



FDA Oversight of Clinical Investigations

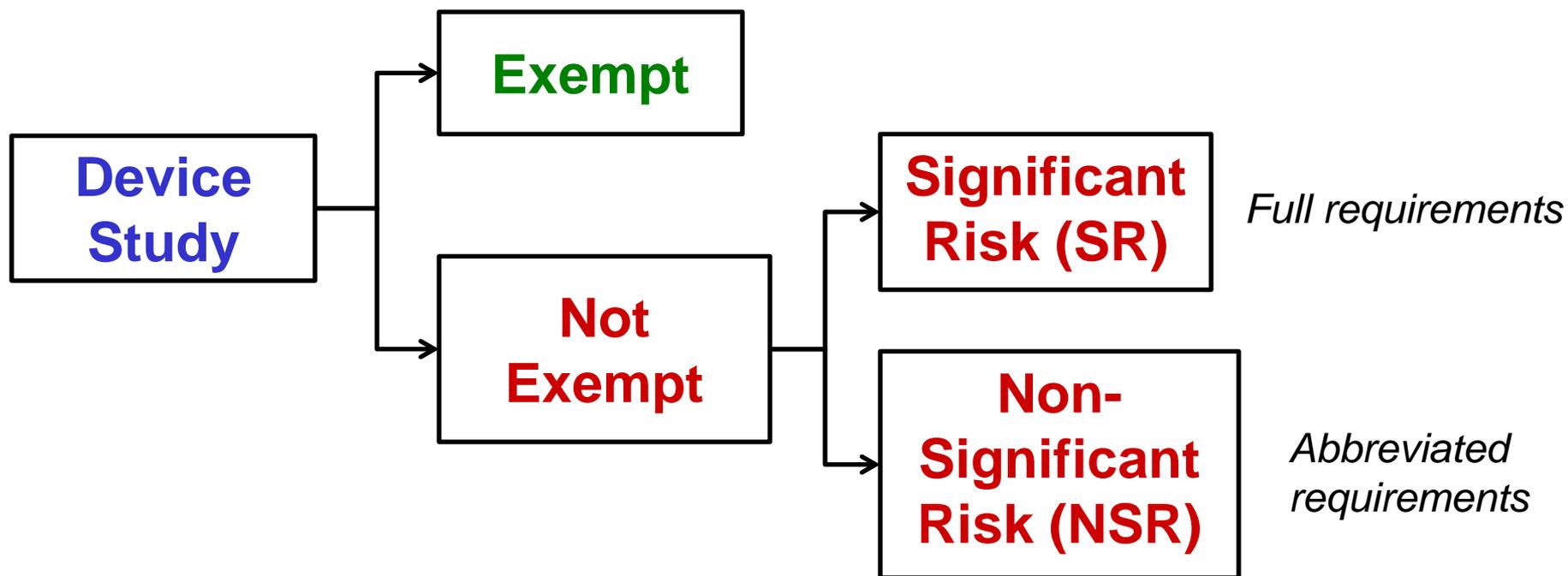
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Overview

- What studies does FDA review?
- Decisions for IDEs
- FDASIA Section 601
- Information Communicated in FDA's decision letters

Medical Device Studies – IDE Requirements



Medical Device Studies – IDE Requirements



Significant Risk (SR) Study

- 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
 - otherwise poses a risk
- See 21 CFR 812.3(m)

Device Use/Studies not Reviewed by FDA

- Exempt studies per 21 CFR 812.2(c), for example
 - Studies of approved devices used in accordance with their labeling
 - Certain diagnostic device studies
- **Basic physiological research**
 - Not for the purpose of evaluating safety/effectiveness of the device
- “Practice of medicine” - care of specific patient
- Non-significant risk studies

Investigational Device Exemption

- Established in section 520(g) of the FD&C Act and in 21 CFR Part 812
- FDA approval of an IDE is required for US human study of a significant risk device which is not approved or cleared for the indication being studied.
- Exempts sponsor from certain provisions of FD&C Act (e.g., requirement for a marketing application, compliance with full GMPs)
- Requirements for informed consent, labeling, monitoring of the study, records/reporting
- Initiation of the study requires approval by Institutional Review Board (IRB)

Significant Risk Studies

- Full IDE requirements apply
- Sponsor submits IDE application to FDA
- FDA renders **decision** within 30 calendar days
- If approved, sponsor obtains **IRB approval**
- After **both FDA and IRB** approve the investigation, study may begin

Possible FDA decisions for IDEs

- **Approval**
 - Approval of full study cohort
 - Staged Approval
- **Approval with Conditions**
 - Approval with Conditions of full study cohort
 - Staged Approval with Conditions
- **Disapproval**

Decisions: Approval

- FDA does not have remaining questions that must be addressed prior to enrollment of the approved number of subjects
 - the proposed study design is acceptable with regard to reasonable protection of study subjects.
- Study is approved for a specified number of enrolled subjects and investigational centers
- Study may be initiated upon IRB approval

Approval with Conditions

- FDA has determined that the information provided is sufficient to justify human clinical evaluation of the device and the proposed study design is acceptable with regard to reasonable protection of study subjects, **provided that certain conditions are addressed.**
- Sponsor may begin study upon receipt of IRB approval on the condition that, within 45 days from the date of FDA's decision letter, the sponsor submits information addressing the issues identified in FDA's letter.

Approval with Conditions

- Examples of typical Conditions:
 - Requests for additional information, data or changes that relate to protecting subjects in the study and can be addressed in a timely (45 days) manner but FDA determines do not need to be resolved prior to study initiation
 - Late stage follow-up procedures and assessments that relate to the care of study subjects but, because they occur late in the study, will likely be addressed prior to subjects reaching that point in the study
 - Minor issues related to the informed consent document that must be corrected before study initiation (i.e., subject enrollment) but can be reviewed by FDA after study initiation

Staged Approval

- Approval or Approval with Conditions is granted while certain outstanding questions are answered concurrently with enrollment of a **limited number** of subjects
- Allows initiation of a study that might otherwise be disapproved while providing additional mitigation of risk by limiting exposure of the device to a smaller subject population
- The sponsor may expand enrollment once an IDE supplement containing the necessary additional information is submitted to FDA and found to be acceptable.

Disapproval

Sponsor may not initiate the clinical investigation until the sponsor submits an amendment to the IDE to respond to the deficiencies identified in FDA's letter and subsequently receives a new letter from FDA granting approval or approval with conditions.

FDASIA Section 601

Amends Section 520(g)(4)(C) of the FD&C Act

- FDASIA became law on July 9, 2012
- FDA shall not disapprove an IDE because:
 - the investigation may not support a substantial equivalence or de novo classification determination or approval of a device;
 - the investigation may not meet a requirement, including a data requirement, relating to the approval or clearance of a device; or
 - an additional or different investigation may be necessary to support clearance or approval of the device.

FDASIA Section 601

This means that an IDE cannot be disapproved on the basis of FDA's belief that the study design is inadequate to support a future PMA, 510(k), HDE, or de novo classification.

The standards for market approval (PMA/HDE) or clearance (510(k)) have not changed.

IDE disapproval and FDASIA Section 601

- Standards for protection of study subjects remain unchanged
- Only issues regarding the study design that are related to protecting study subjects may be the basis for a disapproval or approval with conditions decision

Disapproval

Consistent with 21 CFR 812.30(b) and section 520(g) of the FD&C Act, FDA may disapprove an IDE for any of the following reasons:

- There has been a failure to comply with any requirement in 21 CFR Part 812 or section 520(g) of the FD&C Act, any other applicable regulation or statute, or any condition of approval imposed by an IRB or FDA. (21 CFR 812.30(b)(1))
- The application or a report contains an untrue statement of material fact, or omits material information required by 21 CFR Part 812. (21 CFR 812.30(b)(2))
- The sponsor fails to respond to a request for additional information within the time prescribed by FDA. (21 CFR 812.30(b)(3))

Disapproval

- There is reason to believe that 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)), such as
- The informed consent requires changes to adequately inform subjects of the study, and must be reviewed by FDA prior to study initiation (21 CFR 812.30(b)(4))
- The investigation, as proposed, is scientifically unsound because it does not pose a reasonable scientific question or the investigation does not include the collection of data or information related to that scientific question (21 CFR 812.30(b)(4))

Disapproval

- There is reason to believe that the device as used is ineffective (21 CFR 812.30(b)(4)), such as
- It is otherwise unreasonable to begin or to continue the investigation owing to the way in which the device is used or the inadequacy of (i) the report of prior investigations or the investigational plan; (ii) the methods, facilities, and controls used for the manufacturing, processing, packaging, storage, and where appropriate, installation of the device; or (iii) monitoring and review of the investigation (21 CFR 812.30(b)(5)), such as

Study Design Considerations (SDCs)

- FDA recommendations to a sponsor regarding changes that FDA believes should be made in order for the study to support its primary goals
- Examples include issues related to:
 - Primary and major secondary endpoints
 - Randomization, control, and blinding
 - Follow-up duration and assessments
 - Statistical analysis plan
 - Enrollment criteria (if not related to subject protection)

Future Considerations (FCs)

- Intended to provide helpful advice to sponsors regarding important elements of the future application that the IDE may not specifically address.
- Examples
 - Known limitations of the IDE clinical investigation with regard to supporting certain claims or indications.
 - Specific non-clinical testing that, while not necessary to support approval of the IDE, will be needed to support the marketing application.

Summary: FDA Letter –What?

- Decisions - Can you start the study?



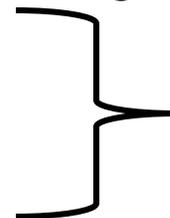
Approval



Approval with Conditions



Disapproval



Require
deficiencies to be
addressed

- Study Design Considerations and Future Considerations do NOT require a response.

- *Guidance “FDA Decisions for Investigational Device Exemption (IDE) Clinical Investigations”*

Summary: FDA Letter – How?

- Letter body communicates FDA decision
- Letter body states
 - FDA believes that the study design is adequate to support the study goals
 - or
 - FDA recommends study design considerations in order for the study to do so.
- Study design considerations and future considerations are communicated via an attachment to the letter
 - “These recommendations do not relate to the safety, rights or welfare of study subjects and they do not need to be addressed in order for you to conduct your study.”

Marketing Application Considerations

- Sponsor may or may not modify their study to address study design considerations
- Upon review of study data in a marketing application, FDA may raise study design considerations or future considerations that have not been addressed for panel comment and guidance

References

- Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors

<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm113709.htm>

- Frequently Asked Questions About Medical Devices
- Significant Risk and Nonsignificant Risk Medical Device Studies

- Device Advice:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm>

- CDRH Learn:

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

- IDE Decisions Guidance:

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM279107.pdf>