U.S. FOOD & DRUG ADMINISTRATION

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Factors to Consider When Making Benefit-Risk Determinations for Medical Device Investigational Device Exemptions (IDEs): Final Guidance

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February 23, 2017 CDRH Webinar

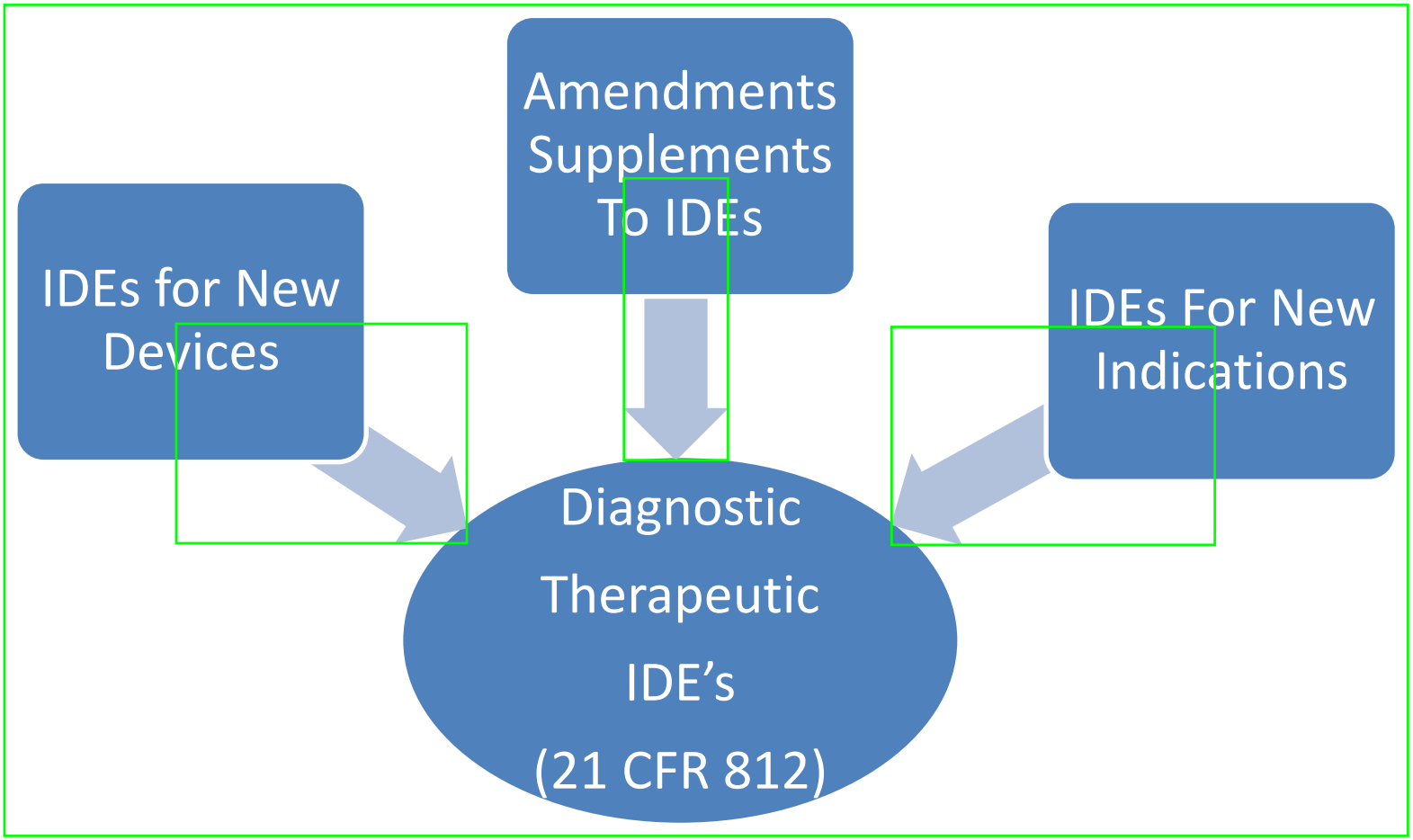
Agenda

- Highlights and Scope of Final Guidance
- Differences Between Draft and Final Guidance
- Overview of selected Benefit-Risk (B-R) Guidance Sections
  - Regulatory Standards and Subject Protections For IDE's
  - B-R Framework Applied To Stages of Device Development
  - Assessing Benefits and Risks For IDE Applications – Risk Characterization and Risk Management
  - Appendix A – Recommended General Framework for B-R Assessment
- Questions

Highlights of Final Guidance

- Contributes to FDA's on-going efforts to improve patient access to new devices by strengthening and streamlining clinical trials.
- Clarifies the principal factors that FDA considers when assessing the benefits and risks of medical devices in IDE submissions to improve transparency, predictability and consistency of this process.
- Does not propose to revise the sponsor requirements for providing a Benefit-Risk analysis as part of an IDE application or the way FDA reviews IDE submissions.

Scope


Amendments Supplements To IDEs
IDEs for New Devices
IDEs For New Indications
Diagnostic
Therapeutic
IDE's
(21 CFR 812)

Differences Between Draft and Final Guidance

- Minor changes included clarification on terminology and modify language to align with our regulations.

- Minor modifications to the text and the examples to clarify how study design considerations, the stage of device development and incorporation of patient preference principles and tools can impact the B-R assessment.

Regulatory Standards for IDEs

Regulations that apply to the review of IDE applications in the context of B-R and grounds for disapproval:

- *21 CFR 812.30(b)(4)* "There 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, or informed consent is inadequate, or the investigation is scientifically unsound, or there is reason to believe that the device as used is ineffective"

- *21 CFR 812.30(b)(5) "*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"

Regulatory Standards for IDEs

A Key principle of subjects protections in Clinical Investigations is the Informed Consent Process

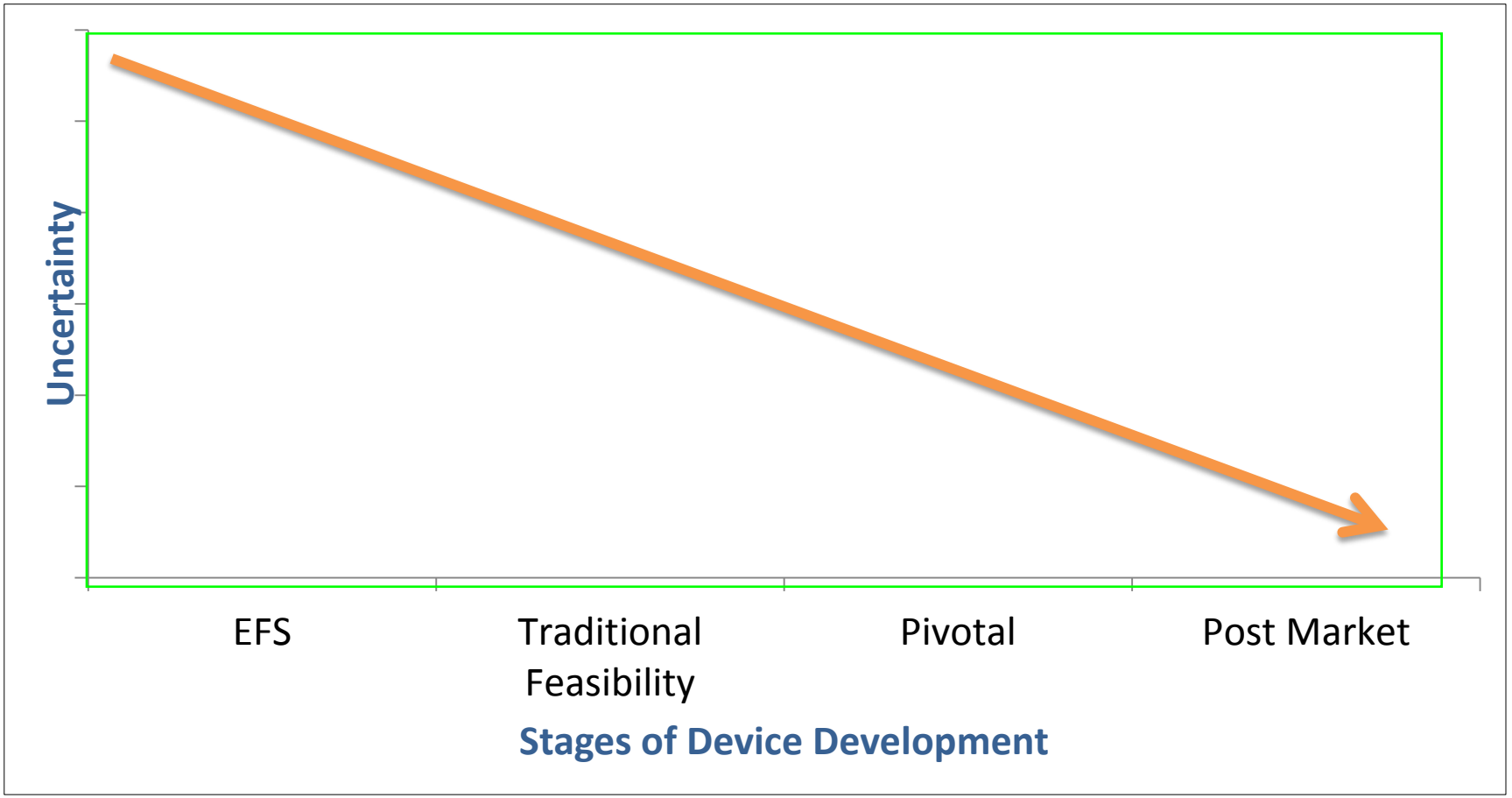
Sponsors are required to address B-R in the clinical study Informed Consent Document–

- *21 CFR 50.25 Basic elements of informed consent.* In seeking informed consent, the following information shall be provided to each subject:…

(2) A description of any reasonably foreseeable risks or discomforts to the subject.

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research.

B-R Framework Applied To Device Development Regulatory Pathway



How Does the B-R Assessment For IDEs Differ From B-R assessment For Marketing Applications?

- Clinical investigations by definition are research studies with greater uncertainty regarding :
  - Relative benefits and risks of a given device
  - Device technology
  - Treatment with the Device
- Less evidence available for IDE applications compared to marketing submissions.
- Benefits of the research study are considered directly to the subject and to others (e.g., indirect – knowledge to be gained from research or contribute to developing treatments)

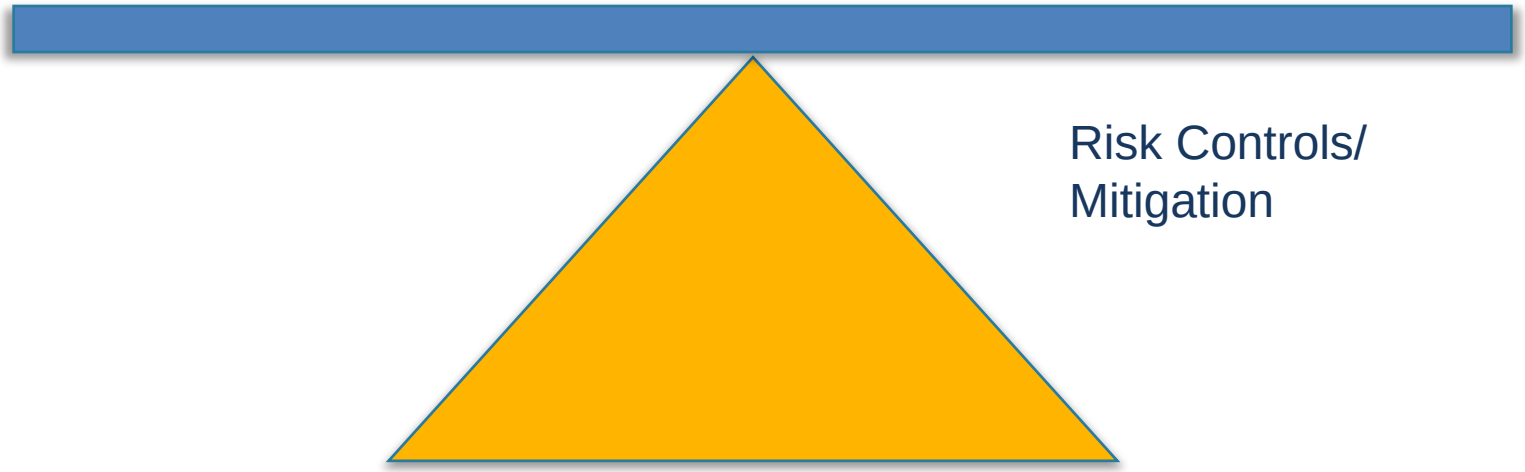
Assessing Benefits and Risks in the IDE Realm

BENEFITS

Type
Magnitude
Probability
Duration

RISKS

Type /Severity
Likelihood
Duration
Management



Risk Controls/
Mitigation

Assessing Risks for IDE Applications

21 CFR 812.25

The investigational plan shall include…

(c) *Risk analysis*.

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

Risk Management

The B-R Guidance incorporates the principles from ANSI/AMMI/ISO 14971: *Application of risk management to medical devices*

- ISO 14971 describes a process through which the medical device manufacturer can…estimate and evaluate risks, control these risks, and monitor the effectiveness of those controls through the product's lifecycle.

Assessing Risks for IDE Applications

Assessing Risk of the Investigation:

- Harms – Specifying how a hazard could lead to clinical sequelae including length of time experienced and residual affect (if any) or other harmful event
- Likelihood – Focusing on severity of a risk along with likelihood is important for a complete estimation of that risk.
- Residual risk and completeness of risk control – Many identified risks are reduced to an acceptable level through effective risk controls.

Assessment of Risk to Study Subjects

- Focus on risks supported by objective scientific evidence and are reasonably foreseeable

- Include a description and analysis of incremental risks subjects will be exposed to in the study and how the risks will be minimized

- Describe the relationship between Hazards (potential source of harm) and ultimate Harm (injury or damage)

Assessment of Risk – **Characterization**

The extent of risk(s)/harm(s) in an IDE study takes into account the following factors, individually and in aggregate:

1. Type of Risk(s) (including severity) – Basic safety, device-related serious and non-serious adverse events, procedure-related complications due to the investigation, risk associated with the study itself (not resulting directly from use of the device), and Risk from false-positive or false-negative results for diagnostics.

Assessment of Risk – **Characterization**

2. Probability or Likelihood of Risk(s) – Use of relevant historical data, prediction using analytical or simulation techniques, use of data from prior investigations, reliability estimates, production data and post production information, and use of expert judgment.

- During earlier device development stages, this may be less certain. Probability levels within an estimated range may be acceptable.
- Includes the likelihood of the hazard resulting in a harmful event. FDA considers whether an event occurs once or repeatedly in assessing the probability of risks.

Assessment of Risk – **Characterization**

3. Duration of Risk(s) - Exposure to subjects temporary, minor harm; cause repeated but reversible harm; cause permanent, debilitating injury.

- Duration or how long the adverse consequence lasts should be considered along with severity of risk.

Assessment of Risk – **Management**

4. Risk Management – Provides a summary and assessment of efforts to mitigate the identified safety concerns, or ensure device use is directed to participants for whom the risk is considered acceptable so not to outweigh the potential for benefit.

- Risk control measures (including risk mitigation):
  - reduce the likelihood and severity of harm to study subjects
  - improve the B-R profile of the proposed study
  - intended to reduce the risk to an acceptable level

Assessment of Risk – **Management**

- Sponsors should:
  - Conduct an initial determination of which risk controls are appropriate
  - B-R assessment should focus on residual risk and reduction to acceptable levels relative to the anticipated benefits to subjects
  - Provide a clear justification for the investigation considering risks for the intended study participants and plan for minimizing those risks.

Assessment of Risk – **Management**

- Forms of risk controls that may be applied to IDE studies are outlined in detail in the guidance under A.4. Risk Management.

Examples:

- Safety by Design
  - Device features and/or modifications to improve safety
- Protective Measures
  - Study Design
  - Study Oversight
  - Adverse Event Reporting

Assessment of Risk – **Management**

5. Residual Risk Evaluation – After risk control measures are applied, the following measures may be considered when evaluating residual risk:

- Risk communication and disclosure of residual risk during the informed consent process (e.g., how subjects can/should act to further control or mitigate risk)
- When reliable information is available, consider subject perspective and tolerance for assuming risk relative to anticipated benefit
- Initially limit study subjects most likely to experience benefits or subject subset where B-R profile is more favorable (e.g., treatment-refractory patients)

Assessment of Other Risks Considerations

In addition to the previously discussed Risk Characterizations and Management FDA may consider other risks as well:

- Risks related to interpretation of the study data
  - Risk of drawing a false conclusion based on clinical data obtained
  - Risk of data which are inconclusive or difficult to interpret
- Risks to others to consider for example:
  - Risk of radiation exposure of health care practitioner
  - Treated subjects become drowsy while operating a vehicle

Assessing Benefits and Risks in the IDE Realm

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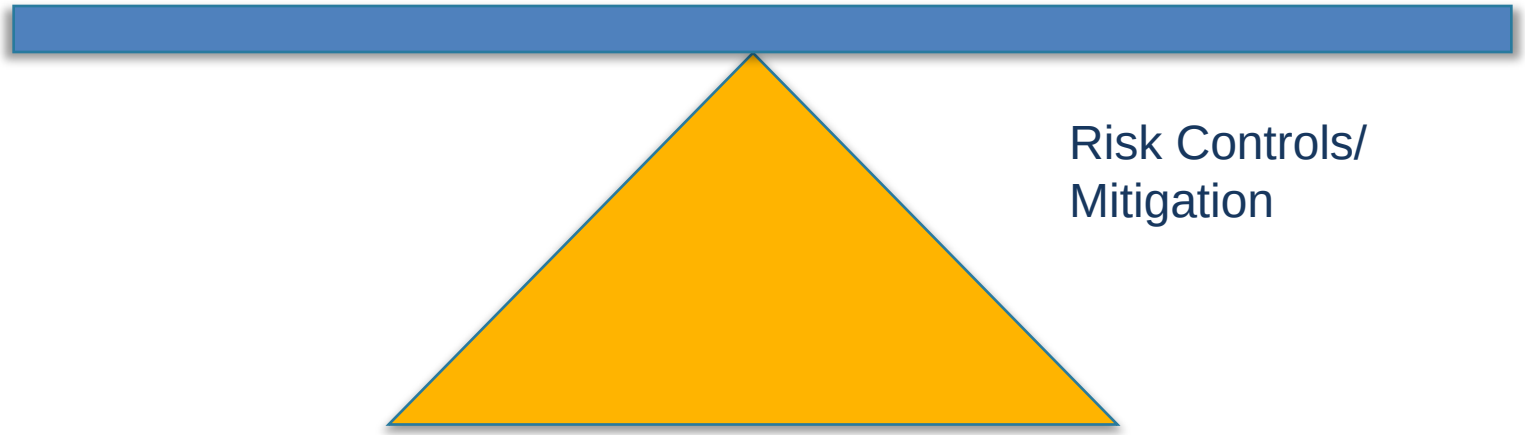


Risk Controls/
Mitigation

Assessment of Anticipated Benefits to Study Subjects

Direct Benefits: Benefits that may be realized by subjects participating in the research include:

- Type of benefit(s) – Examples include; closer surveillance of clinical management and QoL. For diagnostics; identify a specific disease for early intervention, or identify patients more likely to respond to therapy.
- Magnitude of benefit(s) – anticipated change in subjects condition or clinical management, questionnaire analysis provides insight into subjects' preference

Assessment of Anticipated Benefits to Study Subjects

Direct Benefits (cont.):

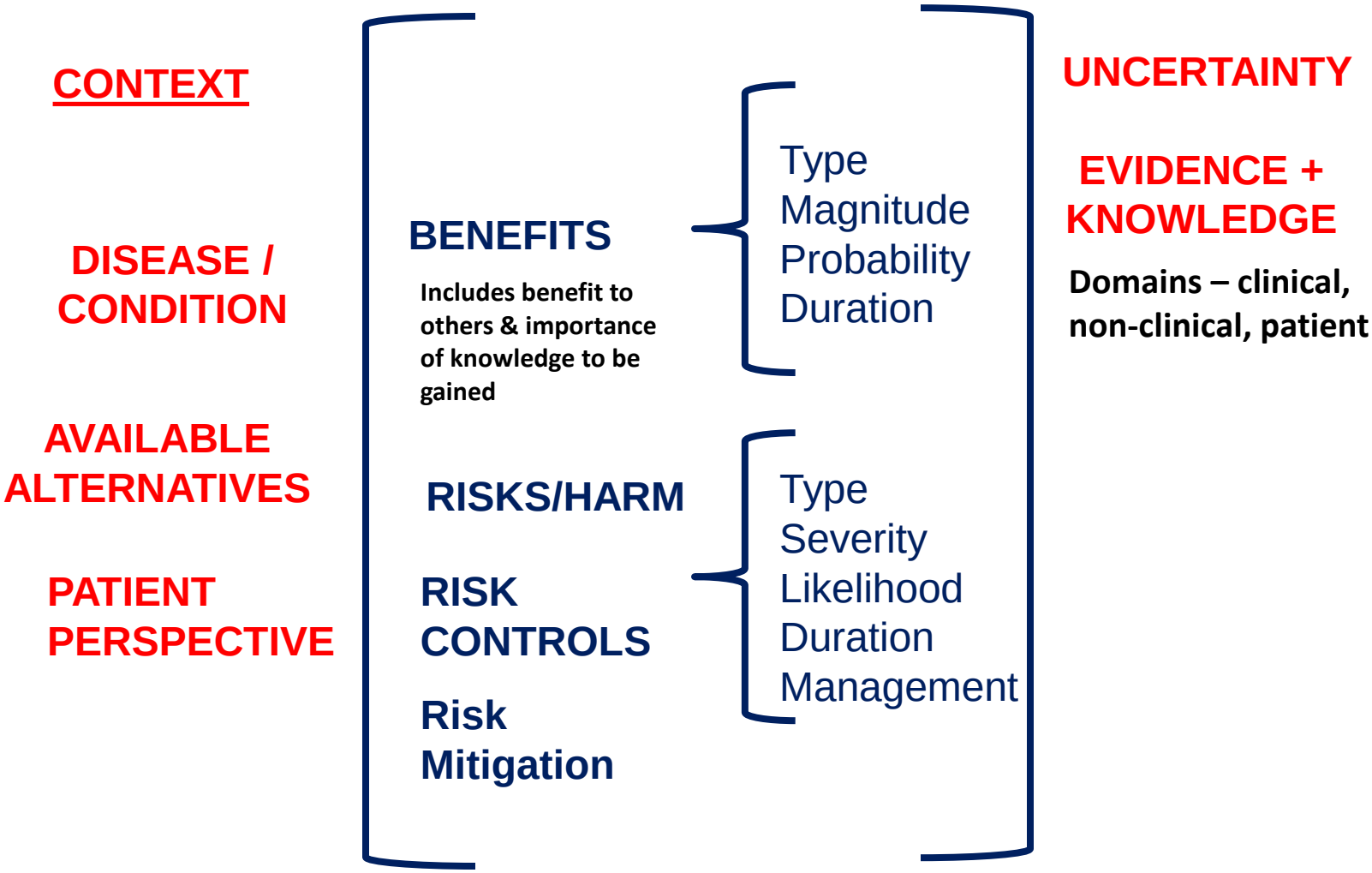
- Probability of subject experiencing one or more benefit(s) – Based on evidence from prior investigations and early stages of device development it may not be possible to assess the probability of subjects experiencing one or more benefits.
- Duration of effect(s) – How long can the benefit be expected to last? Some treatments are curative and others are repeated over time. To the extent the effect is known, the duration of effect may influence how the benefit is defined over time.

Assessment of Benefits to Others

A benefit to others of an investigational study is the "importance of knowledge to be gained" (21 CFR 812.30(b)(4))

- A societal benefit or increases the understanding of a disease condition, potential treatment or diagnostic applications
- Benefit unique to research (e.g., doesn't apply to marketing applications)
- Subjects may not receive direct benefit but willingness to participate due to indirect benefits of increasing generalizable about the disorder or condition being studied.

Putting It All Together - Framework For B-R Assessment



Assessing Benefit and Risks for IDE Applications – **Device Description**

Regulations require that the Investigational Plan includes:

Description of this device (a description of each important component, ingredient, property, and principle of operation of the device and any anticipated changes in the device during investigation - 21 CFR 812.25(d)

- Appendix C in the guidance lists the device attributes that FDA recommends to include in the IDE application; Device Description Section
- Deficiencies related to an incomplete or inadequate device description are the single most common type of non-protocol related deficiency and results in failure to attain full IDE approval

Assessing Benefit and Risks For IDE Applications – **B-R Framework**

Appendix A – Guidance

1. Context of Proposed Investigation
   - Summary of the disease/condition, context of currently available treatment or diagnostic options, brief description of trial objective/design.
2. Assessment of Risks
   - Summary of key risk elements identified in Section 5 of the guidance including risk characterization, risk control measures (i.e.; risk mitigation) and residual risk.

Assessing Benefit and Risks For IDE Applications – **B-R Framework**

3. Assessment of Benefits
   - Summary of key benefits identified in Section 5 of the guidance including direct benefits to study subjects and benefits to others (importance of knowledge to be gained or contribute to developing a treatment)
4. Consideration of Patient Preference Information
   - Summary of patient preference information if available. If none, state that none available.

Assessing Benefit and Risks For IDE Applications – **B-R Framework**

5. Assessment of Uncertainty
   - Summarize key sources of uncertainty in the available evidence and proposed investigation identified in Section 5 of the guidance.
   - Provide a rationale for why the level of uncertainty is acceptable for the proposed investigation.
6. Conclusions
   - Summarize how the consideration of the factors discussed in this summary justify the decision to proceed with the clinical investigation.

References

Guidance Document Links

- *Factors to Consider When Making Benefit-Risk Determinations for Medical Device Investigational Device Exemptions - 2017*
- *Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications - 2016*
- *FDA Decisions for Investigational Device Exemption Clinical Investigations - 2014*
- *Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies - 2013*
- *Patient Preference Information – Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling - 2016*

Panel Discussants

- *Karen Ulisney, M.S., CRNP*, Policy Analyst, Clinical Trials Program, Office of Device Evaluation
- *Owen Faris, Ph.D.*; Director, Clinical Trials Program, Office of Device Evaluation
- *Soma Kalb, Ph.D.*; Director, IDE Program, Office of Device Evaluation
- Special Thank you to *Katie O'Callaghan* (CDRH, Assistant Director for Strategic Programs) for her expertise and contribution to this guidance development

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Questions?

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Under Heading: How to Study and Market your Device
Clinical Studies/IDE