Clinical Trials Management for Molecular Diagnostics

April 2016

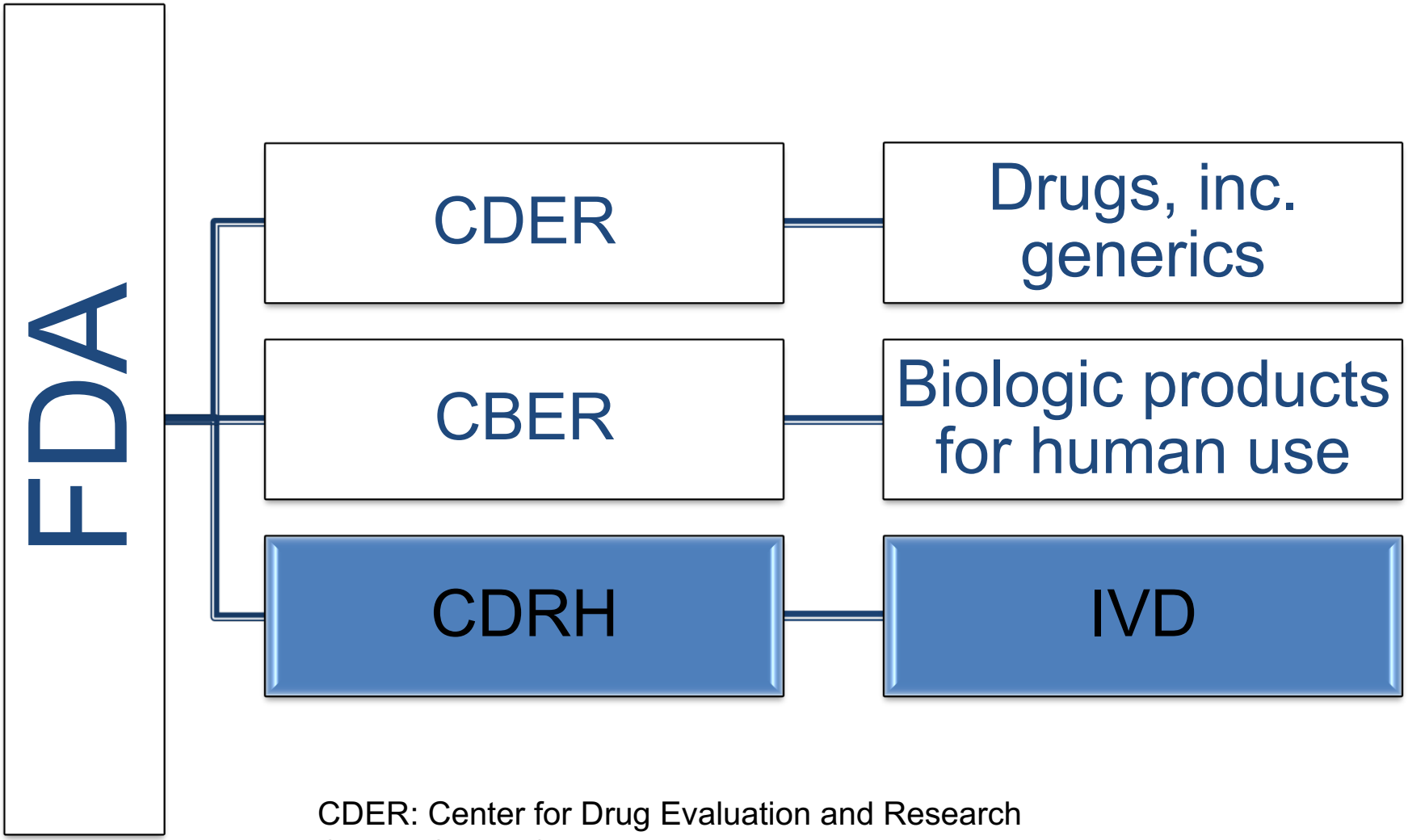
Clinical Operations Responsibilities

- Accrue samples that have proper informed consent for use
  - Retrospective cohorts
  - Remnant samples
  - Prospective collection
- Ensure
  - Samples collected and handled according to protocol
  - Associated necessary clinical annotation
  - Clinical data is verified
  - Samples are available for use at required time intervals
- Define gold standard
- Describe practice patterns and workflow

Types of Studies

	Analytic Validation	Clinical Validation	Health Economics	Clinical Utility	Patient Outcomes
Shows product	Is robust and reproducible	Delivers a consistent, valid clinical result based on a Gold Standard	Has an effect on the overall payer market	Changes the real-world clinical setting Physician behavior	Changes the real-world clinical setting Patient outcomes
Achieves	CLIA launch	FDA submission OUS regulatory strategy	Payer dossier	Payer dossier	Payer dossier
Types of studies	• Sample collection	• Sample collection	• Economic and payer modeling	• Questionnaires • Retrospective chart reviews • Patient registries	• Patient registries • Randomized controlled trials

Regulation of In Vitro Diagnostics (IVD)



CDER: Center for Drug Evaluation and Research
CBER: Center for Biologics Evaluation and Research
CDRH: Center for Devices and Radiologic Health

LDT vs. IVD (FDA-regulated)

- IVD that is designed, manufactured and used within a single laboratory
- Regulated by CLIA via CMS
- FDA has enforcement discretion and has asserted intent to oversee LDTs

	LDT (CLIA)	IVD (FDA)
Includes	• Designed, manufactured and used in single lab	• LDT • Kit used in multiple labs • Companion diagnostics • Direct-to-consumer • Point-of-care
Analytic validity	• Identifies specified analyte • Performed by lab prior to testing in patients • Reviewed during routine survey, after testing has started	• Test system safety and effectiveness • Conducted premarket (prior to use in patients)
Clinical validity	Not reviewed	• Intended use • Gold standard comparator

CLIA: Clinical Laboratory Improvement Amendments
CMS: Centers for Medicare and Medicaid Services

FDA Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs). 2014
www.cms.gov

Good Clinical Practices (GCP)
Human Subject Protection (HSP)

	Food and Drug Administration (FDA)	Office for Human Research Protections (OHRP) U.S. Department of Health and Human Services (HHS)
Protection of Human Subjects (Informed Consent)	21 CFR Part 50	45 CFR part 46 The Common Rule
Institutional Review Boards	21 CFR Part 56	
Investigational Device Exemptions	21 CFR Part 812	N/A
Premarket Approval of Medical Devices	21 CFR Part 814	N/A
Institutional adherence to HHS requirements	N/A	Federalwide Assurance (FWA)

www.fda.gov
www.hhs.gov

Adherence to GCP and HSP Regulations

- Protocol
- Institutional Review Board/Ethics Committee (IRB/EC)
- Investigator qualifications
- Informed consent
- Case Report Form (CRF)
- Critical study documents

Protocol

- General information
- Background
- Objectives and purpose
- Study design
- Selection and withdrawal of subjects
- Management of subjects
- Assessment of efficacy and safety, if applicable
- Statistics
- Direct access to source data/documents
- Quality control and quality assurance
- Ethics
- Data handling and recordkeeping
- Financing and insurance
- Publication policy
- Supplements

FDA Guidance for Industry. E6 Good Clinical Practice: Consolidated Guidance. 1996

Institutional Review Board (IRB)
Ethics Committee (EC)

- Safeguards the rights, safety and wellbeing of study subjects
- Special attention to studies that include vulnerable subjects
- Requirements regarding standardized procedures, membership, frequency of meetings and adherence to regulations
- Registered with HHS via FWA
- Composition
  - At least 5 members
  - At least 1 member with nonscientific primary area of interest
  - At least 1 independent member
- Voting restricted to members who are independent of investigator and study sponsor
- Decisions made at announced meetings with a quorum present according to standard operating procedures
- May invite nonmembers with content area expertise to assist (but not vote)
- Written documentation
  - Member roster with qualifications
  - Operating procedures
  - Records of activities
  - Meeting minutes

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IRB/EC cont'd

- IRB oversight
  - Protocol, including all amendments/revisions
  - Written informed consent form, including all revisions
  - Written information provided to subjects, including questionnaires and advertisements
  - Safety information, if applicable
  - Payment/compensation to subjects
  - Investigator qualification to oversee/enroll in study
  - Deviations from protocol
  - Subject withdrawal of consent
  - Study-related injury
  - Any new information that may adversely affect subject safety or conduct of the study
  - Study results and publications related to the research
- Periodic continuing review of the research (usually annual)
- Written results of IRB review
  - Approval/favorable opinion
  - Modifications required prior to approval/favorable opinion
  - Disapproval/negative opinion
  - Termination/suspension of prior approval/favorable opinion

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Vulnerable Subjects – Special Considerations

- Defined as those whose willingness to participate may be unduly influenced or who are fearful of retaliation for non-participation
- May be additional recruitment, procedural and/or informed consent requirements when enrolling vulnerable populations as determined by IRB/EC
- Includes
  - Medical, dental or nursing students
  - Employees of investigator or sponsor
  - Members of armed forces
  - People kept in detention
  - People with incurable diseases
  - People in nursing homes
  - Unemployed or impoverished people
  - Patients in emergency situations
  - Ethnic minority groups
  - Homeless people
  - Refugees
  - Minors
  - People incapable of giving consent
  - Pregnant or lactating women

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Investigator Qualifications

- Qualified by education, training, experience and specialty to
  - Assume responsibility for conduct of the study
  - Oversee medical care of applicable subjects
- Familiar with conduct of study
- Aware of GCP and applicable regulatory requirements
- Oversees appropriately trained personnel to conduct study activities
- Sufficient time and resources to conduct study and enroll subjects
- Ensures IRB/EC approval prior to subject enrollment
- Complies with protocol
- Complies with requirements governing informed consent
- Documentation
  - Current CV, signed and dated
  - Current active medical license
  - Documentation of training in HSP and/or GCP

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Informed Consent

- Informed consent is a process that culminates in the signing of a written informed consent form (ICF)
- No coercion or undue influence to participate
- No language that causes subject (or legally acceptable representative) to waive or appear to waive legal rights
- Non-technical and understandable language, including appropriate certified translation when needed
- Allow time for all questions to be answered
- Signed and dated by subject/representative before any study-related activities can proceed

FDA Guidance for Industry. E6 Good Clinical Practice: Consolidated Guidance. 1996
FDA In Vitro Diagnostic (IVD) Device Studies – Frequently Asked Questions. 2010

Elements of ICF

- Statement that the study involves research
- Purpose of study
- Study procedures
- Subject's responsibilities
- Expected duration of participation
- Approximate number of subjects who will be enrolled
- Aspects of the study that are investigational
- Reasonably foreseeable risks or inconveniences
- Reasonably expected benefits; if none, disclosure of this
- Statement that subject will be informed of any new information which may affect the decision to participate
- Foreseeable circumstances under which subject's participation may be terminated
- Alternative procedure/course of action to participation
- Compensation and/or treatment available to subject in the event of research-related injury
- Anticipated payment and expenses for participation
- Statement that participation is voluntary, that the subject may refuse to participate or withdraw at any time, and that refusal or withdrawal will have no negative consequences to medical care
- Who may have access to medical records, including sponsor's representatives (monitors, auditors), IRB/EC and regulatory authorities
- Statement that records identifying subjects will be kept confidential and will not be made available in publications/public records
- Contact information regarding the study and the subject's rights as a human subject (usually the IRB/EC)

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Case Report Form

- Paper or electronic document designed to record all protocol-required information on each study subject
- Submitted to sponsor in a timely manner
- Data becomes part of clinical database
- Incomplete or suspected inaccurate data is queried and documentation of responses to all queries is maintained

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Study Reports

- Progress reports
- Safety reporting, if applicable
- Final report

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Study-related Forms and Logs

- Delegation of authority
- Screening/enrollment of subjects
- Sample collection/handling
- Sample shipment
- Refrigerator/freezer temperature tracking, if applicable
- Withdrawal of consent
- Protocol deviation
- Monitoring

Sample Handling and Chain of Custody

- Sample collection, handling and shipping instructions
- Sample labeling/ID
- Site documentation
  - Subject/sample ID
  - Date of collection
  - Time of collection
  - Critical processing time points (e.g., start/stop of centrifuge, time in freezer)
  - Other sample-specific requirements
  - Date and time of preparation for shipment
  - Location (e.g., box), if applicable
  - Shipping information (e.g., tracking number)
  - Deviations from instructions
- Sponsor documentation
  - Date of receipt
  - Received as expected (e.g., frozen, dry ice remaining in box)
  - Date, time and location in freezer
  - Deviations from instructions
  - Actions in response to deviations (e.g., site retraining)

Monitoring

- Verify
  - HSP via IRB approval and informed consent
  - Accurate, complete and verifiable data
  - Study conduct in compliance with GCP and regulations
  - Findings documented in written report
- Risk-based monitoring
  - Establish protocol-appropriate monitoring plan
  - Monitor critical data elements at higher rate than non-critical elements
    - Informed consent for samples used in validation
    - Subject eligibility
    - Justification of diagnosis used for gold standard

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Critical Study Documents

	Trial Master File	Site
Correspondence with FDA, regulatory authorities	X	
Clinical research agreement	X	X
Protocol and amendments	X	Signed by investigator
IRB documentation	X	Site-specific
ICF	X	Site-specific
Clinical research agreement	X	X
Subject recruitment materials	X	Site-specific
Investigator qualifications	X	Site-specific
Site/investigator training, including sample handling	X	Site-specific
Shipping records	X	Site-specific
Executed informed consent forms		X
Completed CRFs	X	Site-specific
Study-related forms and logs	X	Site-specific
Study-related reports	X	Site-specific

THANK YOU

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