Will standardizing site qualifications reduce site burden?

Session Objectives

• Discuss challenges with the current practice of assessing site qualifications for clinical trials
• Discuss potential solutions to improve efficiencies and reduce site burden

Qualifying Sites for Clinical Trials

Dax Kurbegov, MD, Sarah Cannon
Past Chair, ASCO Research Community Forum
Potential Solutions to Improve Efficiencies

1. Uniformity
   - Core criteria and standards
   - Questions asked on feasibility questionnaires
   - Standardized processes and requests for all sponsors and CROs
2. Streamline sponsor requests
   - Standardize requests
   - Centralize requests
3. Leverage technology

Current Momentum to Harmonize Site Standards

Common Goal: Establish, standardize, and harmonize clinical trial site and investigator qualifications to ultimately reduce the amount of oversight and redundant requirements by trial sponsors.

(Examples)
- Alliance for Clinical Research Excellence and Safety (ACRES)
- Site Accreditation and Standards Initiative - Uniform global standards for clinical research sites and third party accreditation (Ongoing)
- National Academy of Medicine
- Recent manuscripts call for harmonizing site standards and site accreditation
- Consensus building exercise to identify core standards (Ongoing)

1. Johnston et al. It’s Time to Harmonize Clinical Trial Site Standards, National Academy of Medicine, 2017
2. Johnston et al. Voluntary Site Accreditation – Improving the Execution of Multicenter Clinical Trials, NEJM, 2017
3. Nishi et al. Accreditation for Clinical Research Sites: Moving Forward, NEJM, 2018
Prior Work to Develop Site Standards

- NCI Clinical Trials Working Group and Institute of Medicine
  - 2006: Issued recommendation for development of a clinical trial site certification program and registry recognized and accepted by NCI, industry sponsors, clinical investigators, and clinical trial sites to reduce the amount of oversight and redundant requirements by trial sponsors
  - 2010: NCI recommendation was adopted by a consensus committee of the IOM
- ASCO
  - 2008: Statement on Minimum Standards and Exemplary Attributes of Clinical Trial Site
  - 2009-2011: Series of papers in Journal of Oncology Practice identifying best practices for the attributes
  - 2014: ASCO RCF released Research Program Quality Assessment Tool (Manual & Checklist)
  - 2015-present: RCF site qualification initiatives exploring standardization, centralization, certification
- Others

ASCO RCF Site Qualifications Task Force

- Previously explored site certification and centralization of feasibility assessments
- Main objectives of current project is to move forward the concepts of standardizing and centralizing the qualification of research sites
- Leverage existing initiatives and momentum
- Collect data to understand process and site implications (quantify)
- Convene stakeholders to discuss
  - Solution(s)
  - Core criteria
  - Barriers to uptake

Other Initiatives

- Recommendations for streamlining GCP and qualifying investigators and staff
- Competency guidelines
  - Certification
    - CRC
    - PI
    - CRA
    - CP
- GCP mutual Recognition
- Shared Investigator Platform
- Site Centric Leadership Advisory Board
FDA Perspectives on Site Qualification

Lynn Howie, MD
Medical Officer,
Division of Oncology Products

Responsibilities of Study Sponsors

- 21CFR314.126 Clarifies that the Agency must rely on “adequate and well-controlled trials” as the basis for determining the effects of a drug apart from other influences

- Adequate and well-controlled is defined as:
  - Clear objectives
  - Clear endpoints
  - Measures taken to minimize bias

- 21CFR312 Sponsors are responsible for selecting qualified investigators, to provide them with adequate information to conduct study, and to provide study monitoring and oversight to ensure the study is conducted in accordance with the protocol and to ensure that any new risks identified are disseminated

Responsibilities of Sites and Investigators

- Investigators are responsible for ensuring the investigation is conducted according to the investigational plan, for protecting the rights, safety and welfare of subjects, and for the control of drugs under investigation (Section 312.60)

- Investigators are to keep records of drug disposition, case histories with source documentation (medical records, imaging, and laboratory tests), and documentation of informed consent

- Investigators must submit progress reports, safety reports, and final reports when the primary organization conducting the study

The Purpose of FDA Inspections at Trial Sites

- FDA inspections are conducted to ensure that Sponsors and Investigators are working in accordance with Federal Regulations

- What does the Agency look for at the time of inspection?
  - Ensure that there is a building and people in it who can collect and house data that are verifiable and traceable
  - Ensure that documentation is maintained and is accurate
  - Ensure that the Principal Investigator at the site has appropriate expertise is providing appropriate oversight
  - Ensure that the Protocol is being followed appropriately
  - Ensure appropriate chain of custody for investigational agent(s)
  - Ensure that appropriate monitoring by the Sponsor during study conduct has occurred
**Trial Decentralization**

**Centralized Trials (Current Structure)**
- Conducted at designated study sites
- Study procedures performed by investigators and clinical research staff via face-to-face encounters

**Decentralized Trials (Future Structure)**
- Opportunities to obtain and exchange information between patients and study sites at remote locations such as patients’ homes

*Source: IQVIA*

**Summary**

- The requirements of study sponsors and investigators are laid out in the CFR
- Site qualification may help to streamline identification of sites for study sponsors
- The definition of “site” is evolving for FDA as new technologies create greater flexibility to decentralize trials and the FDA is working to define best practices in a new guidance
- Based on the CFR, FDA inspections will continue to ensure that appropriate procedures for record maintenance and control of investigational product are in place

**Thank you**

- Lauren Iacono-Connor, Office of Scientific Investigations
- Gideon Blumenthal, Oncology Center of Excellence

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**Will Standardizing Site Qualifications Reduce Site Burden?**

-Joanne Dourado, BSN, MBA
Site Engagement Director-United States
Eli Lilly & Company
Pharma’s Perspective For Site Qualification & Selection

- Aspects of Site Qualification Requirements:
  - Protocol Specific Requirements
  - Regulatory Requirements
  - Local Regulatory Specifics
  - Sponsor Procedures
  - Quality Expectation
  - Business Operation Commitment

Site Qualification Requirements

- Opportunity for Pharma to Leverage Technology to Streamline Process Requirements

  Site Selection Required Category
  - PI trial specific qualification requirement
  - Site Staff trial specific qualification requirement
  - Equipment
  - CT-Materials Distribution
  - CT-Material Returns/Disposal
  - CT-Material Traceability (only applicable)
  - FHD (only applicable)

Technology Enabled Solution

Sponsor Qualification

Potential for Tiers of Qualification

- Leverage enrollment performance data from previous trials
- Recognize that evolving requirements for tissue and bio specimens may challenge previously successful high accruers
- Communicate clear enrollment expectations during feasibility and site selection

Potential Value in Streamlining Site Qualification

- Minimizes administrative burden for clinical trial site & sponsor
- Allows focus of efforts on:
  - Feasibility of key protocol elements
  - Protocol specific aspects of clinical trial execution
- Minimizes time from protocol completion to first patient visit
Standardizing Site Qualification: Reducing Burden?

Jill Johnston, BSc, CCRA, CPM
President, WCG Clinical, Site Activation Solutions

During the study startup phase of a trial, what percentage of trials experience delays?

D. 70%

According to a Blair investment report, a MAJORITY of problems come during the study startup phase (after the protocol is written, but before patient enrollment ramps up). 70% of trials experience some sort of delay in this phase and 60% of trials have some sort of amendment to the initial protocol.

Site Start Up – Survey Answer #2

On average, how many months does it take to move one (1) investigational site from pre-study visit through site initiation?

C. 8 Months

A study conducted by the Tufts CSDD determined that it takes an average of eight months to move one site from pre-visit through site initiation.

In addition,
- Cost of initiating a site is $20,000 to $30,000 (est.)
- Cost of maintaining a site is $1,500 per month (est.)
Identification to Activation: The Burning Platform

Identification to Activation – A One-Year Cycle

<table>
<thead>
<tr>
<th>Phase</th>
<th>Site Identification</th>
<th>Pre-Study Visit to Contract Executed</th>
<th>Site Initiation to Activation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time in Months</td>
<td>3.0</td>
<td>6.0</td>
<td>9.0 (GW)</td>
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Site Qualification Challenges: CRO Perspective

<table>
<thead>
<tr>
<th>Performance versus Promises</th>
<th>Lack of adequate communication</th>
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</thead>
<tbody>
<tr>
<td>Hurry and wait</td>
<td>Complex process and changing requirements</td>
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</tbody>
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Discussion