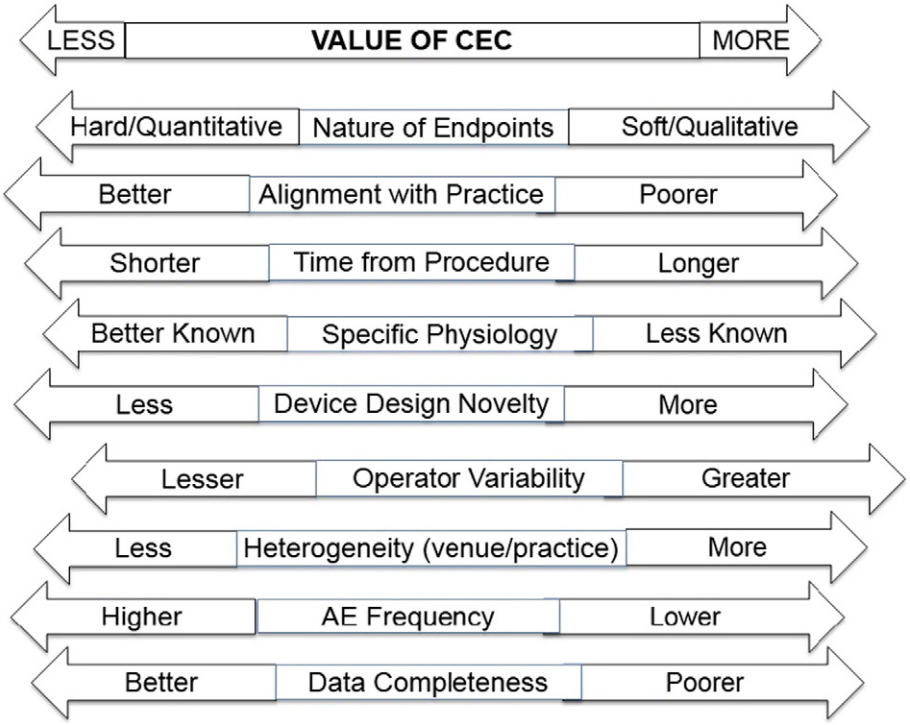
Rationale for adjudication: Why do central adjudication?

Limit bias

The possibility of bias at the investigative site arises from a number of factors. First, particularly in device trials, an investigator that uses the investigational product

Figure



illustrates the value of CEC adjudication as a function of the study elements which should be considered in determining whether a CEC should be utilized in a clinical trial.

may be an enthusiast for the new therapy, and this may influence the interpretation of an event and the relatedness of the event to the device. As a result, sites may underreport events associated with the intervention being studied. The potential for real or apparent bias is exaggerated if the investigator has a financial or scientific relationship with the device manufacturer or a competitor. Second, a site investigator might interpret events erroneously due to their direct involvement in the patient's care, particularly relating to a complication or inadequate care. Third, external factors may inappropriately influence the interpretation or reporting of clinical endpoint events. For example, heart failure might be assigned as a discharge diagnosis even though the findings do not support that diagnosis based on established clinical trial criteria. These coding errors may be influenced by reimbursement incentives or local practice variation and can confound efforts to document bona-fide clinical endpoints.

Standardized definitions

Another issue arises when there are no event definitions pre-specified in the clinical study protocol. This problem is magnified in large multicenter and increasingly global trials, as was observed in the early Studies of Left Ventricular Dysfunction (SOLVD) trials, in which site-reported outcomes used for the interpretation of cause-specific mortality differed from the results of subsequent trials that used central adjudication.[1] An exercise in comparing central adjudication to site evaluation in the assessment of mode of death noted the wide variability in event interpretation among sites from SOLVD.[2] In cardiovascular studies, a general agreement has emerged on endpoints of interest with acceptance of uniform event definitions[3-6] which greatly enhances the ability to assess outcomes within a trial and to compare outcomes across different clinical trials.

Furthermore, it is important that endpoint definitions are relevant to disease progression and are consistently applied. The determination of worsening heart failure as a study endpoint illustrates many of the challenges in adjudication. An event indicating worsening of heart failure should include a reasonable threshold for event severity and primarily focus on the escalation of therapy in response to heart failure signs and symptoms, rather than be limited to a heart failure diagnosis based only on insurance claim coding without adequate supporting documentation (which may occur during a hospitalization for another reason). Alternatively, worsening heart failure noted during a hospitalization for an unrelated procedure or illness may fail to be coded as a discharge

diagnosis or recognized as a potential clinical endpoint. In these examples, the key to optimal ascertainment and assessment of clinical events relies on established data collection procedures and the uniform application of pre-specified event definitions. One cannot assume that every clinical investigator will apply these definitions in a consistent manner.

When is adjudication appropriate?

Independent adjudication is useful in all studies where clinical endpoints require interpretation of clinical information to determine if an event has occurred. The need for independent adjudication is amplified in pivotal studies of novel technology, especially for trials having inadequate masking of patients and investigators, as is the case for many device studies. Formal adjudication by an independent CEC may be less critical in small feasibility studies or if endpoint events rely on objective metrics rather than on the interpretation of complex data that require high levels of clinical judgment. For feasibility studies, adjudication may still be helpful for estimating clinical endpoint rates and determining data requirements for subsequent pivotal trials. The need for clinical endpoint adjudication in post-marketing studies depends on the objectives of the study and the practicality of a central adjudication process. The increased use of post-market studies to provide supplementary information on safety and effectiveness for newly approved devices [http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm393994.pdf] make this question especially relevant. For studies in which the primary outcome is all cause mortality (i.e., cause-specific deaths or nonfatal events are of secondary importance), adjudication is probably unnecessary. However, most studies test interventions in which cause-specific composites of morbidity and mortality are critical to the interpretation of safety and effectiveness. Furthermore, in many studies, important events occur at low frequencies, and errors or omission of a few events can have a substantial impact on whether statistical significance is reached for the primary endpoints. In these circumstances, independent adjudication is needed to reduce bias and assure that accurate event rates are reported. In general, the more clinical judgment and experience needed to evaluate an endpoint event, the more useful is independent adjudication.

The CHARM PRESERVED trial is an example of a site-based assessment of events that differed from the independent CEC evaluation; a benefit with candesartan administration was seen with investigator-adjudicated events, which was not found with CEC adjudication.[7] In this circumstance, there was a small magnitude of benefit at issue, but since the trial concerned heart failure with preserved ejection fraction (HFpEF) patients in whom no beneficial therapy exists, even a nominal effect could be considered clinically relevant. Of note, a lack of benefit with the drug class studied in CHARM PRESERVED—an angiotensin receptor blocker—was observed in the subsequent I-PRESERVE study, supporting the CEC adjudicated results. This example illustrates how the increased rigor associated with independent adjudication could lead to a potentially promising therapy being abandoned or erroneously pursued. The use of a CEC can also impact the sample size of a larger pivotal trial based on the accuracy of event identification in a feasibility study. Adjudication, by adding additional precision to evaluation of the endpoint, can eliminate the statistical 'noise' produced by inaccurate diagnoses. Therefore, demonstration of a 'true difference' should take fewer cases to demonstrate. For example, in the Beta-Blocker Evaluation of Survival Trial (BEST), the CEC identified 21% fewer heart failure events in the treatment group, with no increase in the confidence interval, resulting in the same effect size with fewer[8] subjects evaluated.

In trials where there is a large treatment benefit, such as in the COPERNICUS[9] trial or the PARADIGM study,[10] small differences in event categorization might not alter an outcome due to the large effect size in the former and the sample size in the latter. It is worthwhile to consider, however, that most clinical trials are performed in mature fields that involve a relatively small difference in the number of events between treatment groups even when the observed difference is statistically significant. In these cases, even small differences between investigator assessment and central adjudication could influence interpretation of the results. In addition, compared to typical pharma studies, most device trials have a smaller sample size so that differences in a limited number of events can make trial results appear much more or less robust.

Best adjudication practices

The Cardiac Safety Research Consortium held a think tank on March 11, 2016 to discuss best practices in endpoint adjudication. Although there are notable differences between drug and device trials (such as the need for operator expertise and impracticality of operator blinding in most device studies), which may impact the specifics on endpoint adjudication, many of the drug trial adjudication principles previously described by the CSRC[11] are also applicable to device studies.

All CECs should operate according to a pre-approved charter. Key elements of a charter include: (a) qualifications of CEC members; (b) descriptions and definitions of the endpoints to be adjudicated; (c) methods for the identification of events to be adjudicated; (d) minimum data to be provided to the adjudicators in order for them to reach a decision (including whether case report form information vs. hospital records are needed; whether

clinical images vs imaging study reports will suffice); (e) processes for event review and adjudication; (f) processes for decision-making when there is disagreement among adjudicators or when required minimum data are missing; and g) methods for quality assurance.

Qualifications of CEC members

Capabilities required of CEC members usually encompass clinical and procedural expertise, expertise in the arena of potential safety concerns, and expertise/knowledge of variations in clinical practice in the geographies in which the trial is being conducted. It is often difficult to find comprehensive expertise within each individual adjudicator. Therefore, when constructing the committee, it is important consider the collective skills among CEC members. For instance, in a global study, it would likely be important to have adjudicators from (or, at least, familiarity with practice patterns in) the regions participating in the trial. To address the need to break voting ties, CECs should have at least three voting members. It is also crucial that adjudicators agree to follow the charter-described voting process.

Adjudicators must be independent from the study sponsor in order to avoid actual or perceived conflicts of interest. From a financial perspective, adjudicators should not receive direct financial benefit from the study sponsor, which also applies to investigator-initiated trials. Additionally, CEC members cannot benefit from the trial's outcome (e.g. by being stockholder in company or a competitor). With regard to non-financial conflicts of interest, adjudicators should not serve as an advisor, consultant, or member of clinical trial organizations if these activities relate to the clinical trial sponsor or a relevant competitor. Finally, adjudicators should not be an investigator or participate in clinical activity at the study site. A potential exception to this recommendation is a study that is so narrowly focused that all study personnel are located at the study site. If this is the case, extra caution must be taken to ensure the adjudicator does not engage in meaningful study-related interchange with the principle investigator or other study personnel.

Description and definition of endpoints

The CEC charter must clearly detail which events or endpoints will be adjudicated and provide event definitions. The CSRC recommends that the CEC focus on primary and secondary endpoints that require clinical interpretation of the event and related data. Classification of *all* adverse events or serious adverse events that are not clinical trial endpoints is typically beyond the scope of the CEC.

The CEC, study sponsor, and investigators should agree on the endpoint definitions before study initiation. In general, these definitions should follow criteria already established by medical professional societies, independent data standards groups, or prior studies, and meet regulatory objectives. A justification should be provided if event definitions deviate from established criteria. Likewise, if causality is to be adjudicated, the criteria or scales used for causality need to be referenced. The FDA *Standardized Definitions for Cardiovascular and Stroke Endpoint Events in Clinical Trials*[12] is a useful reference for definitions in the adjudication of cardiovascular events. For causality, the European Commission Guideline on Medical Devices provides standard definitions.[13]

Methods for identification of events to be adjudicated

Successful CEC operation requires the identification of all suspected endpoint events to be adjudicated and the accumulation of the supporting information required for determining whether the suspected event meets the event definition. CEC members are not involved in the initial identification of events (which typically occurs at study sites) or the compiling of source documents, but rather determine if the identified, suspected events meet the study protocol definitions based on the data presented. However, the overall CEC *process* does include the capture of the necessary data to allow for complete ascertainment of suspected events, collection of source documentation and central laboratory or imaging data (where appropriate), and presentation of this information to the CEC for adjudication.

For many endpoint events, complete ascertainment requires a systematic screening of investigator reports, safety summaries, local and central laboratory data, hospitalization records, and case report form fields that may indicate that an event occurred even if not directly reported. Adjudication of only those events reported by investigators may be limited by under-reporting. Site reporting may be based on bedside clinical impressions that vary from protocol-based definitions, and interpretation of angiographic, ultrasound, or other imaging modalities may differ from central core laboratories or the CEC itself. The impact of the CEC in establishing accurate event rates and the potential for variance with the site investigators highlights the importance of a rigorous data collection process. Since the CEC can only review data that are made available, the members should review information regarding the processes used to identify events and obtain the data required for adjudication. This information should include the level of clinical site monitoring for unreported events, database audits to assess accurate data entry, screening of local or central laboratory reports for potential endpoints events, and reviews of the safety database for hospitalizations or other adverse events that may indicate that a potential study endpoint event has occurred.

Minimum data requirements

The CEC charter should specify the minimum data requirements for each adjudicated endpoint. Case report forms should be designed for the collection of necessary data, but in many instances, source documents may be

needed to provide important supplemental information for accurate event adjudication. There should be agreement among the CEC, the Sponsor, and data management group on these requirements and assurance that the data collection is adequate.

Process for event review and adjudication

The CEC charter should provide details on the methods to be used for event review. Historically, formats have included face-to-face panel meetings or independent parallel review. Independent parallel review offers the advantages of increased efficiency and independent decision making. Most commonly, this involves review of an event by 2 adjudicators with discordant decisions either reviewed by a third adjudicator or by committee.

Regardless of the method, adjudication should be done on an ongoing basis during the trial. There are several disadvantages if the CEC does not begin the adjudication process until close to trial completion. For instance, if additional site information is needed for adjudication, it is often difficult to retrieve such information once a trial is completed. After they review initial cases, the CEC may modify minimum data requirements and determine that the collection of additional source documents or the creation of a new CRF worksheet is needed. These changes are easier to execute if they are implemented early in the trial, and they may not be possible if the trial is near completion. Ongoing adjudication of events during the study is also important for optimal monitoring by the Data and Safety Monitoring Committee. Finally, delaying adjudication until trial completion may jeopardize timelines for study closure in the event that core information is missing or inaccurate.

Process for reaching a final decision

The CEC charter should include provisions for reaching a final decision when there is either discordance among CEC members or the minimum required data are not available for review. In the case of panel meetings or when a committee approach is used to manage discordance among 2 or more independent parallel reviewers, there should be an attempt to reach consensus. When it is determined that consensus is not possible after adequate case discussion, then a majority vote should guide the final decision. Given the widespread availability of electronic adjudication platforms, independent voting can be enabled in an efficient manner. Resolution of discordant votes does need to be resolved in committee, but original voting results, including the reason for the decisions reached, should be recorded in the CEC meeting minutes. The charter should specify the number of members from various specialties that constitute a quorum for voting purposes.

It is sometimes necessary for the CEC to adjudicate suspected events even if some of the information described in the event definition is missing. Since adjudication in these cases requires a consistent approach throughout the trial, it is imperative that these situations be recognized and tracked, such that all similar occurrences are adjudicated using the similar methods. In most cases, reaching a conclusion that an event occurred or did not occur is preferred to a default adjudication of "no event" or "unable to adjudicate."

Methods for quality assurance

Support for the validity of the CEC adjudication decisions requires quality assurance of the CEC process. Quality assurance should include verification of complete ascertainment of endpoint events based on all relevant available data, support for the accuracy of the CEC determinations based on the endpoint definitions, methods for recording CEC results into the study database that minimize data entry errors, and an audit of the CEC results to confirm consistent approaches in decision-making. The CEC charter should specify the quality assurance methods to be used, and the final study summary should report on the process.

Challenges with device trials

For medical device trials, an independent central adjudication process can play a particularly important role in minimizing bias and increasing the validity of study results. Investigative sites in device clinical trials often include individuals with particular technical skills and knowledge to utilize the therapy being tested. However, individuals with these skillsets are often those who are particularly enthusiastic about new and innovative therapies. Therefore, the interpretation of events at the site level might be prone to a biased interpretation. Unlike drug trials, device studies are rarely double-blinded, and in many device trials, blinding might not be feasible (such as a study comparing a percutaneous treatment to open surgery). Thus, it is important that a CEC has as much equipoise as possible to fairly adjudicate clinical events, which can be enhanced by CEC review of records in which the treatment group assignment is masked. In some cases, however, this might have the unintended consequence of making the clinical record difficult to assess or interfering with determining device/procedure causality. Thus, the need for blinding should be balanced with the potential limits placed on the adjudication process.

Practical issues in device adjudication: Considerations for implementing a CEC

Once clinical study endpoints have been identified, the following factors should be considered in determining whether a CEC would be a worthwhile component of the investigational plan:

(1) Nature of study endpoints

Some endpoints are intrinsically more straightforward to interpret than others. Death is definitive, but stroke or heart failure hospitalization require additional clinical

evidence and clinical judgment. Events such as clinically-indicated revascularization require supporting information, which may not be pre-specified for collection in the clinical study protocol.

Qualitative data are often subjective, and therefore may require CEC review. Quantitative data are generally easier to interpret. When case report forms are well-designed to collect the relevant information (particularly for a well-known disease state), and an algorithm can consistently and accurately identify the event, CEC adjudication may have limited value-added.

(2) Alignment with practice

How well study protocol endpoints align with data that are routinely collected in standard medical care affects data reliability (and availability) and impacts the value of event adjudication. The more an endpoint requires data capture that extends beyond usual clinical practice (especially protocols for imaging studies), the greater the likelihood that the data may be missing or incorrectly collected. For example, a standard chest x-ray is generally inadequate to evaluate the integrity of an endovascular thoracic stent graft. Imaging parameters optimized to evaluate the device are necessary, but without thorough training and diligent attention by research staff, the quality of the specialized imaging study may be unacceptable. Worse yet, the coding systems in some hospitals may not even allow a non-standard study to be ordered.

(3) Time from procedure

Greater temporal proximity to the index procedure intrinsically increases the recognition that an adverse event may be associated with the procedure or device; as time passes, the likelihood generally decreases. Furthermore, concurrent progression of the underlying disease can increasingly confound the determination of causality.

(4) Specific physiology

In device studies, the target anatomy can affect study endpoints and the value of adjudication. For example, coronary stent thrombosis often results in sudden death or an acute MI, and the recognition and adjudication of these events would likely be more straight-forward than events associated with thrombosis of a renal artery stent. Similarly, the lack of validated biomarkers and the variability in the recurrence of claudication to assist in the identification of peripheral artery stent thrombosis makes the adjudication of peripheral arterial events more challenging than coronary stent thrombosis.

(5) Operator variability

Medical device performance has greater reliance on operator skill and judgment than drug administration. Operator expertise is needed to assure that patients are well-suited for device use, select the device appropriate for the patient's anatomy, and apply recommended techniques to use the device in the correct location. When faced with highly complex anatomic conditions, a physician may use unapproved or unorthodox techniques in an effort to achieve a good clinical outcome. In some cases, liability concerns may influence reporting, and adjudication may be essential for accurate attribution of an event.

(6) Heterogeneity of venues

The reliability of endpoint reporting can be influenced by variations in medical practice as well as by variations in definitions. Each of these can in turn be affected by applicable regional or national standards or norms and by the particular medical specialty delivering the care or interpreting the results. For example, the meaning of lower extremity vessel patency may be discordant between surgical versus endovascular practitioners. Reports of heart failure in a multi-national study may have variable meaning when the diagnoses differ among reporting locations.[11] The greater the variability, the greater the value of CEC event adjudication.

(7) Device design factors

Greater device complexity/novelty may increase the value of event adjudication but may not always reflect the complexity of the device itself. For example, cardiac pacemakers are quite complex, but the adverse events (AEs) associated with these devices are generally well understood. On the other hand, more novel products such as bioabsorbable or drug coated devices may introduce new types of AEs and therefore warrant adjudication.

This potential effect can be illustrated by considering a hypothetical drug coated balloon (DCB) for treating vascular lesions. In current DCB designs, the drug is not entirely delivered to the vessel wall, leaving some theoretical potential for distal embolization of the coating on the balloon. One below-the-knee trial was stopped due to an apparent increased amputation rate observed with DCB use.[14] Under such circumstances, adjudication is critical to evaluate whether the observed AEs was causally related to the DCB.

(8) Expected frequency of AE

Serious CV events are often relatively infrequent,[15] and adjudication may be particularly important when AEs are rare by increasing the likelihood that the observed event rates are reliable.

(9) Completeness of data

Accurate event adjudication relies on adequacy of the data provided for CEC review. If too much data are

missing, adjudication may be of little value, because many events will be categorized as "unable to adjudicate." However, adjudication may be especially helpful in cases where only a portion of required data are missing. For example, a recurrent MI typically requires stabilized or declining cardiac biomarker levels followed by a rise in value.[16] However, serial biomarker measurements can be challenging to collect. In the absence of biomarker data, adjudication may be based on other supporting clinical information (e.g., duration of chest pain, ECG changes, and/or new myocardial perfusion defects or wall motion abnormalities on imaging studies).

The decision to include independent CEC adjudication for individual endpoints should be justified to the clinical study stakeholders who would be interested in the outcomes of the clinical study (e.g., investigators, regulators, payors).

Future directions: Role of event adjudication for post-market and real-world evidence data

On July 27th 2016, FDA released a draft guidance entitled, "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices."[17] The primary aim of this document is to clarify how FDA evaluates real-world evidence (RWE) to determine whether it may be sufficiently relevant and reliable to generate evidence that can be used in regulatory decision-making for medical devices. RWE can potentially by used to: (1) support pre-market clearance or approval of new devices; (2) support new indications for use for approved devices (using pre-or post-market data); and (3) monitor for infrequent safety events for which the pre-market evaluation was underpowered or became evident following commercial release. FDA has also issued a guidance document on the appropriate balance of pre and post-market studies to facilitate timely patient access to safe and effectiveness new medical technology while maintaining appropriate standards for patient safety.[18] When considering risk and benefits and addressing unmet clinical needs, balancing pre and post-market data requirements may lead to less costly and more efficient pre-market studies.

There is a growing interest in the use of an ongoing clinical registry infrastructure in which to conduct clinical studies. The use of registries for regulatory decision-making is exemplified by the Transcatheter Valve Therapy (TVT) registry. After the first transcatheter aortic valve device was approved based on prospective randomized controlled clinical trial data, the Centers for Medicare & Medicaid Services (CMS), FDA, the device manufacturer, and the relevant medical professional societies collaborated to design a registry aimed at providing data to support FDA and CMS data requirements and a provide national quality assessment program. The TVT registry tracks stroke, all-cause mortality, transient ischemic attacks, major vascular events, acute kidney injury, repeat aortic valve procedures, and quality of life through one year post-implant. This registry is linked to Medicare claims data to: (1) collect surveillance data on devices with similar designs and indications; (2) analyze data to support new indications for use; and (3) support embedded prospective clinical investigations under investigational use exemptions (IDE) for new devices and new uses approved devices. There are also examples of performing randomized clinical trials within registries to evaluate therapeutic strategies to guide clinical practice and for regulatory review.[19,20]

The utilization of RWE by FDA requires an assessment of whether the data are of sufficient quality for regulatory decision-making. For regulatory review, observational data must be reliable, complete, consistent, accurate, and contain all necessary elements for evaluating device performance. FDA's guidance includes a number of quality standards related to RWE including methods of accrual, source verification, completeness, and consistency. When used to support approval of new devices or new uses of approved devices, RWE may be required to undergo CEC adjudication similar to a traditional research study submitted for FDA review.

The broad range of data types and collection methods for post-market RWE creates challenges for developing of uniform standards or routine methods for adjudication of clinical outcomes. Nevertheless, there are several common processes that should be a part of the data collection and data management plan that will facilitate adjudication when it is needed. These include preparing sites for complete and accurate collection of data, use of a common data form, use of uniform event definitions, and a data audit program. It is possible that some of these study elements need to be augmented when the data are to be used for specific regulatory questions beyond the original design of the data collection. For example, conducting an RCT within a device registry may require specific clinical endpoint data fields or increased data monitoring.

The methods and objectives of event adjudication may also vary depending on the regulatory question and scope of the project. For example, event adjudication for an RCT nested within a medical device registry for which a new or expanded device indication is sought may be very similar to the processes already outlined and frequently associated with pre-market studies. However, when working with very large datasets, an assessment of infrequent but important safety events identified in part through links with administrative data, may require a streamlined adjudication approach. Automated adjudication algorithms which may detect certain key terms, values or combinations of data points may be appropriate

when working with very large datasets in order to define the characteristics of the potential population. The results of a programmatic approach can be supplemented with independent adjudication of a random sample of events to provide an assurance of accuracy. The random sample should include a representation of all event types being tracked, and the CEC charter should describe the methods for complete ascertainment of events and the adjudication algorithm.

An Example: The Kaiser Permanente (KP) Cardiac Device Registry

In response to increased cost, volume, and concerns about risk of medical devices, KP's Cardiac Device Registry (KP-CDR), is designed to monitor post-procedural patient outcomes and provide post-market surveillance of implantable cardioverter defibrillators (ICD), pacemakers (PM), and cardiac resynchronization therapy (CRT) devices.[21] The database contains over 100,000 implanted devices and device data for initial and replacement procedures are imported at scheduled intervals from multiple sources including device manufacturers, Paceart,[22] and Apollo.[23] Additionally, device data are integrated with the KP electronic medical record (EHR) to obtain patient characteristics and procedural characteristics.

The KP-CDR monitors four main endpoints associated with device and/or lead procedures:

- Early procedural complications
- Mechanical complications of the pulse generator
- "Premature" explant of a device
- Surgical site infections (SSI) occurring within 90 days

Role of adjudication in quality control and validation

There are data quality assurance processes to confirm completeness and accuracy of data elements in the KP-CDR. Ongoing quality control procedures carried out by automated algorithms flag patient and device data anomalies. Automated data quality checks correct duplicate implants, invalid model/serial numbers, conflicting patient identifiers, and incorrect surgeon or facility names. Despite these algorithms and quality control checks, approximately one third of implant procedures added to the KP-CDR require manual adjudication to resolve clinical data inconsistencies between the data sources.

Part II – Need for adjudication in the Postmarketing environment

At least two targeted efforts, FDA in collaboration with Mini-Sentinel and Observational Medical Outcomes Partnership (OMOP), have assessed the validity ascertaining select outcomes from real world evidence derived from administrative claims data. During year one of the Mini-Sentinel contract, from a list of approximately 100 potential Health Outcomes of Interest (HOIs), a subset of 20 HOIs were selected.[24] In addition to the health outcomes developed under the Mini-Sentinel contract, OMOP established an open-source library of 10 HOI definitions for use in observational studies.[25]

In the absence of validation studies supporting the accuracy of these outcomes, big data efforts need to incorporate adjudication into the endpoint ascertainment methodology. For example, the recent CMS National Coverage Determination (NCD) for Percutaneous Left Atrial Appendage Closure (LAAC) (20.34),[26] requires that the patient is enrolled in a prospective, national, audited registry that (1) consecutively enrolls LAAC patients and (2) tracks the following annual outcomes for each patient for a period of at least 4 years from the time of the LAAC: operator-specific complications; device-specific complications including device thrombosis; stroke (adjudicated by type); transient ischemic attack; systemic embolism; death; and major bleeding. It would be expected that an event adjudication process included in the analysis of this registry would enhance the accuracy and reliability of these event rates associated with LAAC procedures.

Beyond an assessment of clinical event rates, adjudication can evaluate the appropriateness of patient selection for selected therapies of interest. An analysis[27] of the American College of Cardiology–National Cardiovascular Data Registry's (ACC-NCDR) ICD Registry[28] showed that ICDs are implanted outside of evidence based guidelines 22.5% of the time. In contrast, a report from Kaiser Permanente[29] examined 2846 patients registered with the ACC-NCDR, of which only 701 patients (24.6%) met inclusion criteria. From this group, 62 patients (8.8%) were classified as having non-evidence based implants. After comprehensive chart review of these cases within the electronic health record (EHR), the authors found the criteria for appropriate ICD use were entered incorrectly and contradicted the data entered into the ACC-NCDR; the actual "non-evidence based" treatment was only 3.1% (22 patients).

The nationwide adoption of EHRs creates opportunities and challenges for the use of RWE to guide clinical and regulatory decision-making. Before RWE can be effectively utilized for these purposes, however, there needs to be standardized and accurate data collection processes that can be subjected to data quality checks. Event adjudication will likely continue to have a role in the assessment of medical technology based on EHR-derived data.

Conclusion

Endpoint adjudication has been critical to the assessment of the safety and efficacy of medical devices throughout the total product lifecycle. Independent adjudication of clinical outcomes limits bias related to inadequate blinding and lack of equipoise among some investigators. The use of a rigorously defined adjudication process plays an important role in assuring high quality study results. This includes stringent criteria to define the expertise required among CEC members, safeguards to promote the independence of the CEC, prospective definitions of the endpoints to be adjudicated, and established procedures used to make endpoint determinations. In addition, implementation of the adjudication processes need to be carried out with a rigor that would withstand review by study stakeholders.

The importance of independent adjudication of clinical endpoints for pre-market device approval studies is well-recognized, but post market data from medical device registries or other "big data" sources used for device surveillance will also often need independent adjudication in order to ensure the accurate assessment of clinical outcomes. While adjudication methods are generally well-established for pre-market studies, adjudication of post-market data may require different approaches depending on the scope of the clinical questions being addressed and size of the dataset. In all cases, a CEC charter is a critical document to assure that best practices are implemented for providing the most efficient and highest quality reporting of trial outcomes.

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