



U.S. Food and Drug Administration

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# FDA's Clinical Investigator Course

*Cosponsored by*

*FDA's Office of Critical Path Programs (OCCPP)  
and  
The Clinical Trials Transformation Initiative (CTTI)*



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# The Clinical Investigator's Role in Drug Development

FDA Clinical Investigator Training Course

The Clinical Trials Transformation Initiative  
Steering Committee

November 9, 2011



U.S. Department of Health and Human Services

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## ■ ■ ■ 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



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## ■ ■ ■ A Noble Calling

But for clinical investigators and the participants in clinical trials, there would be no new therapies, or new information about existing therapies.

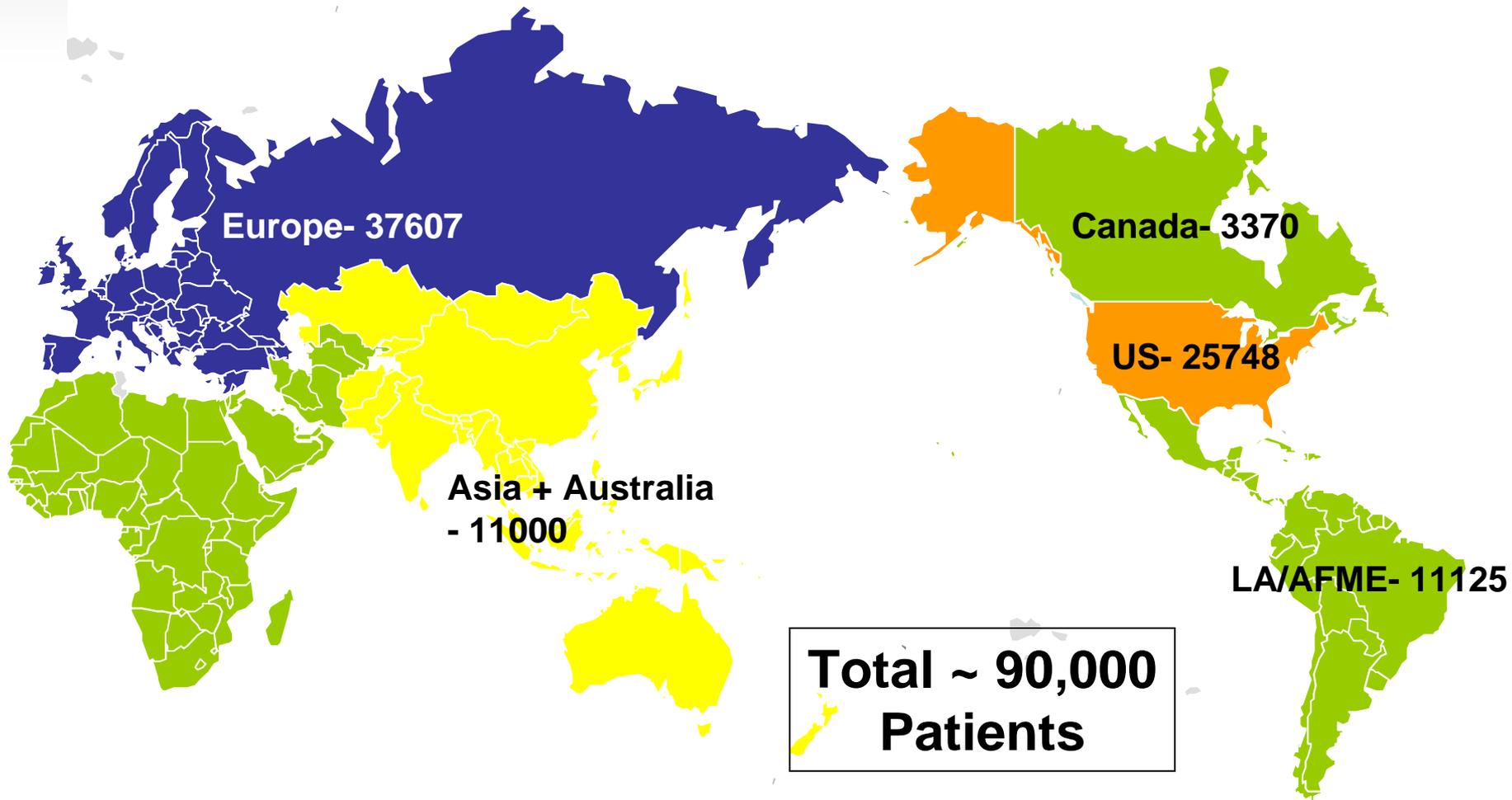


# Communicating the Importance of Clinical Trials

- 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





# 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



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# 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



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# 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



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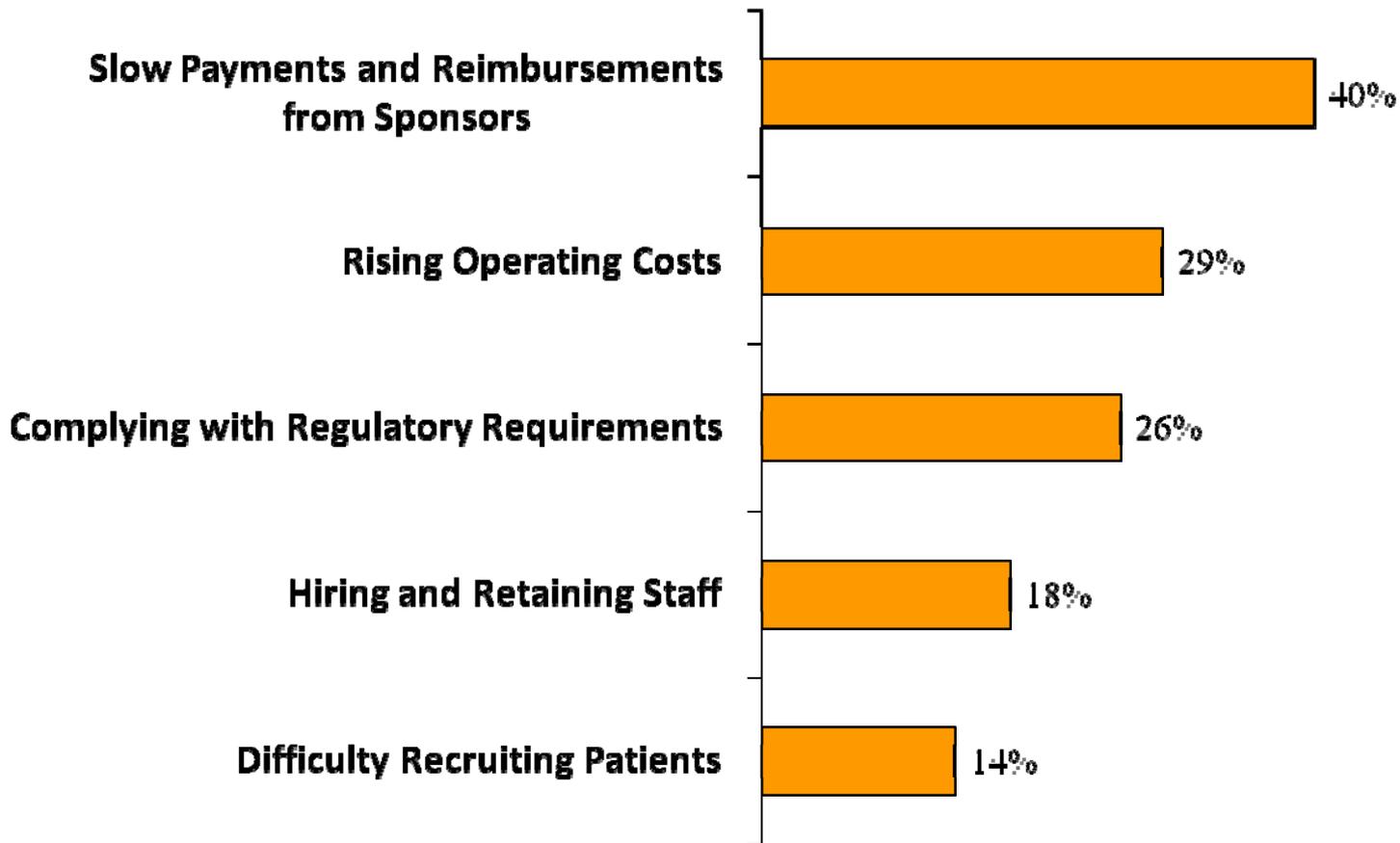
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# Top Investigative Site Operating Concerns

*(Percent of Respondents)*



*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

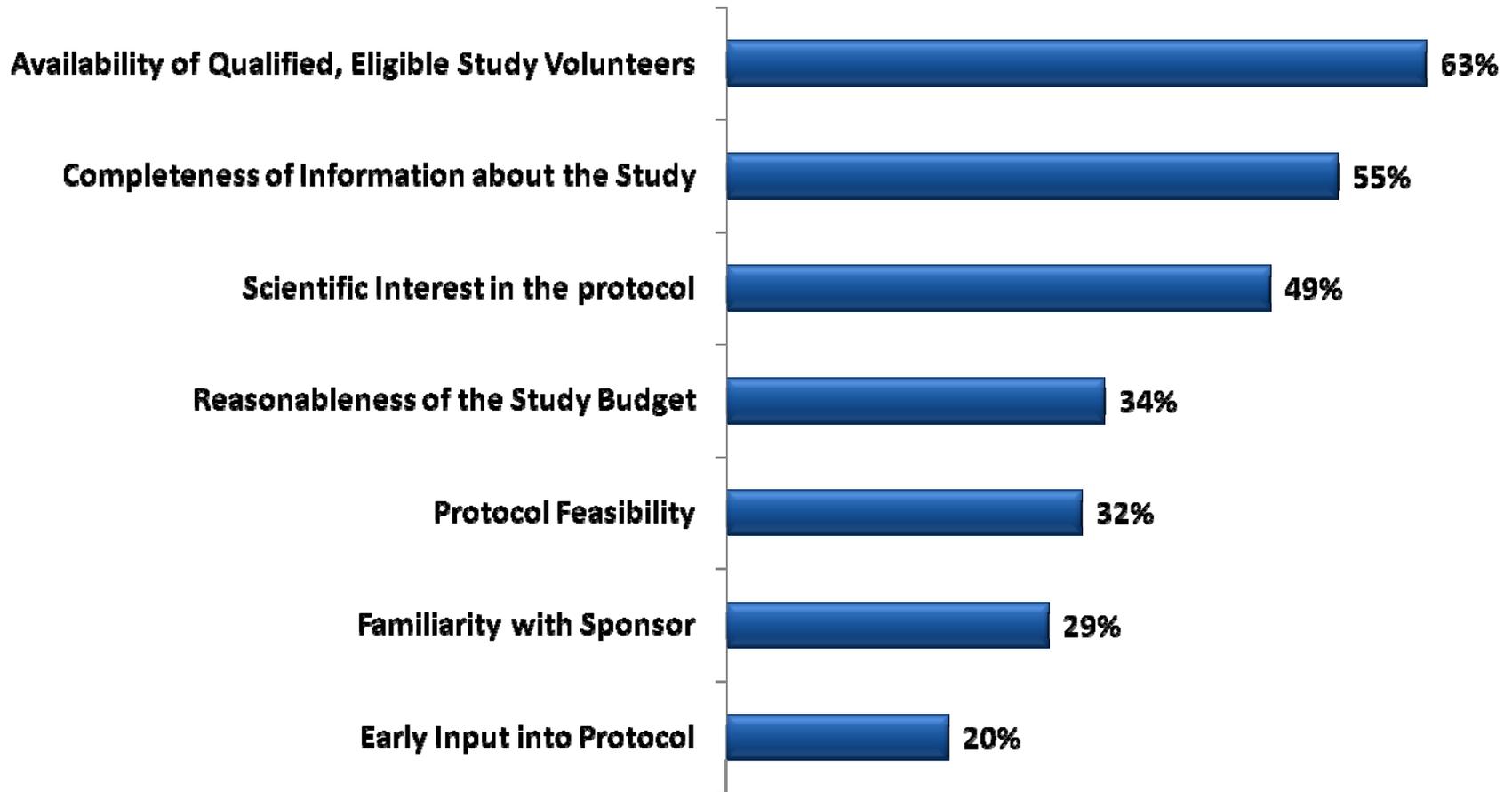
- Study staff
  - Study coordinator: What qualifications do you need in a study coordinator? What kind of training will be required?
  - Regulatory, legal and budgeting: who is going to handle these items?
  - Sub-investigator: Who is going to be the sub-I and what are they expected to do?
  - Communication 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



Sources: TCSDD Survey of 3,516 Sites, 2010