Clinical Trial Innovation

Josh Chetta, PhD

Clinical Trials Program

Office of Device Evaluation, CDRH, FDA

Presentation Overview

Collecting High-Quality Clinical Evidence

- Investigational Device Exemption (IDE)
- Early Feasibility Studies
- Breakthrough Devices Program
- Real-World Evidence

Investigational Device Exemption (IDE)

Section 520(g) of the FD&C Act

*"It is the purpose of this subsection to encourage, to the extent consistent with the **protection of the public health and safety** and with ethical standards, the **discovery and development of useful devices** intended for human use and to that end to maintain optimum freedom for scientific investigators in their pursuit of that purpose."*

Investigational Device Exemption

- 21 CFR 812.1:

  *"An approved **investigational device exemption (IDE)** permits a device that otherwise would be required to comply with a performance standard or to have premarket approval to be **shipped lawfully** for the purpose of **conducting investigations** of that device."*

- An IDE is a **regulatory submission** that permits clinical investigation of devices.

Approved IDEs are Exempt from Regulations Pertaining to:

- Misbranding
- Registration
- Performance Standards
- 510(k)
- PMA
- HDE

- Good Manufacturing Practices (GMPs) except Design Controls
- Color Additive requirements
- Banned Devices
- Restricted Device requirements

21 CF 812.1

Applicability of IDE Regulations

- 21 CFR 812.2

Clinical Investigation to determine device safety and effectiveness

- New device or

  New use of legally marketed device ("off-label use")
- Possible Examples:
  - Sponsor-investigator/Academic studies - even if no marketing application planned
  - Study to gain initial safety and effectiveness information to support further study (e.g., feasibility study)
  - Manufacturer-sponsored study to support marketing application [PMA, HDE, 510(k) or de Novo]

Study Risk Classification

Study risk based on the **proposed use** of a device in an investigation, **NOT** the **device alone**

Significant Risk (SR)	*812.3(m) Full Requirements*	Requires Approval from FDA A significant risk ***device*** presents a **potential for serious risk to the health, safety, and welfare of a subject…**
Non-Significant Risk (NSR)	*812.2(b) Abbreviated Requirements*	No submission to FDA required. IRB review required.
Exempt	*812.2(c)*	No submission to FDA required. IRB review required. *Example – Commercial devices used in accordance with labeling*

IRB Role in Risk Determination

- **Sponsor** makes initial determination
- **IRB reviews** the sponsor's determination (21 CFR 812.2(b)(1)(ii))
  - Information provided by the sponsor includes device description, prior investigations, investigational plan, subject selection, risk assessment and rationale used in making its SR or NSR determination
- If the IRB disagrees with a sponsor's NSR assessment, the IRB must inform the clinical investigator, and where appropriate, the sponsor. (21 CFR 812.66)
- FDA is available to help and is final arbiter when IDE is submitted or if asked by sponsor, investigator, or IRB

Common Pitfalls for Submissions

- Inadequate detail regarding the **device or the methods** used in the study
- Inadequate **basic safety/performance** data
- Inadequate **justification** for why clinical data are truly needed at this stage.
- Inadequate **procedures** in place (or discussion of those procedures) to **maximize patient safety**
- Inadequate **informed consent** document

Early Feasibility Studies

Early Feasibility Studies (EFS)/ First in Human

- **Voluntary** program that allows **devices in an early stage of development** be evaluated in a **small human clinical study in the US**.

- Goals: To **provide patients in the US access to technology that may benefit them** & to encourage US innovation

EFS IDE

- EFS IDE - A standard IDE except…
  - There are significant unknowns about how the device will perform
    - Device is generally early in development or
    - Device has a new intended use

- Small number of subjects in the clinical investigation
  - Initial evaluation of safety and/or effectiveness

EFS Process

EFS is an informal designation

- Processes are normal except…
  - You may work with an **EFS representative** informally to prepare for the first submission
  - FDA review teams may interact more

- Submissions are normal except…
  - They may contain **significant detail regarding risks** and how they will be mitigated
  - Less nonclinical testing may be needed
  - Mechanisms to accommodate expected device iteration

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Breakthrough Devices Program

Breakthrough Devices Program

- Voluntary program for certain medical devices that provide for **more effective treatment** or **diagnosis** of **life-threatening or irreversibly debilitating diseases or conditions**.

Breakthrough Devices Program

- Previous Final Guidance on Expedited Access Pathway

- 21st Century Cures Act codified Breakthrough Devices Program (Sec. 3051)

Priority Review | **EAP** | **Innovation Pathway**

→ **Breakthrough Device**

Expedited Access for Premarket Approval and *De Novo* Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions

Guidance for Industry and Food and Drug Administration Staff

Document issued on April 13, 2015.

The draft of this document was issued on April 23, 2014.

Breakthrough Devices Program

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.

Document issued on October 25, 2017.

Breakthrough Eligibility

Devices subject to PMA, De Novo and 510(k) that:

- 1: “provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease or conditions; and

- 2A: that represent **breakthrough technologies**; or
- 2B: for which **no approved or cleared alternatives** exist; or
- 2C: that offer **significant advantages over existing** approved or cleared **alternatives**, including the potential, compared to existing approved alternatives, to reduce or eliminate the need for hospitalization, improve patient quality of life, facilitate patients’ ability to manage their own care (such as through self-directed personal assistance), or establish long-term clinical efficiencies; or
- 2D: the availability of which is in the **best interest of patients**.”

Priorities for Program

Interaction, collaboration, and prioritization

- High level of interaction between FDA and sponsor
- Senior management involvement
- Maximize predictability and shared problem-solving

Tailored approach to expedite development and review

Flexibility

- Acceptable level of uncertainty considering benefits and risks
- Pre-post market balance

Innovation

- Innovative trial designs
- Patient perspectives
- Real-world evidence

Designation Process

- Sponsor should submit request for Breakthrough Designation as a Q-Submission
  - Include adequate device description and background information
  - Justification for designation – address each eligibility criterion

- FDA intends to interact with Sponsor by day 30 to request additional information interactively

- Final decision on Designation Request issued within 60 calendar days

Real World Data and Real World Evidence

Guidance Document

Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

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Guidance for Industry and Food and Drug Administration Staff

Document issued on August 31, 2017.

Definitions from the Guidance

Real-World Data (RWD)

Data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources

Real-World Evidence (RWE)

Clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD

Turning Data into Evidence

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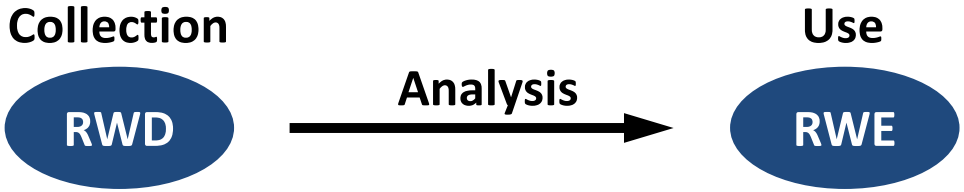
Clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD



Guidance addresses issues related to processes of:

- Generation and collection of RWD
- Analysis of RWD
- When results might be considered valid scientific evidence

Data Quality

'Fit for Purpose'

Data should be assessed for completeness, consistency, accuracy, and whether it contains all critical data elements needed to evaluate a medical device and its claims.

Relevant & Reliable

Benefit

Risk

Safety

…probable benefits to health from use of the device *outweigh any probable risks? [860.7(d)(1)]*

Effectiveness

…the use of the device in the target population will provide *clinically significant results? [860.7(e)(1)]*

Characteristics for RWE Evaluation – Relevance –

The data adequately addresses the applicable regulatory question or requirement.

- Examples of factors to be evaluated:
  - Appropriate variables collected, e.g. device exposure.
  - Endpoint definitions consistent and meaningful.
  - Assessment schedule captures endpoints of interest.
  - Population is appropriate and representative.
  - Study protocol and/or analysis plan appropriate for question.

Characteristics for RWE Evaluation – Reliability –

Reliability includes factors related to overall data quality

- Data Accrual
  - Data sources and technical data capture methods
  - Patient selection
  - Patient protections
- Data Assurance - Quality Control
  - People and processes in place during data collection and analysis to minimize errors and ensure integrity.
    - Data source verification procedures
    - Data completeness and consistency
    - Evaluation of on-going training programs

Conclusions

- Contact us with Questions!
  - CDRHClinicalEvidence@fda.hhs.gov

- CDRH is committed to ensuring that patients have access to safe and effective medical devices.
- The Breakthrough Devices Program and Real World Evidence Guidance Document are part of the Center's efforts to support innovation in medical devices while ensuring adequate protection of patients and study subjects.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