Investigational Applications in OBRR

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Presentation Outline

- **What is an IND/IDE and when do you need one?**
- Components of the application
- Review process
- Amendments, supplements and annual reports
- Open Protocol INDs

What is an IND/IDE?

- An exemption to the regulations regarding interstate commerce permitting clinical investigations
  - "An **investigational new drug** for which an IND is in effect in accordance with this part is exempt from the premarketing approval requirements that are otherwise applicable and may be shipped lawfully for the purpose of conducting clinical investigations of that drug." (21 CFR 312.1)
  - "An approved **investigational device exemption** (IDE) permits a device that otherwise would be required to comply with a performance standard or to have premarket approval to be shipped lawfully for the purpose of conducting investigations of that device." (21 CFR 812.1)

How are INDs and IDEs used in OBRR?

- In OBRR, INDs are used for biologics and required for blood donor infectious disease screening devices
  - CMV, syphilis blood donor screening devices are not subject to the IND requirements
- In OBRR, IDEs are required for PMA and 510(k) significant risk studies for devices

When do you NOT need an IND?

- You will need an IND unless your drug, biologic or device investigation is exempt
- IND exemptions under 21 CFR 312.2 (b): see regulations for full list
  - Blood grouping reagents/reagent RBC/anti-human globulin
  - Studies with approved devices if not involving changes to intended use, labeling, advertising or risks of product use
  - Product meets definitions of a tissue (21 CFR 1200s)

When do you NOT need an IDE?

- IDE exemptions listed under 21 CFR 812.2 (c)
- Studies may be significant-risk (SR) or non-significant risk (NSR)
- IDEs are required for significant-risk clinical studies only [21 CFR 812.3 (m)]
  - "…presents a potential for serious risk to the health, safety, or welfare of a subject"
  - Most device studies are NSR under IDE regulations
  - You may request for study risk classification (Q-submission)

When do you Need an IND/IDE? – Before You Begin Your Clinical Study

- If your study involves a new device
- If your study with a licensed/approved device
  - Involves a new patient population
  - Increases the risks associated with use
  - Is intended to support a labeling or advertising change for the licensed/approved device
- You may request an INTERACT meeting and/or pre-submission feedback as you prepare your study
  https://www.fda.gov/vaccines-blood-biologics/industry-biologics/interact-meetings-initial-targeted-engagement-regulatory-advice-cber-products

Additional regulations applying to IND/IDE

- 21 CFR 50 Protection for Human Subjects, Informed Consent (IC) Regulation
  - Provides requirements for informed consent for human subjects and additional safeguards for pediatric subjects
- 21 CFR 54 Financial Disclosure of Investigators
  - Requires disclosure of certain financial arrangements between sponsors and clinical investigators, to minimize bias and allow FDA to assess data reliability
- 21 CFR 56 Institutional Review Boards (IRBs)
  - Standards for composition, operation and responsibilities of IRBs that review FDA-regulated clinical investigations

Presentation outline (2)

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IND components – 21 CFR 312.23

- Cover letter/Form FDA 1571
- Table of contents
- FDA Form 3674: compliance with clinical trials.gov data bank
- FDA Form 3454/3455: financial statement
- **Investigational plan**
- **Investigator's brochure**
- **Clinical protocol(s)**
- **Manufacturing information**
- **Labeling**
- **Analytical data**
- **Prior human experience**
- Environmental assessment or claim for categorical exclusion

IND components – Investigational plan

- Name of device and manufacturer
- Proposed Intended Use with infection(s) and analyte(s) detected
- Population to be tested (e.g., blood donors, tissue donors, living donors, geographic or seasonal restriction)
- Matrix to be tested (serum, plasma, whole blood, anticoagulants, etc.)
- Summary of prior human experience with device
- Any withdrawals from investigation or marketing in any country for any reason related to safety and effectiveness
- Brief description of the overall investigational plan for the next year

IND components – Investigator's brochure

- Prepared for study participants
- Name of device, infection(s) and analyte(s) detected
- Description of test technology, including platform
- Bibliography of relevant publications
- Summary of study data supporting safe use in humans
- Risk analysis

IND components– Clinical study protocols (1)

- Protocols for each planned study
- Objectives and purpose of study
- Investigator information
  - Statement of investigator/Form FDA 1572 (include all investigators, sub-investigators, research facilities)
  - Statement of qualifications for each investigator (CV)
- Information for all reviewing IRBs
- Informed consent*
- Inclusion/exclusion criteria
- Size of study/studies

IND components– Clinical study protocols (2)

- Study design
  - Include how true positive/negative will be determined (FDA- approved comparator assay, laboratory diagnostic testing)
  - Follow-up study plans
  - Data management/statistical analysis plan
  - Controls

IND components – Manufacturing information (1)

- Sufficient info on design and biological principle to establish safety – **not** the full package that is submitted with a marketing application
- **In vitro substance** – the active component for detection, i.e. primers and probes, antigens, antibodies
- **In vitro product** – all components used in manufacture
- Limited stability information

IND components – Manufacturing information (2)

- Manufacturing sites and locations
- Outline of manufacturing procedures
  - cGMP compliance
- Packaging and storage
- Platform/instrument/hardware
- Software

IND components

- Submit copies of proposed IND labeling
- Device labeling
  - Name of device
  - Name and address of manufacturer
  - “Investigational Use Only” statement
- If there is no approved test, blood units should be labeled noting use of investigational test
- Marketing is not permitted under IND
  - Cost recovery must be approved by FDA (21 CFR 312.8)
  - See https://www.fda.gov/media/85682/download for more information on cost recovery

IND components – Non-clinical/analytical data

- Analytical information supporting the safety of the device under IND
  - Limit of detection
  - Reproducibility/precision
  - Cross-contamination
  - Endogenous/exogenous interference/cross-reactivity
  - Matrix studies
  - Stability under conditions of use
- GLP compliance

IND components – Prior human experience

- If device has been investigated or marketed previously in the U.S., provide detailed information from that experience that is relevant to safety and/or effectiveness
- Copies of published material related to safety or effectiveness
- If no prior human experience, say so

Presentation outline (3)

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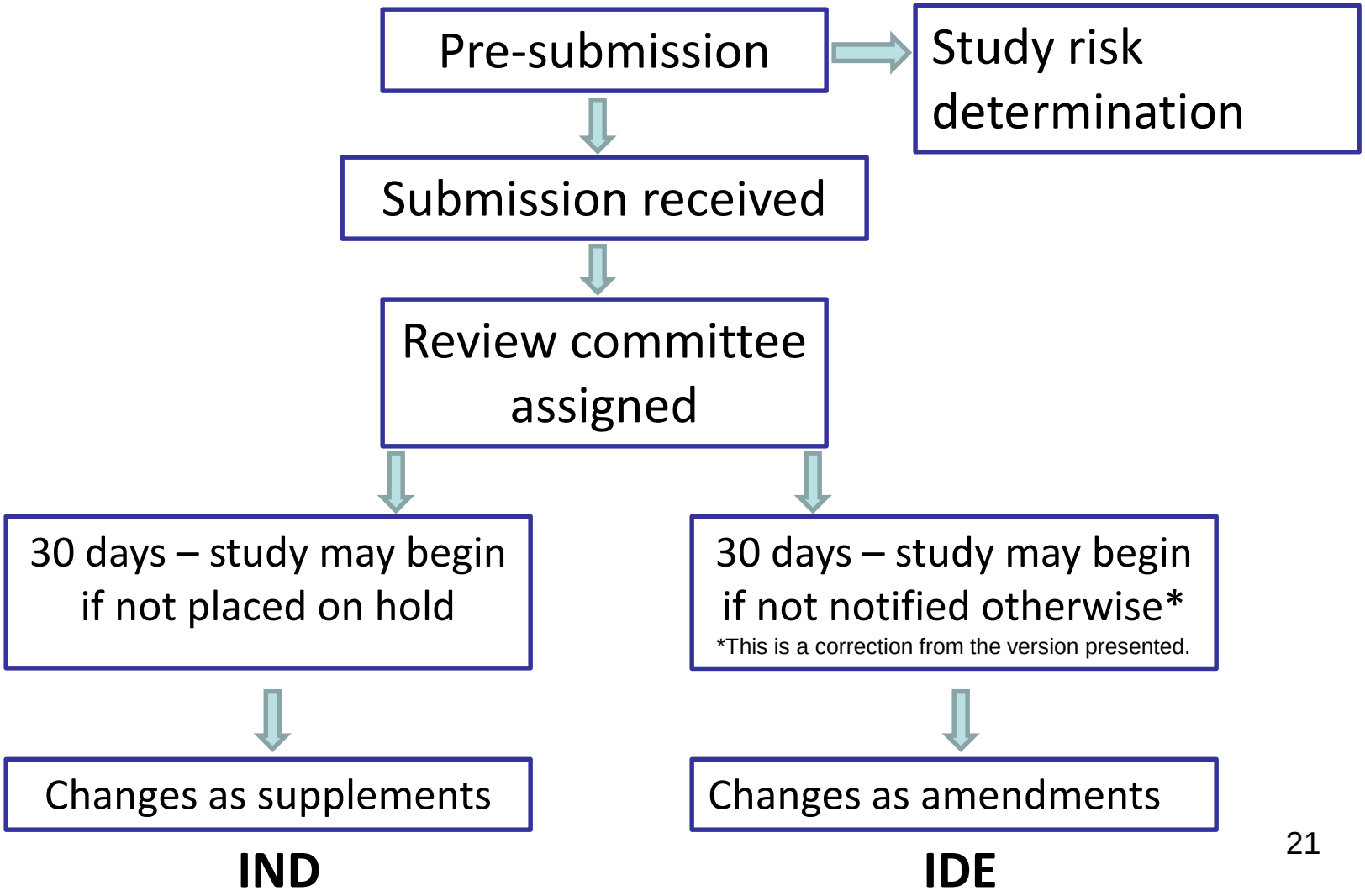
IND/IDE review processes



IND reviews are based on safety

- If, during IND review, it is found that:
  - Human subjects would be exposed to an unreasonable and significant risk of illness or injury
  - The IND does not contain sufficient information to assess the risks to human subjects
  - The clinical investigators named in the IND are not qualified by reason of their scientific training and experience to conduct the described investigation

➢ The IND application may be placed on hold

  - Study may not begin until issues are resolved

IND/IDE reviews are based on safety

- Effectiveness may also be considered for INDs if data is available
- In addition to IND/IDE decision, FDA may provide feedback regarding clinical trial design/technical data and/or future marketing submissions
  - This feedback does not affect the IND/IDE decision

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IND supplements

- Protocol amendments
  - Submit clean and redlined versions of amended protocols
- Informational supplements
  - Update clinical investigators/sites
  - Update technical information
- Safety reports
  - Notify FDA and all investigators ASAP (no less than 15 days) of potential serious risks
  - Occurrence or increase in rate of serious adverse events, findings from other studies or testing
- Withdraw an IND

IND annual reports

- https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-application-reporting-annual-reports
- Individual study information for each study completed and in progress during the previous year
  - Title/protocol number, purpose, patient population, completed or in progress
  - Subject number updates
  - Any available results
- Summary information on IND studies
  - Adverse events, safety reports, dropouts, deaths (if applicable)
  - Preclinical studies completed or in progress
  - Manufacturing/facility changes

IND annual reports (2)

- Update to the general Investigational Plan with plans for upcoming year
- Any revisions to Investigator's Brochure
- Any unreported protocol updates
- Foreign marketing developments
- Log of any outstanding business with FDA (optional)

Presentation outline (5)

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- **Open Protocol INDs**

Open Label Protocol/Open Protocol IND (21 CFR 312.300)

- To obtain additional safety data after controlled trial has ended
- Treatment/study can continue so that subjects and controls may receive the benefits of the investigational device until marketing approval is obtained
- IRB approval/informed consent still applies

Submitting your IND

- https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/information-submitting-investigational-new-drug-application
- Send forms to CBER DCC
- See website for Emergency Use IND requests

IND review process – important considerations

- Secure email is best!
- Please ensure we can reach you during the review period – if we need additional information and cannot reach you or your designated contacts, your submission may be placed on hold when the action due date is reached

Thanks!

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