FDA’s Clinical Investigator Course

Cosponsored by

FDA’s Office of Critical Path Programs (OCPP)
and
The Clinical Trials Transformation Initiative (CTTI)
The Clinical Investigator’s Role in Drug Development

FDA Clinical Investigator Training Course

The Clinical Trials Transformation Initiative Steering Committee

November 9, 2011
Speakers / Panel

Elliott Levy, MD
Bristol-Meyers Squibb

John Orloff, MD
Novartis

Barbara Tardiff, MD
Parexel International

Yvonne McCracken, MPH, CCRC
Carolinas Research Associates
Agenda

• Opening Remarks

• Presentations
  ▪ The Investigator as collaborator in promoting the clinical research enterprise
  ▪ The investigator as the responsible physician
  ▪ The investigator as the custodian of the data chain
  ▪ The investigator as a trusted partner

• Question and Answer
The Investigator as collaborator in promoting the clinical research enterprise

John Orloff, MD
Novartis
But for clinical investigators and the participants in clinical trials, there would be no new therapies, or new information about existing therapies.
Communicating the Importance of Clinical Trials

- To establish new therapies for unmet needs
- To increase knowledge transfer to clinical practice
- To provide “evidence-based” patient care
- To improve the quality of care
  - Patients participating tend to receive better care
  - Future patients benefit from the knowledge gained
One world – one expectation

Europe - 37607
Canada - 3370
US - 25748
LA/AFME - 11125
Asia + Australia - 11000

Total ~ 90,000 Patients
Establishing and maintaining the environment

- Community outreach to educate and inspire practicing physicians and the general public, and share best practices with other investigators
- Support and participate in clinical investigator training programs
- Advocate for policies to increase the efficiency and quality of clinical trials
- Actively seek to reduce barriers and facilitate smooth operational efficiency at your own institution
  - Contracting / legal reviews
  - Informed consent / IRBs
  - Dedicated trials liaison/operational group
- Convey site learnings to sponsor to improve future trial conduct
Communicating Results and Adopting Innovation

- Communicating results to trial subjects in patient-friendly manner
- Communicating results to the scientific community
- Communicating results to peers and colleagues
- Assist in the interpretation of results posted on CT.gov
- If you participated in a clinical trial that yielded an important medical innovation, you have an obligation to contribute to the adoption of that innovation
The Investigator as Responsible Physician

Elliott Levy, MD
Bristol-Meyers Squibb
The Investigator as Responsible Physician

• The sponsor contributes to safeguarding the patient through:
  – Deep knowledge of investigational product
  – Design of protocol with appropriate safeguards, drawing on know-how from diverse scientific disciplines
  – Monitoring the evolving study and program level safety database for signals
  – Training the investigator and providing interim safety updates

• Other parties, such as IRBs, also make important contributions to patient safety

• But the sponsor is not at the bedside – the investigator is the critical link to the patient
The Investigator as Responsible Physician

- The investigator acts as the responsible physician by:
  - Selecting subjects who meet all inclusion and exclusion criteria and are otherwise suitable (applying judgment and giving the benefit of the doubt to the patient)
  - Informing and engaging the patient, beginning with the informed consent process and continuing throughout the study, to promote adherence to the protocol as well as other health promoting behaviors
The Investigator as Responsible Physician

- The investigator acts as the responsible physician by:
  - Maintaining a high level of involvement in the care of the patient, and documenting that involvement
  - Managing the patient according to the protocol, obtaining all protocol mandated evaluations and following all safety procedures, such as dose modifications and interruptions
  - Applying clinical judgment, in consultation with the sponsor, in situations that are beyond the scope of the protocol
The Investigator as Responsible Physician

• The investigator acts as the responsible physician by:
  – Managing the team who care for the patient, and ensuring appropriate levels of institutional support
  – Functioning as the link with other providers of health care to the patient while they are participating in the trial
  – Maintaining high levels of vigilance for adverse events, understanding that many AEs are ‘unexpected’ in early phases of the lifecycle of a medicine
The Investigator as Responsible Physician

- Outcomes in clinical trial participants are typically more favorable than in similar patients managed outside clinical trials.
- While patient selection plays a role in producing favorable outcomes, the role of the investigator in meticulously managing the care of trial subjects is a larger factor.
- With appropriate attentiveness to study treatment, evaluations, and adverse events, the risk inherent in receiving experimental therapy is managed so to assure a favorable balance of benefit and risk.
The Investigator as the Custodian of the Data Chain

Barbara Tardiff, MD
PAREXEL International
Agenda

• The investigator as the custodian of the data chain.
What does good look like

• A relentless attention to detail and an impeccable ability to:
  – Follow GCP
  – Carry out the protocol precisely as written

• An insatiable passion for
  – accurate,
  – complete, and
  – contemporaneous documentation.
Following GCP and regulations

- Read and understand the Investigator’s Brochure
- Obtain EC/IRB approval
- Obtain and document Informed Consent for every subject
- Report Adverse Events
- Principal Investigator must personally conduct or supervise the study
- Ensure that all study personnel understand their obligations to meet all of the above and are trained appropriately
Carry out protocol as written

- **Right patients, randomized correctly, dosed correctly, and accurate and complete data to evaluate endpoints of study**
- Instruct the subject to disclose his/her trial participation if he/she receives emergency medical attention for any reason (or is treated by another medical practitioner)
- If there are challenges to executing as written it is important to communicate this to the study sponsors
Accurate Data

- Develop a data quality management plan focusing on areas of highest risk for errors that matter
- Encourage the use of subject diaries where provided (written or electronic)
- Try to elicit as much information as possible about AEs
Complete data

- **AEs**
  - Discuss the occurrence of AEs with subjects
  - Emphasize the importance of reporting all events
  - Tell the subject how long he/she will be required to report AEs
  - Capture as much data as possible about serious AEs

- **Efficacy endpoints**
  - Avoid “lost to follow-up”

- **Conformance to Protocol (Inclusion/Exclusion Criteria, Dosing and compliance)**
  - “The site failed to document that all of the subjects enrolled met the inclusion criteria of health status and age, as required by protocol sections [redacted].”
Contemporaneous Data

• Enter data at time of visit or other event
  – Minimizing latency between when information is known and available to study sponsor improves patient safety
    • “For subject X, the worksheet was signed off on 11-Mar-05, with boxes checked indicating eligibility for XXX levels and run-in drug compliance. However, these results were not available until 01-Apr-05.”

• Document activities as they occur
  – Creates record that study was executed in accordance with GCP and protocol
    • “The Delegation of Authority Log was not signed by the Principal Investigator prior to delegated duties being carried out.”
    • “Two of the subjects enrolled in the study by [redacted] had no documentation in their study records that informed consent was obtained.”
    • “There was no documented GCP training for one of the Sub-Investigators.”
The Investigator As Trusted Partner

Yvonne McCracken, MPH, CCRC
Carolinas Research Associates
Top Investigative Site Operating Concerns
(Percent of Respondents)

- Slow Payments and Reimbursements from Sponsors: 40%
- Rising Operating Costs: 29%
- Complying with Regulatory Requirements: 26%
- Hiring and Retaining Staff: 18%
- Difficulty Recruiting Patients: 14%

Source: CenterWatch Survey of 347 Investigative Sites (2009)
Ken Getz from Site Solutions Summit 2010
The Investigator As Trusted Partner

• Protocol review for feasibility
  – Do you have the staff, time, equipment and space to do this study?

• Communication with Sponsor
  – Expectations to be communicated clearly and often… in writing.

• Rapid study start-up
  – Turn around time for CDA, contract & budget, regulatory documents, etc.
  – Local or Central IRB

*Note: Approximately 7% of ALL sites actually deliver what they proposed in the feasibility assessment*
The Investigator As Trusted Partner

- Timely enrollment
  - Do you have the patients in your practice or will need to advertise for them? If advertising is used, what is the best media for a particular indication? How long will it take to find the people who meet the criteria?

Notes:
- 90% of all clinical trials fail to meet enrollment target
- 20% of sites are responsible for 50+% of the patients;
- 20% of sites fail to enroll a single patient;
- 30% under-enroll
The Investigator As Trusted Partner

• Efficient, and businesslike operations
  – Do you know your costs? Will the budget accommodate the resources required for this study: time, staff, OH, equipment, drug and materials storage, long-term storage, etc.?

• Adherence to FDA Regs/ICH Guidelines
  – Is your staff familiar with the regs/guidelines or do they need training?
  – Do you have SOPs in place?
  – Do you have an internal audit program?

*Note:* 14% of all active sites receive at least one complaint for non-compliance and fraud annually
The Investigator As Trusted Partner

- Study staff
  - Study coordinator: What qualifications do you need in a study coordinator? What kind of training will be required?
  - Regulatory, legal and budgeting: who is going to handle these items?
  - Sub-investigator: Who is going to be the sub-I and what are they expected to do?
  - Communication with staff: how is it done and how documented – staff meetings, hallway meetings?
The Investigator As Trusted Partner

• Delegation of duties
  – What can be delegated? What kind of training is required for duties that are delegated.

• Training
  – When is training to be done?
  – Who is doing the training?
  – How is it documented?
Supporting Sites for Success: Top Factors Ensuring Best Performance

- Availability of Qualified, Eligible Study Volunteers: 63%
- Completeness of Information about the Study: 55%
- Scientific Interest in the protocol: 49%
- Reasonableness of the Study Budget: 34%
- Protocol Feasibility: 32%
- Familiarity with Sponsor: 29%
- Early Input into Protocol: 20%

Sources: TCSDD Survey of 3,516 Sites, 2010