Highlights from

SOCRA

SOCIETY OF CLINICAL RESEARCH ASSOCIATES

FDA Clinical Trial Requirements, Regulations, Compliance and Good Clinical Practice.

Atlanta Ga. November 6th and 7th , 2013

Presentation Objectives:

- Describe how Good Clinical Practice works to regulate clinical trials
- Develop an increased awareness of current adverse events, risks and problems that occur in human research
- Define FDA expectations in Pharmaceutical trials
- Review how studies with investigational devices differ from drug and biologic studies
- Discuss the array of actions taken when research fails to meet standards enforced by the FDA

FDA changing policies to modernize

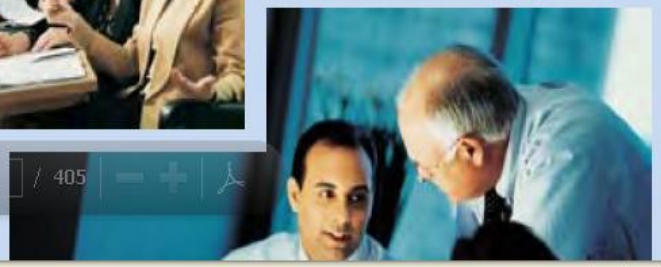
- Complex clinical trials
- Novel Therapies
- Multi-site
- International studies
- Vulnerable populations

- Ever-changing pool of investigators
- More independent IRB's
- Outsourcing of responsibilities
- Increasing IRB burdens
- Increasing public mistrust in clinical trial process

GCP and New FDA Initiatives

- **Concern that human subjects may not be adequately protected**
- **Original regulations written in the ‘70s and *‘80s***
- **Critical Path Initiative – 2004**
- **HSP/BIMO Modernization – 2006**
- **Other Collaborative Efforts**

Human Subjects Protection Resource Book



Human Subject Protection

- **Everyone is Responsible!**
- **FDA regulations and ICH E6 comparable**
- **IRB registry was created to have greater oversight by the FDA**
- **Increased oversight of financial disclosures**

Critical Path Initiative

Transforming the way FDA-regulated products are developed, evaluated, and manufactured

Modernizing the FDA

- **HSP/BIMO Modernization Initiative – formation of the HSP/BIMO Council – 2006**
- **This council is the guiding body and decision-making group for GCP policy/regulation development**

FDA Initiatives

- *Not a complete list – recent guidance's*
- 21 CFR 50, Subpart D- Additional Safeguards for Children in Clinical Investigations [final rule published February 2013]
- Q&As on charging for investigational drugs under an IND [draft guidance May 2013]
- Q&As on Expanded Access to Investigational Drugs for Treatment Use [draft guidance May 2013]

FDA Initiatives

- A Guide to Informed Consent [draft not released yet]
- IRB Responsibilities for Reviewing the Qualifications of Investigators, Adequacy of Research Sites, and the Determination of Whether an IND/IDE is Needed [final guidance August 2013]
- Oversight of Clinical Investigations - /a Risk-Based Approach to Monitoring [final guidance August 2013]
- Electronic Source Documentation in Clinical Investigations [final guidance September 2013]

FDA/CTTI CI Course

- **Conducted yearly 2009-2013**

- **May watch past presentations posted at:**
- **http://www.fda.gov/ScienceResearch/Special**

  Topics/CriticalPathInitiative/SpotlightonCPIProjects/ucm201459.htm

Where is All this Going?

IRB Deficiencies

- Inadequate initial and/or continuing review
- Inadequate SOPs
- Inadequate membership rosters
- Inadequate meeting minutes
- Quorum issues
- Inadequate communication with CI/institution
- Specific to devices – lack of incorrect SR/NSR determination

S/M/CRO Deficiencies

- Inadequate monitoring
- Failure to bring investigators into compliance
- Inadequate accountability for the investigational product
- Failure to obtain FDA and/or IRB approval prior to study initiation

Good Laboratory Practice Deficiencies

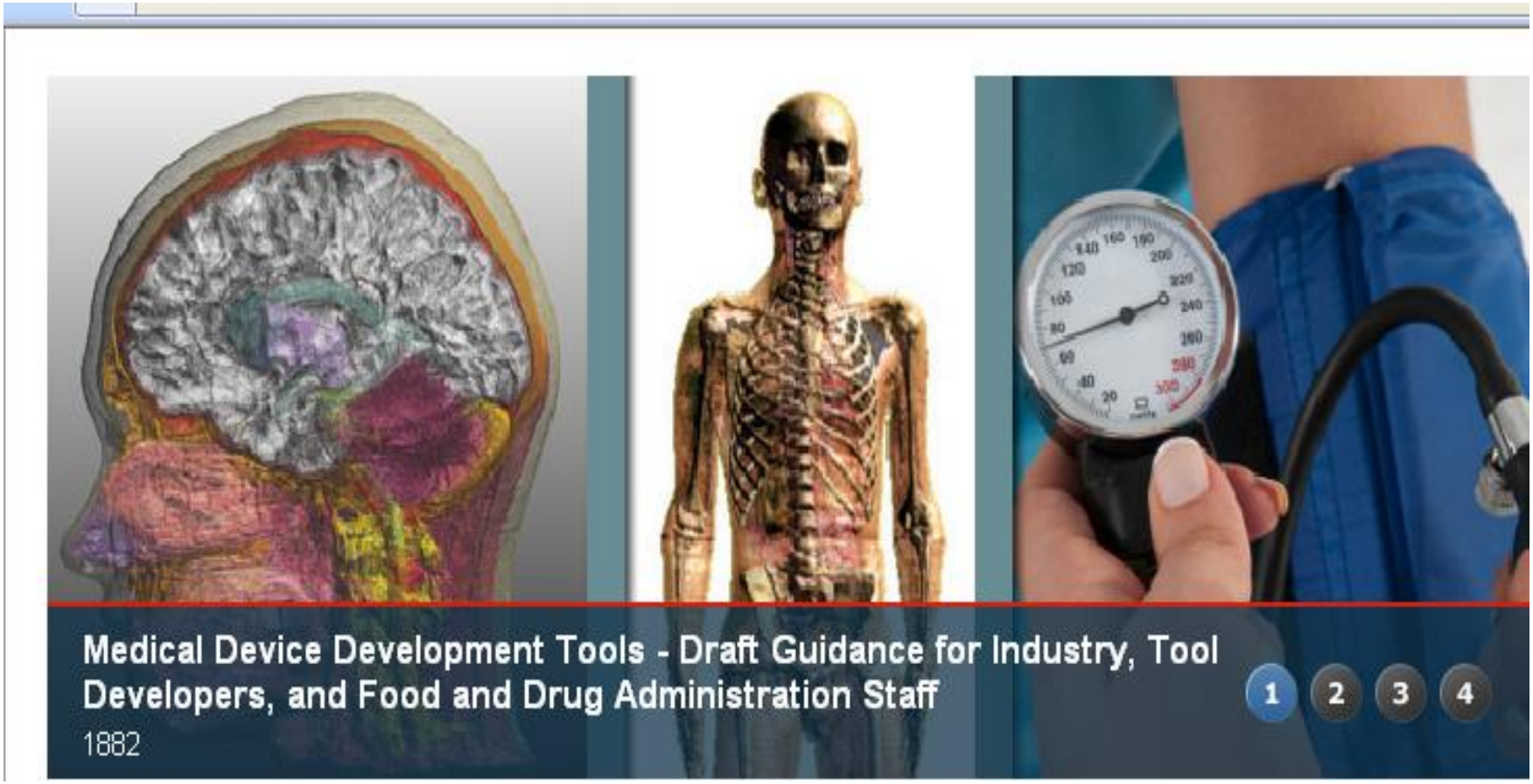
- Organizational and/or Personnel inadequacies
- Incomplete/inadequate/no study records
- Inadequate/no standard operating procedures (SOPs)
- Protocol deviations
- Incomplete/inaccurate study reports

Clinical Investigator Deficiencies

- Failure to follow the investigational plan and/or regulations
- Protocol deviations
- Inadequate recordkeeping
- Inadequate accountability for the investigational product
- Inadequate communication with the IRB
- Inadequate subject protection (including informed consent issues)

Site Conduct

- **Common factors that may affect the ability to provide adequate supervision for trials.**
  - **Inexperienced study staff**
  - **Demanding working load**
  - **Complex clinical trials**
  - **Conducting multiple trials concurrently**
  - **Subject population that is seriously ill**
  - **Conducting a study at multiple sites under the oversight of a single PI**


Medical Device Development Tools - Draft Guidance for Industry, Tool Developers, and Food and Drug Administration Staff
1882
1
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Review how investigational devices studies differ from drug and biologic studies

- Separate team at FDA reviews Device Studies
- Device versus Drug Determination

Regulatory Distinction

- Devices:
- Investigator agreement generated from the sponsor per 21 CFR 812
- Drugs:
- Statement of Investigator Form FDA 1572

Device Trials 21 cfr 812

- 1.LCD
- 2. Implication of device
- 3. Nature of the firms and studies ,
- 4. Statutory distinction, and regulatory distinctions

Research Distinctions Device Trial

- Subject population is usually over 100's not 1000's
- Phases: feasibility then pivotal study
- Blinding less common
- Controls vary no placebo rather a sham.

Strategies to conduct a qualified device study

- Selecting qualified investigators
- Obtain feedback on protocol requirement
- Provide training up front
- Ensure adequate monitoring
- Adequate facilities
- Sufficient number of staff
- Feasibility of tests

Develop an increased awareness of current adverse events, risks and problems that occur in human research

- Be aware of past problems with clinical trials and learn from them
- Research the clinical trial proposal and sponsor for past/current problems
- Negotiate safety processes with the sponsor

Discuss the array of actions taken when research fails to meet standards enforced by the FDA

- Last Objective…
- We will start with Who, What and When

Who will get audited? Most Likely Candidates

- Risk based selection
- Clinical Trials involving vulnerable populations
- Sites with no inspection history
- Sites that have had audit problems in the past
- High risk studies
- Novel products

What will happen?

- You will receive a phone call from an FDA Inspector to set a date
- Inspector will come to site for 3 – 7 days
- Records/Study procedures will be audited per Federal Regulations (Guidances not enforceable)
- Expect 100% of Informed consents to be audited
- Audit results: NAI, VAI, OAI
- Trial can be stopped, Data can be rejected, CIs can be disqualified to receive IP, Prosecution

When can you expect feedback?

- Daily wrap-up meetings during the audit
- Closing Discussion – may include issuing a Form FDA 483
- If FDA 483 is issued – a written response is due within 15 business days.
- Your response is very important and will be taken into consideration in the determination of a final regulatory action
- Documentation of the corrective and preventative actions is very important

Take home – Safety

- Stand up to issues that affect patient safety!
- Have Quality Assurance Practices that maintain Subject Safety
- Use pre-printed order sets
- Use units of measure when recording data
- **Coordinate research staff with clinical staff providing care**

Take home – Panel Discussion

- Become familiar with Inspection Guidelines
- www.fda.gov/scienceresearch/specialtopics/runningclinicaltrials/ucm160670.htm
- Inspectors use CPGM 7348.811 Part III to guide their inspections
- Keep straight what the sponsors want reported and what the IRB wants reported. It may not be the same.
- FDA does not want to 'double-regulate' products..Biologic/Device if it already has an IND, it does not need an IDE. FDA departments will work together.

Questions?