MDIC HEPV Initiative

Payer and HTA Perspectives on Real-World Evidence for Medical Devices

Final Report

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Main Sections

- Landscape Assessment
- RWE Interviews of Payers, HTAs, Selected Others
- Case Examples of RWE in Medical Device Coverage
- **Principles for Payer and HTA Use of Device RWE**
- Recommendations for Improving Development and Use of Device RWE

RWE Interviews

- 15 organizations represented:
  - CMS CAG
  - FDA CDRH (in its interactive role with CMS)
  - 4 Commercial/private sector payers
    - 1 also affiliated with national-level HTA function
  - 2 Integrated delivery networks
  - 1 Employer community
    - large employee benefits/brokerage consultancy to major US employers
  - 5 HTA organizations that generate reports used by public and private sector payers
    - includes 1 state government
  - 1 RWE methodologist/researcher in health technology
- Interviews conducted using interview guide (15 questions) prepared with input from MDIC RWE Work Group
  - Not all interviewees were able (or chose) to provide answers to all questions
  - Most interviews 60 minutes; one 45 minutes; one 90 minutes
- Consistent with requests of nearly all non-government interviewees, the names and organizations of interviewees are anonymized

Principles for Payer and HTA Use of Device RWE

Principles for Payer and HTA Use of Device RWE

Principles to help inform and educate payers and HTA bodies regarding how to evaluate and apply medical device RWE. Topics:

1. Recognize diverse RWE applications
2. Know study designs fit for purpose
3. Use best evidence approach
4. Recognize complementary roles of postmarket RWE and premarket evidence
5. Support high-quality registries
6. Incorporate selected non-traditional RWD
7. Consult existing guidance, frameworks, standards for RWD/RWE
8. Apply same quality standards to payer-sourced RWE
9. Enable early meetings with manufacturers
10. Explore appropriate implementation of unique device identifiers
11. Support and participate in RWD networks

1. Recognize diverse RWE applications (1)

RWE can be used in multiple ways to assess and otherwise support decision-making for medical devices in routine/community settings. RWE can help to answer such questions as:

- How do effectiveness (especially patient outcomes) and safety (adverse events and clinically meaningful side effects) in real-world/community care populations compare to those in pivotal clinical studies (e.g., RCTs, other controlled clinical trials, or other clinical studies conducted in ideal conditions)?
- To what extent are the patients in pivotal clinical trials representative of particular beneficiary populations (e.g., Medicare) that may be indicated for use of a device?
- How do effectiveness and safety vary between patients in pivotal clinical studies and particular patient subpopulations in real-world settings?
- To what extent do the demographic factors and risk factors of patients in pivotal clinical trials compare to those in a particular beneficiary population?
- How do effectiveness, safety, or other aspects of device performance vary according to delivery setting, provider type, or experience (e.g., number of procedures using the device)?

1. Recognize diverse RWE applications (2)

- What are the long-term effectiveness and safety (including incidence of rare or delayed adverse events)?
- Is there evidence of effectiveness and safety for patient indications beyond current labeled indications?
- What is the long-term durability of the device?
- Are there variations in the delivery of the device that offer potential quality improvements?
- What are the comparative costs to payers, patients, and/or society more broadly of using the device vs. standard of care for an episode of care or other clinically meaningful duration?
- For an outcomes-based/value-based purchasing arrangement, what is the actual utilization of a device intervention and attainment of a prespecified endpoint in the indicated patient population?
- How can real-world device experience be used to: modify device design or delivery, generate research hypotheses, inform the design of clinical trials and other studies, and inform more personalized and nuanced options for evidence-based clinical practice guidelines?

2. Know study designs fit for purpose (1)

RCTs are not the appropriate primary study designs for all evidence questions. Other study designs, including some that generate or draw from RWD, are preferred for certain evidence questions pertaining to, e.g.:

- Prognosis (no additional intervention): prospective cohort studies
- Risk factor identification: case control studies
- Diagnostic test accuracy: cross-sectional, cohort, or case control studies
- Complication rates of surgeries, other procedures: case series
- Incidence of rare or delayed adverse events: surveillance, registries
- Safety, effectiveness of incrementally modified technologies posing no known additional risk: registries

2. Know study designs fit for purpose (2)

Tools for rating the quality of particular study designs for generating RWD, and related documentation and reporting, include, e.g.:

- GRACE (observational studies)
- QUADAS-2 (diagnostic accuracy)
- QUIPS (prognosis)
- ROBINS-I (non-randomized studies)
- STARD (diagnostic accuracy)
- STaRT-RWE (real-world evidence)
- STROBE (observational studies in epidemiology)
- TREND (non-randomized studies)

In some instances, available RCTs of efficacy and safety are of low quality or have other limitations (e.g., small sample sizes, under-representation of patient populations of interest, insufficient duration). In such instances, RWE from large observational studies using claims, EHRs, registries, or other sources can represent the patient populations of interest, are of longer duration, and exhibit consistent, clinically meaningful treatment effects may be of greater value than the available evidence from RCTs.

3. Use best evidence approach (1)

The “best evidence approach” refers to using—and qualifying —the best quality evidence that is available for consideration, rather than relying solely on reports from study designs at the top of conventional evidence hierarchies, which are typically systematic reviews of RCTs or individual RCTs (for assessing outcomes of health care interventions).

- The best evidence approach allows for considering less rigorous study designs when evidence from more rigorous study designs is unavailable (or of poor quality, or less relevant to the population or care setting of interest), such as proceeding to evidence from clinical trials with nonrandomized controls, prospective observational studies, etc. Such moving down the traditional evidence hierarchies must still recognize and account for potential biases and confounders associated with these study designs.

3. Use best evidence approach (2)

- RWE from study designs other than RCTs can be particularly useful when weighing the tradeoffs of internal validity vs. external validity (or generalizability) of available evidence. Most conventional evidence hierarchies are ordered based on the internal validity of study designs to demonstrate cause-and-effect relationships for particular interventions, patient populations, and care settings. As such, their external validity may be limited.
- The best available evidence for a given insured or beneficiary population in community practice may not come from the optimal study type for internal validity. For example, large and consistent treatment effects in well-designed cohort studies of patients in real-world settings may provide more relevant and persuasive evidence than the findings of a weak or flawed RCT (e.g., with small sample size, inappropriate comparator, insufficient duration, unrepresentative of target population or setting) or when conducting RCTs may be impractical or unethical. In these instances, a combination of evidence from high-quality RCTs (where available) and observational RWE may be preferred.

4. Recognize complementary roles of postmarket RWE and premarket evidence (1)

RWE complements traditional premarket evidence of effectiveness and safety. The availability and increasing rigor of RWD are rebalancing the relative utility of premarket and postmarket evidence.

- Premarket evidence generated for market clearance or approval of devices for labeled indications can be limited regarding sample size, patient heterogeneity, duration of follow-up, care setting, and/or other factors. Certain accelerated approvals of devices and other regulated technologies may place further limitations on the usefulness or relevance of premarket data for informing payment decisions.

4. Recognize complementary roles of postmarket RWE and premarket evidence (2)

- Large observational RWD sources, digital applications for linking these, and related analytical tools are increasingly capable of filling these gaps, and extending evidence-based indications where warranted, by:
  - Accruing larger sample sizes
  - Increasing patient heterogeneity
  - Specifying standard-of-care and other comparators
  - Diversifying care settings
  - Extending follow-up
  - Detecting rare or delayed adverse events
- Some early work is being done on evaluating the concordance between RCTs and observational studies using claims and EHRs, and comparing the generalizability of RCT populations with the real-world target populations. Such concordance may increase credibility of RWE as complement to (though not substitute for) clinical trials. (See, e.g., Bartlett et al. 2019; Fralick et al., 2019.)

5. Support high-quality registries

Certain registries of medical and surgical procedures, devices, and diseases/conditions have become essential and well-qualified sources of RWE. However, there is great unmet potential of registries to support RWE to help inform coverage and other policies and decisions. Payers and HTA groups can contribute to the development, support, and/or use of registries.

- Such registries are sponsored by medical professional societies and collaborative arrangements, e.g., the American Academy of Ophthalmology, American College of Cardiology, American College of Radiology, American College of Surgeons, American Urological Association, Society of Thoracic Surgeons, integrated delivery networks (e.g., Kaiser Permanente National Implant Registries), industry, others.
- Guidelines/recommendations for high quality registries are available from, e.g., the Agency for Healthcare Research and Quality *(Registries for Evaluating Patient Outcomes: A User's Guide)*, Patient-Centered Outcomes Research Institute *(PCORI Methodology Report: Standards for Data Registries)*, Medical Device Registry Task Force, International Medical Device Regulators Forum *(Patient Registry: Essential Principles)*.

6. Incorporate selected non-traditional RWD

Payers and HTA groups can enhance and enrich the evidentiary bases of their assessments and decisions by recognizing and considering certain new, evolving, and other non-traditional sources for RWD.

- In addition to generally well-recognized sources of RWD (insurance/payment claims, EHRs, registries, and practical/or pragmatic clinical trials), various non-traditional sources are emerging as important for assessing real-world outcomes, or determinants or risk factors for real-world outcomes (including social determinants of health).
- Such sources include, e.g., laboratory test results; biobanks (tissues, liquid biopsies, other specimens); genomic and other molecular data; vital statistics; sociodemographic data; social determinants of health data (housing, food security, transportation, environmental, broadband internet access, etc.); and patient-generated data (from personal phone, computer apps, social media, etc.).

7. Consult existing guidance, frameworks, other standards for RWD and RWE (1)

Payers, HTA organizations, and other stakeholders can consult a growing set of credible resources for developing and assessing RWD and RWE. Although just a few of these focus specifically on medical devices, most address certain methodological and other aspects that apply across different types of health care technology.

Examples of principles and best practices for the design, conduct, and reporting of RWE:

- ISPOR/International Society for Pharmacoepidemiology (ISPE)/Duke-Margolis/National Pharmaceutical Council (NPC) Real-World Evidence Transparency Initiative; includes:
  - Improving Transparency to Build Trust in Real-World Secondary Data Studies for Hypothesis Testing—Why, What, and How: Recommendations and a Road Map from the Real-World Evidence Transparency Initiative (Orsini et al. 2020)
  - Structured Template and Reporting Tool for Real World Evidence (STaRT-RWE) (Wang et al., 2021)

7. Consult existing guidance, frameworks, other standards for RWD and RWE (2)

- Center for Medical Technology Policy (CMTP) Green Park Collaborative Effectiveness Guidance Documents (specific diseases and technologies) (2009-present)
- Innovative Medicines Initiative (IMI) GetReal Initiative

Examples of frameworks for assessing methodological rigor and quality of RWD and RWE:

- FDA Guidance Document: Use of Real-World Evidence to Support Regulatory Decision Making for Medical Devices (2017)
- Framework for FDA's Real-World Evidence Program (2018)
- MDIC - In Vitro Diagnostic (IVD) RWE Framework (2020)
- NESTcc Data Quality Framework (2020)
- NESTcc Research Methods Framework (2020)
- Organized Structure of Real-World Evidence Best Practices (Jaksa et al., 2021)

8. Apply same quality standards to payer-sourced RWE

Payers drawing on their own or other proprietary RWD (claims, EHRs, etc.) to derive RWE should apply the same principles/best practices for the design, conduct, and reporting of RWE that they would apply to RWE submitted from external sources (e.g., from manufacturers). Such principles/best practices would include, e.g.:

- Pre-registration of research protocols
- Appropriate study design for the evidence questions
- Adequate representation of target population
- Accounting for potential biases and confounders
- Accounting for data gaps
- Peer-review
- Transparency regarding sponsorship and potential conflicts of interest

9. Enable early meetings with device manufacturers

Early meetings of payers or HTA groups with manufacturers and collaborating researchers and innovators can improve the efficiency and utility of evidence generation. The main purpose of these meetings is to review mutual expectations and plans for premarket and/or postmarket evidence generation.

- Early meetings can address, e.g., the relative roles of pivotal (usually premarket) clinical studies and postmarket RWD, clinical and other study design and related aspects of methodological rigor, the use of RWD for control arms or standards of care in clinical studies, and sources and quality of RWD.
- Such early meetings can be conducted as early as product development, prior to regulatory clearance/approval, following regulatory clearance/approval, or subsequently regarding potential expansion of labeled indications.
- The exchanges conducted in these early meetings are for mutually beneficial awareness and typically are not binding on the participating parties.
- The ability of payers and HTA groups to conduct early meetings, and their scope and other conditions, are subject to applicable regulations and policies.

10. Explore appropriate implementation of unique device identifiers

The implementation of unique device identifiers (UDIs) in EHRs and claims can support generation of device model-specific, post-market evidence on real-world comparative effectiveness and safety and other RWD/RWE uses.*

- UDIs can improve the ability to distinguish devices for their effectiveness, safety, and other aspects of performance and quality, including for models of the same type of device from different manufacturers, as well as evolving device models from the same manufacturer.
- Broader implementation of UDIs can assist in reducing medical error and improving patient safety, timely device recalls, and other efficiencies in device-related health care management.
- Although FDA published a final rule in 2013 requiring manufacturers to include UDIs on medical device labels, and certain moves have been undertaken to provide for entry of UDIs into claims and EHRs, various hurdles to implementation remain.

*A UDI is a two-part code comprising: 1) a device identifier with manufacturer and model, and 2) a production identifier with, e.g., device lot number and expiration date.

11. Support and participate in RWD networks

Payers and HTA groups can benefit from participating in, or arrangements with, networks and other collaborations of organizations that compile and share RWD. Network RWD offers such advantages as larger sample sizes and greater representation of geographies, patient heterogeneity, and care settings, all of which can help to inform and shape coverage policies.

- The utility of these networks (sometimes in "federated" models) is enhanced when they can access multiple RWD types (claims, EHRs, pharmacy and laboratory data, registries, patient-generated data); have common data standards, data models, and terminology (e.g., for collecting and organizing demographic data, diagnoses, outcomes); enable linkages across data types; and conduct shared analyses.
- Examples of RWD networks and collaborations include:
  - NESTcc Research Network
  - FDA Sentinel
  - Observational Health Data Sciences and Informatics (OHDSI)
  - PCORnet
  - TriNetX
  - Clinerion

Selected References, Principles for Payer and HTA Use of Device RWE

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