

What is an IDE?

AdvaMed IDE Submissions Workshop

May 18, 2023

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What is an IDE?



- **Regulatory Context**
- When is an IDE needed?
- Roles of sponsors, investigators and IRBs
- The IDE Application and Helpful Tips

Patients Are at the Heart of What We Do



CDRH Vision: Patients in the U.S. have access to high-quality, safe, and effective medical devices of public health importance first in the world



Exemption for Devices for Investigational Use

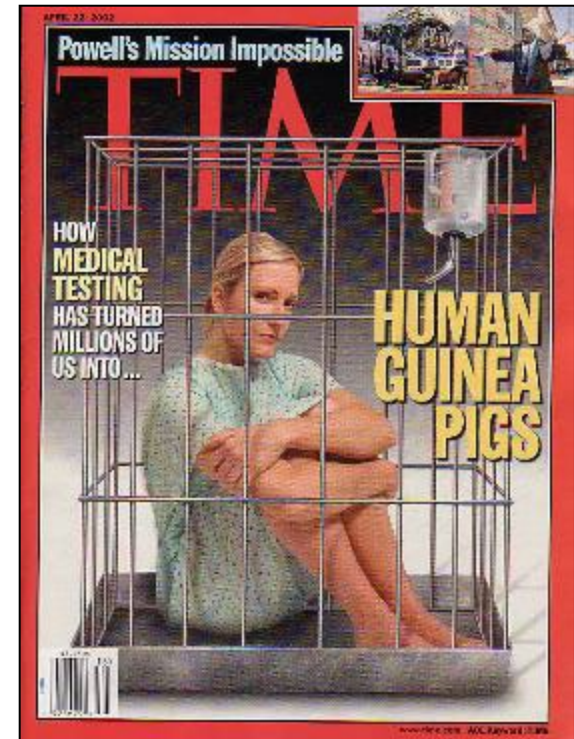
“It is the purpose of this subsection to encourage, to the extent consistent with the **protection of the public health and safety** and with ethical standards, the **discovery and development** of useful devices intended for human use and to that end to **maintain optimum freedom for scientific investigators**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

Ref: Section 520(g) of the Federal Food Drug and Cosmetic Act



What is the challenge?

Physicians and patients want access to the latest technologies, especially when there are unmet needs...



... but all research should include the appropriate human subject protections.

Clinical Trial Regulations

21 CFR Parts

812 - Investigational Device Exemptions

50 - Protection for Human Subjects

54 - Financial Disclosure of Investigators

56 - Institutional Review Boards (IRBs)

11 - Electronic Records and Signatures

45 CFR Part

46 – Protection of Human Subjects (HHS)

42 CFR Part

11 - Clinical Trials Registration and Results



Investigational Device Exemption

- FDA approval of an IDE is required for US human study of a significant risk device which does not have marketing authorization for the indication being studied.
- Exempts sponsor from certain provisions of FD&C Act (e.g., requirement for a marketing application, compliance with full Good Manufacturing Practice (GMP) regulations).
- Specifies requirements for informed consent, labeling, monitoring of the study, records/reporting
- Initiation of the study requires approval by Institutional Review Board (IRB)

Provisions of the IDE Regulation

- ✓ Describes **applicability** of the IDE regulations
- ✓ Provides **administrative** information
- ✓ Outlines the contents of the **IDE application**
- ✓ Describes **FDA actions** on IDE applications
- ✓ Assigns **responsibilities** to all participants in clinical investigations

What is an IDE?

- Regulatory Context
- **When is an IDE needed?**
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- The IDE Application and Helpful Tips





Poll Question!

When is an IDE needed?

- For any new use of an already approved medical device on a patient within the context of a health care practitioner-patient relationship.
- Only for medical device clinical studies that are meant to support a marketing submission (e.g., PMA or 510(k)) to the FDA.
- For all medical device clinical studies using an unapproved medical device or a new use of an approved device.
- For significant risk medical device clinical studies using an unapproved medical device or a new use of an approved device.



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“Practice of Medicine”

“Nothing in this Act shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any **legally marketed** device to a patient for any condition or disease **within a legitimate health care practitioner-patient relationship....”**



“Practice of Medicine”

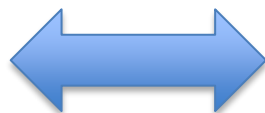
- Not an investigation/study
- Physician should:
 - Be well informed about the product
 - Use firm scientific rationale and sound medical evidence
 - Maintain records on use and effects



- **IDE not required**; institution may require IRB review/approval and informed consent
- Other prohibitions still apply

Types of Studies

- Unapproved device
- Approved device for a **new indication** (“off-label” use)
- Manufacturer-sponsored vs. Academic-sponsored
 - Intent to market?



Types of Studies

Feasibility Study

- Capture preliminary safety and effectiveness data in a small number of subjects
- **Early:** Inform device design
- **Traditional:** Inform design of pivotal study

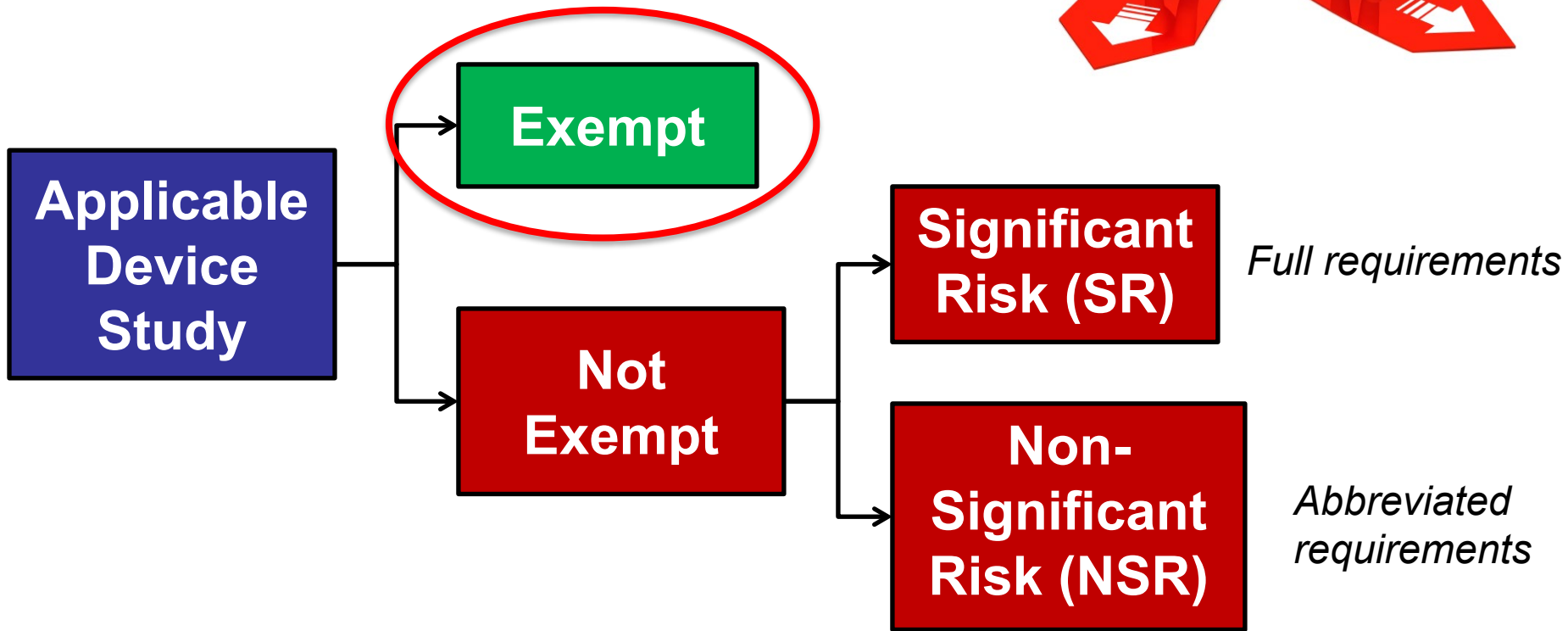
Pivotal Study

- Collect definitive evidence on safety and effectiveness for a specified intended use, typically in a statistically justified number of subjects



[IDEs for Early Feasibility Medical Device Studies, Including Certain First in Human Studies](#)

When is an IDE needed?



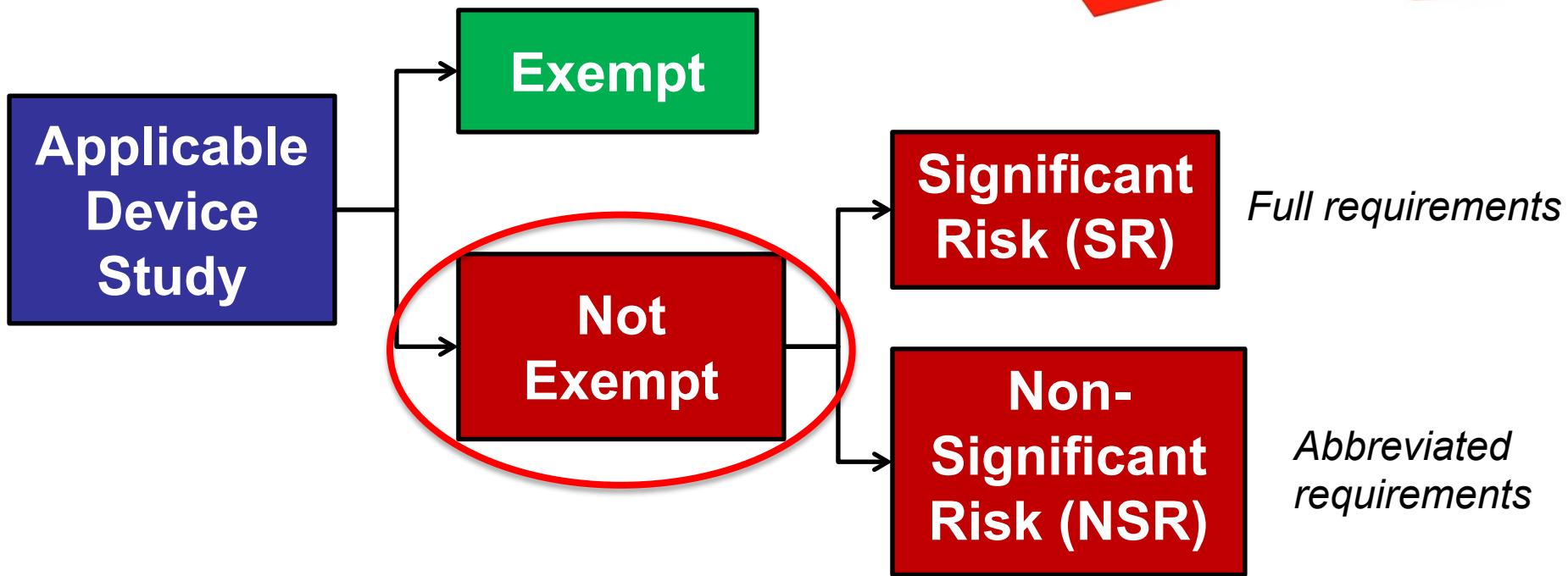


Exempt Studies

No IDE Needed

- Commercial devices used in accordance with labeling
- Certain diagnostic devices
- Testing of consumer preferences, of a modification, or of a combination of devices
 - if not for the purpose of determining safety or effectiveness and not putting subjects at risk
- Veterinary devices
- Research on/with laboratory animals
- Custom devices as defined in 21 CFR 812.3(b)

When is an IDE needed?



Not Exempt Studies

No IDE Needed



Non-Significant Risk:

- Abbreviated IDE requirements:
 - Labeling (21 CFR 812.5)
 - IRB Approval (21 CFR Part 56)
 - Informed Consent (21 CFR Part 50)
 - Monitoring (21 CFR 812.46)
 - Records and Reports (21 CFR 812.140(b)(4)-(5), 812.150(b)(1)-(3) & (5)-(10))
 - Annual and Final Progress Report submission to FDA is not required
 - Promotion (21 CFR 812.7)
- IRB serves as the FDA's surrogate for review, approval, and continuing review of the NSR device studies.
- An NSR device study may start at the institution as soon as the IRB reviews and approves the study.

Not Exempt Studies

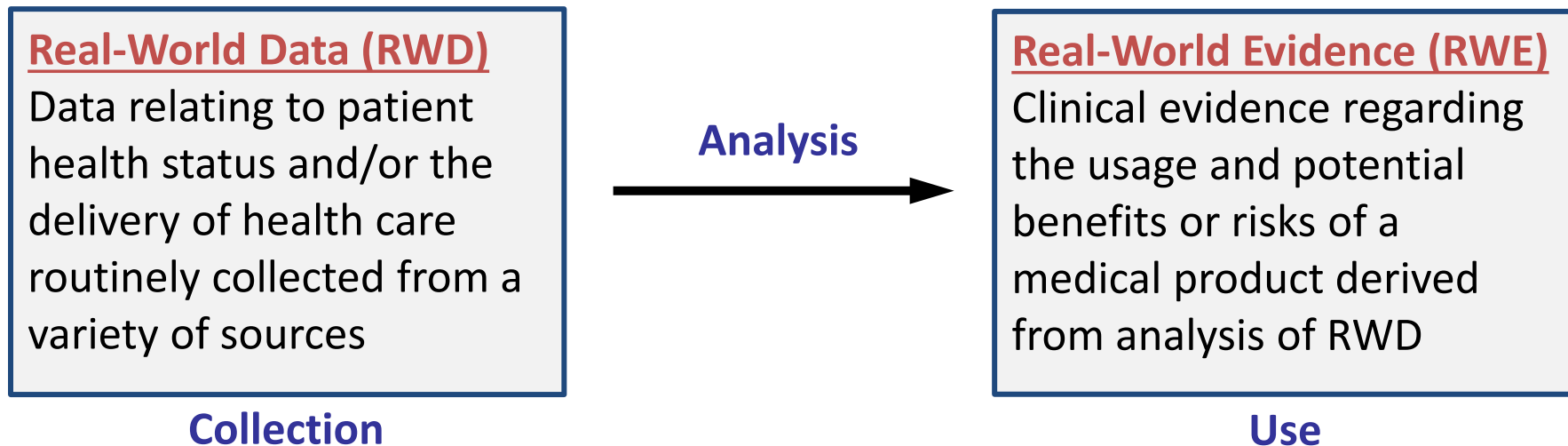
IDE Needed



Significant Risk:

- **Full IDE** requirements apply
- Presents a **potential for serious risk to the health, safety, and welfare of a subject** and is:
 - an implant; or
 - used in supporting or sustaining human life; or
 - of substantial importance in diagnosing, curing, mitigating, or treating disease or preventing impairment of human health; or
 - otherwise poses potential for serious risk
- Sponsor submits IDE application to FDA; decision rendered within 30 days
- After **both FDA and IRB** approve the investigation, study may begin

IDEs and Collection of Real World Data



- The FDA regulations 21 CFR 50, 56, and 812 apply to all clinical investigations of devices to determine safety and effectiveness, with limited exceptions.
 - If the approved or cleared device is used in the normal course of medical practice, an IDE would likely not be required.
 - An IDE may be required when RWD collection that is intended to determine safety and effectiveness of a medical device influences patient treatment decisions



[Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices](#)

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 an 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**



Requests for Study Risk Determination



- Sponsor submits “Study Risk Determination” Q-Submission
 - Cover letter, Device Description, Protocol
- FDA issues letter indicating if study is:
 - Significant Risk (not exempt)
 - Non Significant Risk (not exempt)
 - Exempt
- FDA is final arbiter; IRB does not need to conduct an independent assessment of risk



[Significant Risk and Nonsignificant Risk Medical Device Studies](#)



[Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program](#)

What is an IDE?

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- **Roles of sponsors, investigators and IRBs**
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Key Players

- **Sponsor:** initiates, but does not actually conduct, the investigation
- **Investigator:** conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject
- **Institutional Review Board (IRB):** reviews, approves (initially and continuing) biomedical research at a given institution



Sponsor Responsibilities

21 CFR 812 Subparts A,C



- Obtain **IRB and FDA** review and approval
 - For study initiation and for resumption of terminated studies
 - IDE application and supplements
 - Keep IRB and FDA informed of significant new information
- Ensure proper **monitoring**
 - Select appropriate monitors
 - Secure compliance; evaluate and handle unanticipated adverse device effects
- Select qualified **investigators** and provide them with information they need
 - Obtain investigator agreements
- Control **devices**
- **Comply** with labeling, prohibition of promotion, import and export requirements (Subpart A).

Sponsor Responsibilities (cont'd)



21 CFR 812 Subpart G

- Maintain adequate **records**
 - Correspondence
 - Investigator Agreements
 - Device Disposition
 - Adverse effects and complaints
- Grant **inspections** to FDA (establishments and records)
- Prepare and submit **reports**
 - Unanticipated adverse device effects
 - Withdrawal of IRB Approval
 - Current Investigator list
 - Progress reports
 - Recall and device disposition
 - Final report
 - Failure to obtain informed consent
 - Significant risk device determinations

Investigator Responsibilities

21 CFR 812 Subpart E



- **Conduct investigation** per signed agreement, investigational plan, FDA regulations and conditions of approval
- **Control** of investigational **devices**
 - Supervise device use, appropriate disposal
- Obtain appropriate **informed consent**
- **Protect** rights, safety, and welfare of **subjects** under care

Investigator Responsibilities (cont'd)

21 CFR 812 Subpart G

- Maintain adequate **records**
 - Correspondence
 - Subject case history
 - Case report forms, consent, medical records
 - Device Disposition
 - Adverse effects and complaints
 - Protocol
- Grant **inspections** to FDA (establishments and records)
- Prepare and submit **reports** (to sponsor, IRB)
 - Unanticipated adverse device effects
 - Withdrawal of IRB Approval
 - Progress reports
 - Protocol deviations
 - Final report
 - Failure to obtain informed consent

Institutional Review Boards

21 CFR 56



- **Purpose:** to protect the rights and welfare of human subjects involved in FDA-regulated investigations and investigations that support applications for research (e.g. IDEs) or marketing permits
 - Jurisdiction, Risk determination, Review of protocols and informed consent, Review of changes to protocols, Continuing review
- IRB **registration** is required
- **Composition:** sufficiently qualified and diverse
- An IRB must comply with the IRB (Part 56) and IDE (Part 812) regulations
- FDA does periodic **inspections** of the IRB's records and procedures to determine compliance with the regulations

FDA Submissions after Approval

- **Reports** (21 CFR 812.150)
 - Annual progress
 - Unanticipated adverse device effects
 - Enrollment and follow-up completion
 - Withdrawal of IRB or FDA approval
 - Current list of investigators
 - Final report



[Changes or Modifications During the Conduct of a Clinical Investigation Guidance](#)

- **Supplements** (21 CFR 812.35)
 - Change in protocol
 - Change in device

What is an IDE?

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- Roles of sponsors, investigators and IRBs
- **The IDE Application and Helpful Tips**



The IDE Application (21 CFR 812.20)



- Name and address of sponsor
- Report of prior investigations (21 CFR 812.27) and investigational plan (21 CFR 812.25)
- Manufacturing, processing, packing, and storage of device
- Investigator agreement (example, listing, certification)
- List of the name, address, and chairperson of each IRB
- Participating institutions
- Charge for device
- Environmental assessment
- Labeling
- Subject materials including informed consent
- Additional information requested by FDA

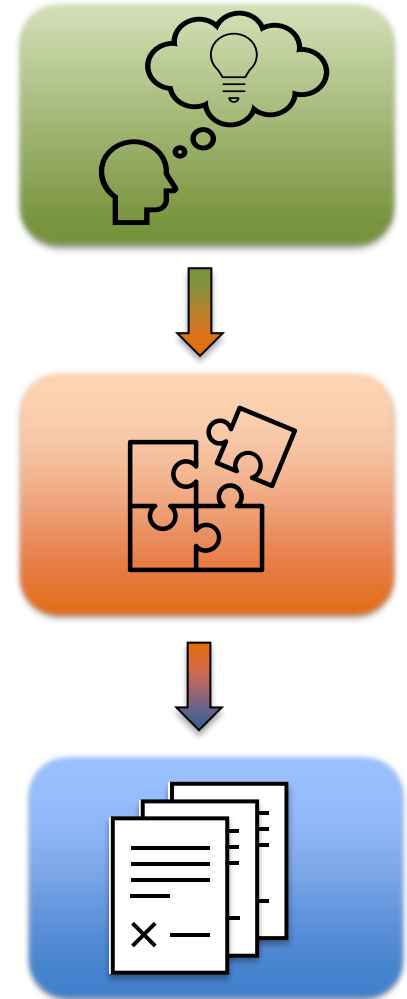


Tips for Successful IDE Submissions



IDE Application:

- **Organize** clearly (e.g., use a master table of contents with continuous numbering and separate sections)
- Ensure all required elements are included
 - Reference [checklist on Device Advice](#)
- Be **consistent** throughout submission
- Address previous FDA submissions, interactions, and feedback
- **“Tell the Story”**
 - Focus on “why” in addition to “what”
 - Provide rationale for adequacy of data provided



Be prepared and available to respond interactively during the **30-day** FDA review clock


FDA Review of the Application



FDA sends acknowledgement with IDE number: GYYxxxxx (e.g. G230001)



IDE sent to appropriate review division based on intended use



Lead reviewer assembles team of experts to review the application and make decision recommendation with management concurrence within 30 days



FDA issues a decision letter to the sponsor

Evaluating Benefits and Risks

- All IDE studies involve risk
- FDA may request additional information or modifications to protect subjects
- Prohibiting the investigation may also delay potential benefits of the technology for subjects in the study and future patients (a different kind of risk)
- Sponsor should mitigate risks to a level that allows a study to begin when appropriate



[Factors to Consider When Making Benefit-Risk Determinations for Medical Device IDEs](#)

FDA Decisions and Letters



Decisions:

✓ Approval


- Approves the trial for specified number of sites and subjects
- Enrollment can begin once IRB approval is obtained

✓ Approval with conditions

- Approves the trial for specified number of sites and subjects, provided conditions (deficiencies) are addressed within 45 days
- Enrollment can begin once IRB approval is obtained

✗ Disapproval

- Study may not begin
- Deficiencies will be listed
- Sponsor must address deficiencies and obtain FDA approval to start study



- **Decision**
 - Fully Approved
 - Approved with Conditions
 - Disapproved
- **Considerations (if applicable)**
 - Study Design Considerations & Future Considerations
 - Recommendations for current study or future marketing application
 - **Not required to be addressed**
- **Deficiencies**
 - If other than Full Approval
 - **Required to be addressed**

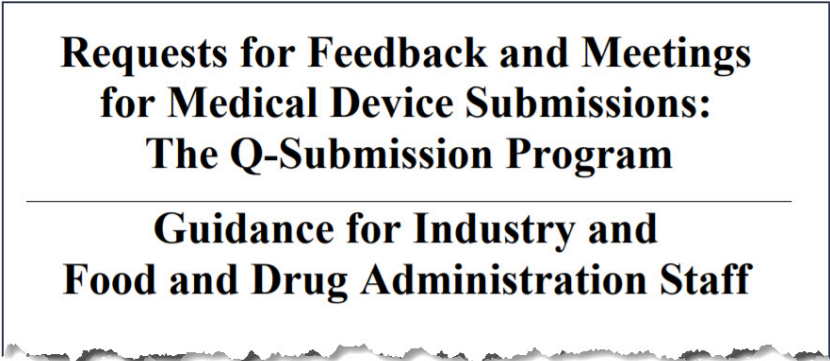


[FDA Decisions for Investigational Device Exemption \(IDE\)](#)
[Clinical Investigations Guidance](#)

Mechanisms for Feedback from FDA

Q-submission Program:

- Study Risk Determination
- Informational Meeting
 - No expectation of feedback
- Submission Issue Request
- Pre-Submission
 - Request for feedback from FDA in the form of a written response or meeting on specific questions



➤ Review relevant guidance and internet resources



[Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program](#)

In Summary

- IDE statute and regulations encourage discovery and development of medical devices while protecting public health and safety
- An approved IDE application is needed to conduct a significant risk study of an unapproved device or new use of an approved device
- Submission and review of a significant risk study under an IDE is subject to full IDE regulatory requirements, which are ongoing for the life of the IDE study, until officially closed
- There are many opportunities available to receive feedback from and interact with the FDA before, during, and after submission of an IDE Application.

Industry Education Resources

1. CDRH Learn – Multi-Media Industry Education

- over 80 modules
- videos, audio recordings, power point presentations, software-based “how to” modules
- mobile-friendly - access CDRH Learn on your portable devices

<http://www.fda.gov/Training/CDRHLearn>

2. Device Advice – Text-Based Education

- comprehensive regulatory information on premarket and postmarket topics

www.fda.gov/MedicalDevices/DeviceRegulationandGuidance

3. Division of Industry and Consumer Education (DICE)

- Contact DICE if you have a question
- Email: DICE@fda.hhs.gov
- Phone: 1(800) 638-2014 or (301) 796-7100

<https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice>

Questions?



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Strategy and Planning

***IDE Submissions Workshop
May 18-19, 2023***

Tony Blank
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Topics

- Early Considerations
 - Market objectives
 - Patient populations
 - Criteria for success and failure
- Preclinical testing before human studies
- Making the best use of pre-Sub meetings
- Using foreign data in a US submission
- What makes an IDE submission successful

Early Considerations

- Market Objectives
 - What is the desired patient population?
 - Size?
 - Accessibility?
 - Willingness / ability to participate?
 - Clinical performance necessary to achieve success?
 - New treatment?
 - Competitive devices / treatments?
 - Reimbursement considerations?
- Patient Population
 - Identification of population for initial study
 - Homogeneity (risk, response to treatment, etc.)
 - Ease of enrollment
 - Scope for initial marketing efforts

Early Considerations (cont'd)

- Criteria for Success and Failure
 - Objective measures of outcomes
 - Complexity of measurement
 - Consistency with clinical practice
 - Clinical relevance
 - Minimum level of performance to demonstrate safety and/or effectiveness.
 - Minimum level of performance to achieve market objectives
- Taking the long view
 - Long term objective of program? (e.g., indications, iterations, etc.)
 - Securing follow-up?
 - Reporting results

Preclinical Testing

- Bench
 - Standards and/or Guidance
 - Connection to identified failure modes
 - Devices in OUS markets
 - Competitive products
 - Representative devices (sizes, materials, mfg, etc.)
 - Identifying limits of design
- Biocompatibility
 - ISO 10993
 - Guidance
- Animal Testing
 - Known models and limitations
 - Clear objectives of testing
 - GLP?

Definition of a Pre-Submission

- » A formal written request from an applicant for feedback from FDA provided in the form of:
 - a formal written response or
 - a meeting or teleconference in which the feedback is documented in meeting minutes
- » When FDA's feedback on specific questions is necessary to guide product development and/or application preparation (i.e., prior to intended submission of an IDE or marketing application)
- » Request **must include specific questions** regarding review issues relevant to a planned IDE or marketing application (e.g., questions regarding pre-clinical and clinical testing protocols or data requirements).

Pre-Submission

- » Intended to be specific to the questions posed
 - however, if other deficiencies or concerns are noted during review, they may be included in FDA's feedback.
- » Generally meant to be a one-time process per topic (i.e., not iterative)
 - but can be utilized at different times and/or for multiple topics for the same device (e.g., prior to IDE submission for bench testing and clinical protocols, then prior to PMA submission regarding data presentation).
 - If significant changes are made to sponsor's proposal in response to initial FDA feedback, may be appropriate to engage in repeat interaction on the same topic.

When should I Submit a Pre-Sub?

- » Voluntary, but encouraged
- » Prior to initiating long term preclinical studies
- » When planning a study that does not require an IDE
 - Studies that are outside the US, exempt, or NSR
- » Before submission of an IDE to:
 - Discuss nonclinical data and clinical study design
- » Before submission of a marketing application to:
 - Apprise FDA review team on specifics of device and clinical study if there have been changes since initiation of the IDE
 - Obtain feedback on preferred data presentation
 - Gain insight into potential hurdles for approval or clearance
- » When preparing a submission for a new device that does not clearly fall within an established regulatory pathway

Timelines

Q-Sub Type	Method of Feedback	Timeframe for Sending Feedback or Scheduling Meeting (from receipt of submission)
Pre-Submission	Meeting (face-to-face or teleconference) with written feedback provided in advance	Written Feedback: 70 days or 5 days prior to scheduled meeting, whichever is sooner Meeting: Date based on mutual agreement (typically at 60-75 days)
	Written Feedback Only	70 days

Guidance Document:
<https://www.fda.gov/media/114034/download>

Foreign Data

- Sources of OUS clinical data
 - Previous clinical studies
 - Marketing of product
 - Data from OUS sites of a Global study
- Considerations
 - Similarities of devices (e.g., design, manufacture, labeling)
 - Variations in clinical practice
 - Differences in patient populations
 - Clinical experience (e.g., complaints, field actions, etc.)
 - Training requirements

Foreign Data

- Possible uses of existing foreign clinical data
 - Supportive of protocol design
 - Endpoints
 - Performance Criteria
 - Patient follow-up (schedule, methods)
 - Identification of anticipated adverse events
 - Incorporation into statistical analysis plan

A successful IDE Application

- A clear narrative which takes the reader through design characteristics to intended clinical use.
- Include documentation and summary of pre-IDE interactions (including agreements and considerations).
- Include all preclinical test reports (not just summaries).
- Clearly presented design of the proposed study.
 - Objective(s) – Primary and Secondary
 - Outcome measurements and necessary justifications
 - Clinical Protocol (including CRFs)
 - Representative IC
 - Statistical Analysis Plan inclusive of all prespecified analyses

A successful IDE Application

- Do not try to limit data presentations to just the 'good data'. Demonstrate scientific and ethical integrity and address up front.
- Be prepared to respond to questions from the reviewer very quickly. *(Don't send the team on a two-week vacation after the IDE Application goes in!)*
- Help FDA plan for the workload – provide a view during the pre-IDE process of when the application is likely to come in.
- Think about timing of application...
 - FDA has 30 days to make a decision
 - Submitting the application on Dec 15th probably is not the ideal choice.

Thank you!

Questions?

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THANK YOU!

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Preparing the Technical and Functional
Aspects of an IDE
AdvaMed IDE Workshop

May 18, 2023

Agenda

- Elements of an IDE
- Avoiding common errors and deficiencies
- The role of risk analysis in an IDE
- Managing planned or unplanned device or study changes

IDE Submissions: What to Consider and When

IDE Study Considerations – Strategic Decisions

- Proposed indications for use – careful selection of study patient population and endpoints
- Manufacturing – where to conduct
- Preclinical testing – choice of testing, where to perform
- Global clinical trial strategy
- Protocol development with KOL involvement – also consider reimbursement
- Clinical investigator and site selection
- Study monitors – selection of, development of monitoring plan
- Database management and data analysis – by company or CRO
- Consider external study units – *e.g.*, DMC, CEC, core laboratories
- Logistical planning – timing of pre-submission, IDE approval, IRB approvals, clinical trial agreements, patient recruitment, follow-up, etc.

FDA Implementation of Good Clinical Practices (GCPs)

- GCPs do not have a single dedicated regulation, but encompass several regulations:
 - 21 CFR 11 – Electronic Records and Signatures
 - 21 CFR 50 – Protection of Human Subjects
 - 21 CFR 54 – Financial Disclosure
 - 21 CFR 56 – Institutional Review Boards
 - 21 CFR 812 – Investigational Device Exemptions
 - 21 CFR 814 – Premarket Approval of Medical Devices

Good Clinical Practices (GCPs)

- Sponsors must implement GCPs in device clinical research
 - IRB-approved protocol
 - Valid informed consent
 - Monitoring plan
 - Adverse device effect reporting [Adverse event (AE) or Serious adverse event (SAE)]
 - Proper documentation
 - Valid data collection/reporting procedures

IDE Contents

Assess Readiness to Conduct IDE Study

- IDE Applications often take considerable time to compile
 - Finalize device description and manufacturing information
 - Plan and complete pre-clinical studies
 - Design pilot or pivotal study, consulting with Key Opinion Leaders (KOLs) in the specific field
 - Plan for external study units (Clinical Events Committee, CROs, etc.)
 - IRBs and investigators do not have to be chosen at the time of IDE submission, but sponsors should have a general idea
 - Prepare actual IDE Submission
- Data and level of detail can vary
 - FIH, EFS, pilot, pivotal study, post-market study (for new indication)

Definitions

- **First in Human (FIH):** A first in human study is a type of study in which a device for a specific indication is evaluated for the first time in human subjects.
- **Early Feasibility:** An early feasibility study is a limited clinical investigation of a device early in development, typically before the device design has been finalized, for a specific indication (e.g. innovative device for a new or established intended use, marketed device for a novel clinical application).
- **Traditional Feasibility:** A traditional feasibility study is a clinical investigation that is commonly used to capture preliminary safety and effectiveness information on a near-final or final device design to adequately plan an appropriate pivotal study.
- **Pivotal Study:** A pivotal study is a clinical investigation designed to collect definitive evidence of the safety and effectiveness of a device for a specified intended use, typically in a statistically justified number of subjects.

Overview of IDE Application Contents (§812.20)

- No user fee
- Report of previous investigations (§812.27)
- Device description
- Investigational plan (§812.25)
- Description of methods/controls/facilities for manufacturing, processing, packing and storage of device
- Sample investigator agreement
- Certification that all investigators will sign agreement
- List of IRBs, institutions, and investigators
- Justification for amount charged for device

Overview of IDE Application Contents (§812.20) (cont'd)

- Labeling (§812.5)
- Sample Informed consent forms (§50)
- Sample case report forms

Report of Prior Investigations

- Preclinical test reports - biocompatibility, laboratory/ bench, animal
 - Describe level of compliance with GLPs
- Bibliography of all publications
- Copies of all published/unpublished adverse information
- Summary of all other unpublished information (*e.g.*, clinical studies), including adverse events
- Describe Level of Compliance with Good Laboratory Practices

Labeling

- Adequate directions for use
- Caution Statement:
 - “Caution - Investigational Device, Limited by Federal (or United States) Law to Investigational Use.”
- Cannot be promoted as safe/effective for investigational use

Investigational Plan

- Purpose
- Protocol
- Risk analysis
- Device description
- Monitoring procedure
- Labeling
- Case report forms (CRFs)
- IRB information
- Other institutions
- Additional records/reports

Informed Consent

- Include all material
- No exculpatory language
- Emphasis that participation is voluntary
- Reading level to be considered
- Required elements

Required Elements for Informed Consent

- Study involves research
- Purpose
- Duration
- Procedures
- Experimental procedures
- Risks/discomforts
- Benefits
- Alternative procedures
- Confidentiality
- Compensation/ treatment for injury
- Contact for subject's rights/inquiries
- Participation voluntary

New requirement – Effective March 2011 – the following statement is required in informed consent:

“A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.”

Additional Elements of Informed Consent

- Risk to embryo/fetus
- Termination of participation without consent
- Additional costs
- Consequences/procedures for withdrawal from study
- Significant new findings

Protocol Considerations

Feasibility Studies (Pilot Studies)

- Open-label, usually uncontrolled
- Small number of sites/subjects
- Initial evaluation of safety
- Preliminary evaluation of endpoints
- Conduct inside or outside U.S.
- Data not considered pivotal evidence for safety/effectiveness
- See relevant FDA guidance at:
<http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm279103.pdf>

Pivotal Studies

- Randomized
- Multicenter
- Double-blind (if possible)
- Controlled
 - Active treatment or placebo/sham
- Sample size based on statistical calculation
- Conduct mostly in U.S.
 - Reviewer willingness to accept OUS data is case specific (branch, device, novelty, risk, etc.)
- Pivotal evidence for safety/effectiveness
 - Primary and secondary endpoints

Protocol Elements

1. *Objectives* - clearly specify the proposed claim and objective(s) of the study
2. *Type of Trial* - describe the overall design of the clinical trial (e.g., superiority or non-inferiority, parallel or crossover, etc.)
3. *Endpoints* - describe the primary and secondary endpoints with particularity
4. *Patient Population* - describe the population to be studied, enumerating all inclusion and exclusion criteria
5. *Investigational Device* - describe the device to be studied and how the treatment will be administered with the device
6. *Control* - describe the nature of the control to be used in the study (e.g., randomized, historical, or patient as own control)
7. *Assignment of Patients* - state how patients will be assigned to each study group (e.g., via randomization)
8. *Sample Size* - provide a statistical justification for the number of subjects planned to be enrolled

Protocol Elements (continued)

9. *Study Procedures* - enumerate all procedures, examinations and other evaluations to be conducted at each visit
10. *Study Assessments* - specify safety and efficacy parameters, including methods and timing
11. *Study Duration* - state projected length of recruitment and expected length of patient follow-up
12. *Adverse Device Effects* - enumerate the nature and frequency of all anticipated adverse device effects
13. *Data Analysis* - prospectively formulate a data analysis plan, including the statistical methods
 - Note, FDA will want to see ITT as well as PP data
14. *Study Monitoring* - describe the procedures for monitoring patient and investigator compliance

Control Examples

- Active control: standard of care treatment
 - Older versions of the same device
 - Different approved device
 - Not another investigational device
- Sham/placebo device
- Patient as own control
- No therapy
- Historical controls
 - Same study population (eligibility criteria) as experimental group?
 - Same treatment as a concurrent control group would receive?
 - Same concomitant care and follow-up as experimental group?
 - Same information available?
 - Availability of raw data?
 - Selected in unbiased manner (chart review, published literature, unpublished data, etc.)?

IDE Statistical Issues

- Hypothesis to be tested
- Prospective data analysis plan
- Sample size justification
- Identification of endpoints (primary, secondary, other)

Risk Analysis in an IDE

FDA Guidance

- *Factors to Consider When Making Benefit-Risk Determinations for Medical Device Investigational Device Exemptions* (January 2017)
 - FDA may disapprove an IDE application if “[t]here is reason to believe that the risks to the subjects are not outweighed by the anticipated benefits to the subjects and the importance of the knowledge to be gained.” 21 CFR 812.30(b)(4)
 - Informed consent is a key element to ensure subjects understand risks and potential benefits
 - FDA may grant staged approval or staged approval with conditions while outstanding questions that may affect the benefit-risk profile for the proposed IDE study are addressed
 - Study stage affects risk-benefit analysis (FIH, EFS, pilot, pivotal, post-market), especially degree of uncertainty
 - Acknowledge individual patient preferences may vary

IDE Checklist – Risk Analysis

Risk Analysis: Are the following items provided and adequate to determine that the benefit and knowledge to be gained from the investigation outweigh the risks to the subjects?

- a description and analysis of all increased risks to the research subjects
- the manner in which risks will be minimized
- a justification for the investigation
- a description of patient population, including number, age, sex and condition

Yes/No

Risk Analysis

- The investigational-use risk analysis should align with the device-specific risk analysis (e.g., Failure Modes and Effects Analysis (FMEA)) as part of the overall device history file and risk management process
- Focus on:
 - Type of risks, including severity
 - Likelihood or probability of risks
 - Duration of risk
 - Risk management
 - Residual risk evaluation
- Risk mitigation can include design features, training, study design (staged enrollment, monitoring, choice of PIs, CEC/DSMB, AE reporting)
- Communicate safety information to subjects, sites, IRBs

Risk-Benefit Analysis

- Risks weighed against benefits
- Factors to consider regarding benefits
 - Direct benefits: type, magnitude, probability, duration
 - Benefits to others (knowledge to be gained)
- Other factors:
 - Characterization of the disease
 - Availability of alternatives
 - Subject tolerance for risk, benefit
 - Uncertainty
 - Least burdensome study design

Framework for IDE Application

- Benefit-risk summary should address:
 - Context of proposed investigation
 - Assessment of risks
 - Assessment of benefits
 - Consideration of patient preference
 - Assessment of uncertainty
 - Conclusions

FDA Decisions on IDEs

Changes in IDE Approval Process

- Congress and FDA have sought to facilitate the IDE process and improve the regulatory climate for U.S. clinical research
- The FDA Safety and Innovation Act of 2012 (FDASIA) revised the IDE approval provisions
 - FDA disapproval of an IDE is now permitted only if a proposed study is deemed unsafe
 - FDA can no longer deny IDE approval based solely on a determination that the proposed study design is unacceptable or not statistically robust, or that the study alone may not support a clearance or approval
 - This change was intended to increase the rate of first-round IDE approvals
- Other elements in decision letters include study design considerations and future considerations
 - Not required for approval, but highly recommended
 - The number of IDE approvals has increased, but the number of study design considerations has also increased

FDA Review of IDE

- FDA sends acknowledgement with IDE number: GYYxxxxx (e.g., G160001)
- IDE sent to appropriate review division based on intended use
- Lead reviewer assembles team of experts to review the application and make decision with management concurrence within 30 days
 - Interactive questions typical prior to 30-day review deadline
- FDA issues a decision letter to the sponsor
- In some cases, may instead convert IDE to a pre-submission

FDA Decisions and Letters

- Approval
 - Approves the trial for specified number of US sites and subjects
 - Enrollment can begin once IRB approval is obtained
 - May include Study Design Considerations and/or Future Considerations from FDA – these are very important
- Approval with conditions
 - Approves the trial for specified number of sites and subjects provided conditions (deficiencies) are addressed within 45 days
 - Enrollment can begin once IRB approval is obtained
- Disapproval
 - Study may not begin; sponsor must address deficiencies and obtain FDA approval to start study

FDA Decisions and Letters

- FDA will approve an IDE if there are no safety concerns
 - But this does not necessarily mean that FDA believes completion of the study under that IDE will lead to a successful marketing application
- Study Design Considerations
 - *“FDA believes that additional modifications are needed in order for your study design to support marketing approval or clearance. We recommend, but do not require, that you modify your study to address the following issues:”*
- Future Considerations
 - *“You should also give serious consideration to the following, which FDA considers important for the support of a future submission:”*

Example Reasons for IDE Disapproval

- Risks outweigh the benefit
- Protocol is scientifically unsound
- Inadequate informed consent
- Reason to believe that the device is ineffective
- Application fails to provide material information

- FDA can no longer deny an IDE because:
 - The study may not later support an approval decision
 - It is likely that the sponsor will need to conduct additional investigations to support future approval

Expanded Access

Early/Expanded Access to Investigational Devices

- Emergency Use
- Individual Patient Access to Investigational Devices
- Treatment IDE
- Continued Access
- Early Feasibility Study

Emergency Use (§ 812.35(a))

- Emergency situations where investigational device may be used in a manner inconsistent with the approved investigational plan
- The patient has a life-threatening condition that needs immediate treatment
- No generally acceptable alternative treatment for the condition exists
- Because of the immediate need to use the device, there is no time to use existing procedures to get FDA approval for the use

Compassionate Use

- Protocol deviation to treat specific patient or limited group of patients
- Prior FDA approval required
- IDE supplement
 - Patient's condition and the circumstances necessitating treatment;
 - Why alternatives therapies are unsatisfactory and why the probable risk of using the investigational device is no greater than the probable risk from the disease or condition
 - Identification of any deviations in the approved clinical protocol that may be needed in order to treat the patient
 - Patient protection measures that will be followed

Treatment IDE

- Facilitate the availability of promising new therapeutic and diagnostic devices to desperately ill patients
- Conditions:
 - The device is intended to treat or diagnose a serious or immediately life-threatening disease or condition
 - No comparable or satisfactory alternative device available to treat or diagnose the disease or condition in the intended patient population;
 - Device is under investigation in a controlled clinical trial for the same use under an approved IDE, or all clinical trials have been completed; and
 - Sponsor of the controlled clinical trial is pursuing marketing approval/clearance of the investigational device with due diligence
- Must submit Treatment IDE

Continued Access

- After IDE study concluded but prior to clearance/approval if:
 - A public health need for the device; or
 - Preliminary evidence that the device is likely to be effective and no significant safety concerns have been identified for the proposed indication.
- Request submitted as IDE supplement
 - A justification for the extension;
 - A summary of the preliminary safety and effectiveness data from the IDE;
 - A brief discussion of the risks posed by the device;
 - The proposed rate of continued enrollment;
 - The clinical protocol as well as the proposed objectives for continued study; and
 - A brief discussion of the sponsor's progress in obtaining marketing approval/clearance for the device

**Changes to Ongoing IDE Investigations
IDE Supplements, 5 Day Notices and Annual Reports**

IDE Supplements – 30 Day Review

Changes in Investigational Plan

- Change may affect scientific soundness
- Change may affect patient's rights, safety, or welfare
- Change may affect validity of data from investigation
- Does not apply to changes to protect life or physical well-being of a subject in an emergency (but this must be reported to FDA within 5 working days after Sponsor learns of it)

Changes Requiring an IDE Supplement

Examples:

- Change in indication
- Change in type or nature of study control
- Change in primary endpoint
- Change in method of statistical evaluation
- Early termination of the study (except for reasons related to patient safety)
- Increasing the number of investigational sites
- Increasing the number of study subjects
- Significant change in device design or basic principles of operation not based on study information

5 Day Notice (§ 812.35(a)(3))

- Certain changes which don't meet the requirements of an IDE supplement
 - Changes do not affect the validity of data resulting from protocol, benefit to risk profile, scientific soundness of the investigational plan, or rights,, safety, or welfare of subjects in the study
- Notice of the change to the IDE within 5-working days, approval not required
 - If FDA disagrees with 5-day notice determination, conversion to 30-day IDE Supplement

Changes Requiring a 5-Day Notice

- Examples
 - Developmental changes in the device that do not constitute a significant change in design or basic principles of operation and that are made in response to information gathered during the course of the investigation
 - Change in design found not to impact safety/effectiveness
 - Certain minor changes to clinical protocol
 - Modification of inclusion/exclusion criteria to better define the target patient population
 - Increasing the frequency at which data or information is gathered
 - Inclusion of additional patient observations or measurements
 - Modifying the secondary endpoints
 - Extension of shelf life

Changes to the Device

- Certain developmental changes are eligible for implementation during the course of the clinical investigation without prior FDA approval
- Changes that constitute a significant change in design or basic principles of operation, or that were not made in response to information gathered during the course of an investigation, cannot be made without FDA approval of an IDE supplement

Changes to the Device (cont'd)

- Changes could include:
 - Changes to the Control mechanism, Principle of operation, Energy type, Environmental specifications, Performance specifications, Ergonomics of patient-user interface , Dimensional specifications, Software or firmware (including certain updates), Packaging or expiration dating, Sterilization, Manufacturing process (including the manufacturing site)
- Each change must be evaluated on a case-by-case basis to determine whether prior approval (and a submission to FDA) is required

Changes Appropriate For Annual Report

- Changes may be reported in the annual progress report for the IDE if the changes do not affect:
 - the validity of the data or information resulting from the completion of the approved protocol or the relationship of likely patient risk to benefit relied upon to approve the protocol
 - the scientific soundness of the investigational plan
 - the rights, safety, or welfare of the human subjects involved in the investigation [812.150(b)(5)] .

Changes Appropriate For Annual Report (cont'd)

- Examples:
 - the purpose of the study
 - risk analysis
 - monitoring procedures
 - labeling
 - limited changes to informed consent materials
 - IRB contact information

What Makes an IDE Submission and IDE Study Successful

Tips for a Successful IDE Submission and Study

- Adherence to Guidance documents and applicable standards for pre-clinical testing
- Develop rigorous clinical study protocol design
- Discussions with FDA and pre-submission meetings
- Anticipate any changes to study or device design
- Careful consideration of advisories in IDE approval letter
- Develop collaborative relationship with FDA

Tips for a Successful Study (cont'd)

- Adopt “quality system” approach to clinical studies (GCPs)
- Select qualified and engaged clinical investigators, largely without substantial financial interests
- Select qualified study monitors and have a clear monitoring plan
- Properly monitor studies
- Adopt written SOPs, but be careful what included in SOPs
- Understand the importance of strict compliance

Tips for a Successful Study (cont'd)

- Assure data quality
 - Attributable, legible, contemporaneous, original, accurate
- Clearly understand what records are to be maintained and how they should be completed
- Don't throw away anything, especially originals
- Expect and prepare for the worst
- Prepare for FDA inspections – prepare investigators, conduct a mock audit
- Coordinate prompt responses to Form 483s, Untitled Letters, Warning Letters

Tips for a Successful IDE Submission and Study (cont'd)

- Take the long view
 - Study completion and results
 - 510(k)/de novo/PMA submission to FDA
 - Possible panel meeting
 - Labeling

IDE Study Leading to Successful Marketing Application

- Have a meeting of the minds with FDA about what constitutes a successful study
- Address all comments raised by FDA in the pre-submissions and IDE correspondence
- Meet primary and key secondary endpoints (statistically significant results)
- Have a favorable safety profile (manageable SAEs and other risks)
- Demonstrate clinically meaningful results (compared to control)
- Minimize missing data (dropouts and individual patient data)
- Eliminate or minimize bias in assessing endpoints
- Demonstrate that benefits of the device outweigh the risks
- Obtain agreement from your KOLs that the study results are compelling



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Regulatory Requirements During Study

***IDE Submissions Workshop
May 18-19, 2023***

Tony Blank
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Overview

- » Introduction
- » Regulations that govern clinical study conduct
- » Organizations involved
- » Roles and responsibilities
 - Sponsors
 - Investigators

Purpose of an IDE

- » Section 520(g) of the Federal Food, Drug and Cosmetic Act
 - Encourage development of devices
 - Protect health consistent with ethical standards
 - Maintain scientific freedom of investigators

Regulations

- » IDE Regulations (21 CFR Part 812)
- » IRB Regulations (21 CFR Part 56)
- » Informed Consent Regulations (21 CFR Part 50)
- » Financial Disclosure (21 CFR Part 54)
- » Electronic Records; Electronic Signatures (21 CFR Part 11)
- » Good Clinical Practice (GCP)
 - But this is not a regulation

Good Clinical Practice

- » Consolidation of regulation and ethical principles for study conduct
 - Ethical conduct of a clinical study
 - Scientific quality of a clinical study
 - Credible data from a clinical study
- » To ensure these qualities in clinical data submitted to regulatory authorities
- » Shares the same intent as many regulations

Organizations

- » Sponsors
- » Food and Drug Administration (FDA)
- » Institutional Review Boards/Independent Ethics Committees (IRBs/ECs)
- » Investigators
- » Others
 - Contract Research Organization (CROs)
 - Central laboratory
 - Data Safety Monitoring Board (DSMB)
 - Clinical Events Adjudication Boards

FDA Regulatory

- » Regulatory framework varies for medical devices
 - Significant risk device (SR)
 - Non-significant risk device (NSR)
 - Exempt
- » Your obligations for study conduct vary based upon the regulatory framework for your device and study

Regulatory Obligations Significant Risk Device

- » IDE Approval
 - FDA
 - IRB/EC
- » Planned changes versus emergency use
- » Three mechanisms for planned changes
 - IDE Supplements
 - 5 Day Notices
 - Annual Reports
- » Other reports specified by regulations

IDE Supplements (812.35(a)(1))

- » Changes that require FDA approval prior to implementing (30 day review)
- » IDE supplement required
 - Scientific soundness of the investigational plan
 - Rights, safety or welfare of subjects
 - Significant change in design or principles of operation of device and others
 - Validity of the study results
 - Relationship of patient benefit to risk

Device Developmental Changes

- » Device Developmental Changes
 - Do not result in a significant change in the design or principles of operation of device and
 - Are made in response to information gathered during the study
- » Credible Information
 - Data generated under Design Controls
 - Preclinical (laboratory and animal) testing
 - Literature
 - Other reliable information

Clinical Protocol Changes

- » Clinical Protocol Changes Which Do Not Affect
 - Validity of the data
 - Likely patient risk to benefit
 - Scientific Soundness
 - Rights, safety or welfare of subjects
- » Credible Information
 - Literature
 - Investigators
 - Data gathered during the study

Annual Reports (812.35(a)(4))

- » All Others
- » Serves to “Increase Patient Safety”
- » Minor Clarifications
 - Clarifying instructions for use
 - Additional monitoring procedures
 - IRB information

Non-Significant Risk and Exempt Studies

- IRB/EC Approval
 - Determination from IRB that it is a non-significant risk
- Abbreviated IDE requirements 812.2(b)
 - IRB approval as a non-significant risk
 - Labeling
 - Informed consent
 - Monitoring
 - Select reports and records
- Ongoing reports as required by FDA and IRB

IRBs/ECs

- » Safeguard rights, safety and well-being of subjects
- » Potential benefits of the study outweigh risks
 - Subjects
 - Information gained
- » Process
 - Initial approvals
 - Ongoing approvals
 - Ongoing reports (varies)

Investigators

- » Perform in accordance with agreements
- » Follow the protocol
- » Control device and supervise its use
- » Obtain IRB approval
- » Obtain informed consent
- » Records and reports
 - Source documentation
 - Case report forms
 - Other reports (deviations and adverse events)
 - Financial disclosure

Other Organizations

- » Contract Research Organization (CRO)
- » Central laboratory
- » Data Safety Monitoring Board
 - Independent safety evaluation
- » Clinical Events Adjudication Board
 - Independent classification of adverse events

Protocol Compliance

- » Screen subjects
- » Obtain consent
- » Enroll qualified subjects
- » Perform protocol required evaluations
- » Evaluate subjects at specified time intervals
- » Control and account for device
- » Complete source documentation
- » Complete case report forms
- » Complete reports as needed

Monitoring

- » Ongoing, documented process to ensure compliance
- » Continual process with feedback
 - Investigators
 - Protocol
- » Quality of data
 - Source documentation review
 - Compliance to protocol
- » Quality of process
 - Consent
 - Reports and deviations

Data Management

- » Ensure the accuracy and reliability of data
 - Completed case report forms
 - Data entered into the computer
 - Consistency of the data entered
 - External logic
 - Internal logic
 - Security of the computer system
 - Validity of the computer program that stores the data
 - Trail of changes (audit trail)

Audit

- » Part of a quality system (quality assurance)
- » Discrete function (as opposed to monitoring)
- » Examples
 - 100% audit of critical variables in database
 - Audit of CRO

Training and Qualification

- » Investigators and staff
- » Sponsor
- » Other organizations
- » Quality principles

Investigator Records (812.140)

- » All correspondence
- » Receipt, use and disposition of devices
- » Subject's case history and exposure to device*
 - Informed consent process*
 - Source documentation
 - Adverse events
- » Protocol and reasons for deviations
- » Others required by FDA

Sponsor Records (812.140)

- » All correspondence
- » Device shipment and disposition
- » Signed investigator agreements
- » Abbreviated IDE requirements*
- » Adverse device effects and complaints*
- » Any other required by FDA

*NSR requirements

Reports – Investigator (812.150)

- » Unanticipated adverse device effects (10 working days)*
- » Withdrawal of IRB approval (5 working days)*
- » Progress (at least yearly)
- » Deviations to protect life or well-being of subject in an emergency (5 working days)
- » Failure to obtain informed consent (5 working days)*
- » Final report (within 3 months)
- » Other as requested by IRB or FDA*

*NSR requirements

Reports – Sponsors (812.150)

- » Unanticipated adverse device effects (10 working days)*
- » Withdrawal of IRB approval (5 working days)*
- » Withdrawal of FDA approval (5 working days)*
- » Current investigator list (6 months)
- » Progress reports (at least yearly)*
- » Recall and device disposition (30 working days)*
- » Final report (30 working days)*
- » Informed consent (failure to obtain; 5 working days)*
- » Significant risk device determination (5 working days)*
- » Other as requested*

*NSR requirements

Additional Considerations

- » IDE regulations are the bare minimum for records and reports
 - GCP recommendations
 - Particularly for non-significant risk and exempt studies
- » Examples of additional reports and records
 - Serious adverse event reporting
 - Subject death (device or non-device related)
 - Subject discontinuation

IRB/EC Requirements

- » Additional requirements compared to the regulations
- » Variable by IRB/EC
 - Deviations in the consent process
 - Deviations in the protocol
 - Adverse events (serious)
 - Unanticipated problems

ClinicalTrials.gov

- » Title VIII of FDAAA (2007), Public Law 110-85
- » Submit certain information to the clinical trials data bank (www.ClinicalTrials.gov)
- » Applicable clinical trials
 - Prospective study of health outcomes with a comparison
 - Device subject to 510(k) or PMA requirements
- » Register your study
 - Study protocol
 - Study status (recruiting)
 - Study data

Example

[Trial of device that is not approved or cleared by the U.S. FDA]

This trial has been identified as being associated with a clinical device that has been approved or cleared by the US Food and Drug Administration. Under the terms of US Public Law 110-85, Title VIII, Section 801, the details of this study are not available to the public.

Resources

- » <http://www.fda.gov/oc/gcp/regulations.html>
- » E6 Good Clinical Practice: Consolidated Guidance
- » <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm082158.pdf>
- » <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080203.pdf>
- » <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM071230.pdf>

Thank you!

Questions?

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THANK YOU!

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AdvaMed Workshop – Investigational Device Exemption (IDE) Submissions

Reporting Results

May 18, 2023

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IDE Studies – Reporting Results

- Clinical study reports (interim and final)
- Dissemination to the medical community
- Incorporation into pre-market submissions
- Assessment of impact to product labeling

Clinical Study Reports (Interim and Final)

Why Report Results?

- Final clinical study report
 - Regulatory submission
- Interim clinical study report
 - Planned, decision point
- Patient safety (DSMB, Adjudication)
- Annual IDE reports
- Publications

Final Clinical Study Report

- Goal depends on purpose
 - Pivotal study: To support clearance/approval (benefits outweigh risks)
 - Pilot study: To support initiation of a pivotal study
 - Post-market study: To address a specific question in post-market setting
- May also be used to delay or terminate project

ICH Guideline – Structure and Content of Clinical Study Reports (E3)

1. Title Page
2. Synopsis
3. TOC
4. List of Abbreviations and Definition of Terms
5. Ethics
6. Investigators and Study Administrative Structure
7. Introduction

ICH Guideline – Structure and Content of Clinical Study Reports (E3)

8. Study Objectives
9. Investigational Plan
10. Study Patients
11. Efficacy Evaluation
12. Safety Evaluation
13. Discussion and Overall Conclusions
14. Reference List
15. Appendices

Introduction and Conduct of Study

- Introduction
 - Purpose of the device
 - Unmet clinical need
- Ethical and regulatory requirements

Investigational Plan

- Overall study design
- Study Population (inclusion/exclusion criteria)
- Treatments (including randomization and blinding)
- Efficacy and safety variables
- Data quality assurance
- Statistical methods (including analysis plan and sample size)
- Changes in the conduct of the study or planned analysis

Study Patients

- Disposition (accountability)
- Protocol Deviations

Efficacy Evaluation

- Data sets
- Demographic/baseline characteristics
- Treatment compliance
- Efficacy results
 - Results of primary and secondary endpoints
 - Analytical issues (adjustment for covariates, dropouts, etc.)
- Efficacy conclusions

Safety Evaluation

- Extent of exposure
- AEs
- Malfunctions
- Deaths, SAEs, other significant AEs (including narratives)
- Clinical laboratory evaluation
- Vital signs, etc.
- Safety conclusions

Appendices

- Study Information
 - Protocol and amendments
 - Sample CRF
 - List of IRBs, investigators
 - Randomization scheme and codes
- Patient data listings
- Completed CRFs

Dissemination to the Medical Community

Investigational Devices

- For Investigational Devices, including those with an approved Investigational Device Exemption (IDE), FDA prohibits:
 - Representing the device as safe or effective;
 - Promoting or test marketing the device [21 C.F.R. 812.7]
- FDA recognizes the need to recruit clinical investigators and study subjects, and allows publishing limited information tailored for these purposes
 - Follow FDA guidance, [Preparing Notices of Availability of Investigational Medical Devices and for Recruiting Study Subjects](#)
 - Must state the purpose to recruit investigators or patients; not to make the device generally available
 - Prominently include the statement: “Caution – INVESTIGATIONAL DEVICE. LIMITED BY FEDERAL (OR UNITED STATES) LAW TO INVESTIGATIONAL USE”
- Technical information (*e.g.*, specifications) about investigational devices may be disseminated if the material is provided in an informational, non-promotional context
 - May not imply/assert that the safety and/or effectiveness of the studied device has been established

510(k)-Pending Devices

- Display/Promotion at a trade show is permitted under FDA Compliance Policy Guide (CPG) 300.600
 - Only for the intended use that is the subject of the pending 510(k) Notice
 - Should include the statement: “Pending 510(k), not available for sale within the United States.”
- Solicitation of purchase orders (commercialization) is prohibited
 - Do not give out price information
 - Do not generate customer lists
- Policy technically applies only after 510(k) notice is submitted
 - CPG explicitly authorizes displays and promotion only for 510(k)-pending products
- NOTE: If clinical data required to support the 510(k) submission, follow the rules for displaying investigational devices instead

New Intended Use for Device Already on The Market

- FDA is most concerned about off-label use of devices that are readily available for sale
- Devices with 510(k) clearance or PMA approval may only be displayed for cleared or approved uses
 - Even if a new 510(k) notice is pending before FDA

Device with Foreign Approval Only

- If a device has foreign approval, the foreign manufacturer may import it for display at U.S. trade shows if the entry forms:
 - disclose its unapproved status;
 - indicate that the device is being imported solely for “testing or evaluation;” and
 - state that remaining product will be destroyed or exported.
- At a trade show, it must be labeled, “Not available for sale in the United States” and no sales orders may be taken from U.S. purchasers
- Should only be displayed at trade shows having a significant portion of foreign attendees, *i.e.*, international trade show
 - May display a video or satellite feed of procedures depicting use of a device consistent with foreign approvals if conducted primarily for scientific and educational purposes, (*i.e.*, non-promotional in manner)
- Display must be clear that the device is not cleared/approved in the United States
 - Separate booth/section of trade show from U.S. marketed products

Incorporation into Pre-market Submissions

Incorporation into Premarket Submissions

- Often the CSR is attached
- A summary of the protocol and results should be provided in the body of the submission to give FDA an overview
- PMAs require submission of additional information (e.g., CSR appendices), database and statistical programs

Assessment of Impact to Product Labeling

Incorporation of Results in Product Labeling

- For de novos and PMAs, FDA expects a summary of the clinical study in the labeling
- Primary endpoint and safety data should be included
- Description of secondary endpoints may be negotiated

Impact of Study Results

- Do the results suggest a revision to the product labeling?
 - Indications or contraindications
 - Warnings or precautions
 - Adverse Events
 - Instructions for Use
- Do the results affect risk assessment?

IDE Reporting Results - Do's

- Develop an outline and template
- Describe the unmet need, study rationale
- Be consistent and clear
- Use flow charts, figures, tables, etc.
- Write with an objective, tell the story, emphasize strengths
- Build clinical and statistical credibility, explain negative results
- Address issues FDA raised during IDE review

IDE Reporting Results - Don'ts

- Avoid challenging topics
- Fail to provide perspective on adverse events
- Fail to disclose important information
- Fail to double-check numbers, ensure consistency
- Use too much detail in the report body
- Lack balance on risks vs. benefits
- Present data without explanation
- Forget the clinical perspective

Conclusions

- Always remember your purpose and audience
- Include the key content elements
- Tell the story
- Be clear and accurate
- Follow FDA guidance on disseminating results, incorporating into premarket submissions and labeling

The logo for Hogan Lovells, featuring the company name in a serif font on a yellow-green rectangular background.

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Thank You!

Optimizing the PreSubmission Meeting

*IDE Submissions Workshop
May 18-19, 2023*

Tony Blank
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Definition of a Pre-Submission

- » A formal written request from an applicant for feedback from FDA provided in the form of:
 - a formal written response or
 - a meeting or teleconference in which the feedback is documented in meeting minutes
- » When FDA's feedback on specific questions is necessary to guide product development and/or application preparation (i.e., prior to intended submission of an IDE or marketing application)
- » Request **must include specific questions** regarding review issues relevant to a planned IDE or marketing application (e.g., questions regarding pre-clinical and clinical testing protocols or data requirements).

Specific Questions

Examples of WELL FORMED questions designed to reduce risk...

- » Are the nonclinical study protocols (bench or animal) sufficient to allow for the collection of data from which conclusions about device safety to support initiation of a clinical study can be drawn?
- » Are the primary and/or secondary endpoints appropriate for the proposed indication for use?
- » Does FDA concur with our worst-case rationale for this device?
- » Does the FDA concur with the use of the proposed alternative test method, which is different than the normally recognized standard?
- » Is the animal model I propose appropriate for testing my device?

Specific Questions

Examples of POORLY FORMED questions designed to reduce risk...

- » Will the information outlined in my Pre-Sub support a substantial equivalence determination?
- » Are the results of my bench testing acceptable?
- » Does FDA have any comments on the nonclinical test results?
- » Does the FDA agree that the proposed clinical study protocol is adequate to support the safety and effectiveness of the device in a marketing application?
- » Does the FDA agree that the clinical results provided in the background package for the meeting are sufficient to support the safety and effectiveness of the device in a marketing application?

Reducing Risks Thru Pre-Subs

Topic	Risk to be Reduced
Acceptability of leveraging data from prior projects to support current project	Leveraging strategy not accepted when submitted
Animal testing – model and protocol	Testing protocol fails to provide necessary data to support submission
Bench testing – planned deviation from published Standard or Guidance	Test results not accepted
Clinical study design (e.g., patient population, endpoints, etc.)	Clinical study fails to generate data to support intended device claims and/or approval

Timelines

Q-Sub Type	Meeting as Method of Feedback?	Timeframe for Meeting/Teleconference (from receipt of submission)
Pre-Submission*	Upon request	75-90 days**
Informational Meeting	Yes	90 days
Study Risk Determination	No	N/A
Agreement Meeting	Yes	30 days or within time frame agreed to with sponsor
Determination Meeting	Yes	Date for meeting agreed upon within 30 days of request
Submission Issue Meeting	Yes	21 days
Day 100 Meeting	Yes	100 days (from PMA filing date)

*As defined in MDUFA III Commitment Letter.

**21 days for urgent public health issues (see Section III.A.6.).

Trade-Offs

» Timelines

- Time to Schedule Meeting
- Time to receive formal response to PreMarket submission

» Cost

- Delayed development
- Need to re-do testing

Timing Pre-Sub Interactions

- » Impact to development schedule
- » Availability of significant background information
- » Balance of time and cost
- » Impact to project risk

Schedule Impact

- » Pre-Sub Interactions take time:
 - Preparation of the request
 - Scheduling Meeting (75-90 days)
 - Post-meeting clarification
- » Keys to integrating into project schedule...
 - Identify Strategy Early
 - Staging Meetings by Priority and Impact

Identifying Questions

- » Greatest time and/or cost impact should be prioritized...
 - Animal study questions
 - Leveraging questions
 - Planned deviations from Standards and/or Guidances
 - Tests which take a long time and/or are very expensive
 - Carcinogenicity
 - Life testing
 - Tests which impact other tests or drive development direction

Identifying Objectives

- » Defining your objective ...
 - Sufficient feedback to reduce a regulatory or program risk
 - Asking questions which can provide significant direction to the program to reduce time or expense
- » Realistic Best Case:
 - FDA concurs with approach
 - FDA has significant concerns about proposal
- » A cadence of meetings to discuss complex issues may be appropriate.

Identifying Your Audience

- » FDA will have a team prepared to discuss and provide feedback on the posed question(s)
- » Expect representatives from the review team assigned to the product as well as internal FDA experts (as necessary) as active participants
- » Sponsor should request individuals with specific expertise, if necessary
- » Do not be surprised if there are other participants not directly associated with the product (e.g., training or new technology)

Team Preparation

FDA Preparation

- » Participants will have closely read all pre-read materials and will be familiar with feedback and follow-up.
- » FDA will have identified and provided questions/comments to the Sponsor in advance of the meeting.
- » FDA will not be prepared to review or provide feedback on new information introduced at the meeting.

Assembling the Sponsor's team

- » Identify a meeting **FACILITATOR**.
- » Responsible for managing the meeting to ensure discussion stays on time and on track.
- » Empowered to direct individuals on the Sponsor's team to respond to questions from FDA.
- » Experienced in reading cues from meeting participants (verbal and nonverbal) to manage discussion tone and completeness.

Assembling the Sponsor's team

- » Identify meeting **SUBJECT MATTER EXPERTS**.
- » Responsible for presenting and responding to questions regarding specific topics and areas of expertise.
 - Biostatisticians
 - Engineers
 - Clinicians
 - Etc.
- » Individuals need to be articulate, well-versed on the topic(s), and comfortable interacting with others who may or may not agree with their point of view.

Assembling the Sponsor's team

- » Identify meeting **NOTETAKER**.
 - Responsible for capturing comments and areas of agreement and disagreement.
 - Goal is to capture areas of mutual understanding (including action items, areas of concurrence, areas of disagreement, etc.)
- » Appropriately **LIMIT** the team to individuals who can materially participate in the discussion
- » Generally, not beneficial to bring...
 - CEO, COO, Marketing VP, Sales VP, Etc.

Assembling the Sponsor's team

Consultants

Need to be managed closely. If using, ensure they:

- » Understand the Company's objectives for the meeting;
- » Understand the information exchanged with FDA; and
- » Have been active participants in meeting prep sessions.

What to Present?

- » Develop an Agenda based on what you want to get out of the meeting
- » Limit the presentation to the critical 1/3 of the material provided in the Pre-Sub package
- » Focus on the issues (scientific, regulatory, etc.) for which discussion is necessary – especially those issues for which feedback has been provided
- » DO NOT send or introduce new questions or material either immediately before or during the meeting (FDA needs time to review)

PreSub Meetings: Best Practices

» Timing of Meetings

- Early enough to reduce the risk of having to repeat bench or animal studies.
- Typically after device design has been established
- After internal determination of project objective
- **NOT** after the IDE Application has been prepared

PreSub Meetings: Best Practices

- » Clearly articulated objectives (with clear QUESTIONS)
- » Provide pre-read materials that provide necessary background
- » Arrive prepared to interact (and allow time)
- » Select appropriate representation from the company
 - Dedicated note-taker
 - Appropriate topic experts (clinician, engineer, pathologist, etc.)
 - Capable facilitator

PreSub Meetings: Best Practices (cont'd)

» Preparation

- Identify areas of likely disagreement
- Identify questions needing answers
- Quantity of material appropriate for allotted time and necessary discussion

» Execution

- Facilitated open discussion
- Ask questions
- Don't presume agreement
- Review agreements
- Identify necessary follow-up

PreSub Meetings: Best Practices (cont'd)

» Practice Sessions

- Identify questions you 'hope are not asked' and develop answers to them.
- Bring in independent experts to 'role play' FDA to challenge the team on difficult issues
- Slides
 - Don't rehash pre-sub materials (FDA has read them)
 - Focus on FDA feedback received before the meeting
 - Limit number of slides to allow enough time for lively interaction on the important stuff.
 - DO NOT waste slides/time with team biographies, company organization, philosophy, etc.
- Practice until you achieve 50 minutes total time for meeting:
 - 20 minutes slides (8-10 slides)
 - 30 minutes discussion

Thank you!

Questions?

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THANK YOU!

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