Ensuring GCP Compliance in Clinical Trials

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Outline of Presentation Content

CLINICAL TRIALS
   – Today’s Environment
   – Concern
   – Expectation

SPONSOR’S RESPONSIBILITY IN ENSURING COMPLIANCE IN CLINICAL TRIALS
   – Quality Control
   – Quality Assurance program: Past, Today and the Future
Clinical Trials

Today’s Clinical Trial Environment

- Has increased in numbers and importance
  - More studies, more sites, greater volume at each site
- Expansion of clinical investigator pool
- “New” players in new roles (CROs, SMOs)
- New technologies (electronic CRF, e-diary, e-medical notes)
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Today’s Clinical Trial Environment

- Large pivotal studies conducted in wide geographic spread (areas new to GCP) with differences in
  - Cultures and practices
  - Emerging regulations
  - Research standards
  - Familiarity of investigators and site staff with e.g. FDA/EMEA’s culture and practice
Clinical Trials

Today’s CT Environment - CONCERN

• In the vibrant and complex clinical trial environment as it is now
  – Who is ensuring GCP Compliance?
  – How is quality ensured?
  – How is quality ensured on a constant and continuous basis?
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Today’s CT Environment - EXPECTATION

• Never forget the goals of GCP
  – Protecting Research Subjects
  – Subject safety
  – Rights as subjects (research ethics)
  – Ensuring the quality and integrity of research data
  – Assuring the existence and operation of “quality systems”
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Today’s CT Environment - EXPECTATION

These goals must be shared, understood, and emphasized – by

- Sponsors
- IRB / IEC
- Investigators and site staff
- Regulatory Authority
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Today’s CT Environment - EXPECTATION

Let’s focus on the Sponsor!
Clinical Trials

Sponsor ICH GCP 1.53

An individual, company, institution, or organization which takes responsibility for the initiation, management, and / or financing of a clinical trial
Ensuring Compliance
Sponsor Responsibility

“The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.” ICH GCP 5.1.1
Ensuring Compliance
Sponsor Responsibility

QUALITY CONTROL

• “The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.”
  ICH GCP 1.47

• “Quality control should be applied at every stage of data handling to ensure that all data are reliable and have been processed correctly.”
  ICH GCP 5.1.3
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Sponsor Responsibility

QUALITY ASSURANCE

• “All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with GCP and the applicable regulatory requirements.”
ICH GCP 1.46
“A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analysed and accurately reported according to the protocol, sponsor’s standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).”
ICH GCP 1.6
Ensuring Compliance
Quality Control & Quality Assurance

BOTH ENSURES

- Adherence to international and national guidelines and internal SOPs
- Patient protection (rights and safety)
- Confidence in the data (for regulatory submission)
Ensuring Compliance

Quality Control & Quality Assurance

THE DIFFERENCE

• QUALITY CONTROL
  – Monitoring
  – In-process activities

• QUALITY ASSURANCE
  – Audit
  – Independent from the process
  – Ensure the performance of those assigned with the QC roles
## Ensuring Compliance
### Quality Control & Quality Assurance

<table>
<thead>
<tr>
<th>What</th>
<th>Who (How)</th>
<th>Where</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitoring</td>
<td>Monitor (CRA)</td>
<td>Site (Investigator) level</td>
</tr>
<tr>
<td>Audit</td>
<td>Auditor</td>
<td>Site level and clinical trial systems</td>
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<tr>
<td><strong>New:</strong> Quality Risk Management</td>
<td>Automatic analysis for detection of systemic quality issues (for a continuous risk evaluation)</td>
<td>On existing gathered data (safety, clinical trial, clinical info)</td>
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Ensuring Compliance

Monitoring

• Sponsor ensures that trials are adequately monitored
  – Specify purpose
  – Selection and qualifications of monitors
  – Extent and nature of monitoring
  – Monitor’s responsibilities
  – Monitoring procedures and report
Ensuring Compliance

Monitoring

• ICH GCP and regulatory requirement (in many countries)
• Extent to be established by sponsor
• Individual monitoring plans for each protocol
  – Outline frequency of visits
  – Data points to be source document verified
  – Plan for how much Source Data Verification to do
  – Critical protocol compliance items to examine
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*Monitoring*

Perform site evaluations of trial-related activities

- Check that Medical Record, Informed Consent, Case Report Form exist for all subjects
- Check that inclusion / exclusion criteria are met as per protocol
- Check that Adverse Events and Serious Adverse Events are timely reported
- Check the accuracy, consistency and completeness of data (Source Data Verification)
- Check the use & storage of study drug, etc.
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Audit

• Perform audits as part of implementing quality assurance
  – Specify purpose
  – Selection and qualification of auditors
  – Auditing procedures
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Audit

• Audits are performed
  – To demonstrate quality oversight
  – To identify improvement opportunities by focusing on root causes
  – To identify potential areas of (regulatory) risks
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Audit

• What questions need answering in a Site / Investigator audit?
  – Have the rights and safety of trial subjects been adequately protected?
  – Are the subjects real and was the correct patient population recruited into the trial?
  – Are the data complete, reliable and verifiable?
  – Were GCP, regulatory and SOP requirements complied with?
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Audit

• How do auditors obtain answers?
  – Interviews
  – Observations
  – Review of records and documents
  – Cross-reference to applicable standards (GCP, Regulations, SOPs)
  – The auditor’s nose...
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QA Program – the Past

In the past

- Site / Investigator audits, to
  - Ensure patient safety
  - Ensure integrity of the data
  - Ensure compliance with regulations and ICH GCP
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QA Program – Today & the Future

Today and the future

- Site / Investigator (Clinical Trial Centre) audits are less frequent
- Focus on system audits, and
- Detection of systemic quality issues with Quality Risk Management (QRM)

However, underlying objectives remain constant

- Protection of human subjects
- Ensuring data quality and integrity
- Compliance with regulations and ICH GCP
Ensuring Compliance
QA Program – Today & the Future

• QRM has been developed to help overcome the challenges in
  – A need for early detection of **critical** quality issues
  – A need for transparency and **prioritization** of quality **risks**
  – Limitations of the current auditing approach calling for a range of new “instruments”
  – Reinforced by new regulatory expectations
THE IDEA IS TO EXAMINE EXISTING DATA FOR INDICATIONS OF QUALITY RISKS

Use the existing data….. to identify areas with increased quality risks

GCP Training for Regulatory Authorities, Taipei, 8-9 April 2008

Source: Booz Allen Hamilton
EXAMPLE: LACK OF MONITORING VISITS EASILY DETECTABLE BASED ON CENTRAL DATA

<table>
<thead>
<tr>
<th>Definition</th>
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<tbody>
<tr>
<td>• <strong>Formula</strong></td>
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| \[
\text{Date of 1st monitoring visit} - \frac{1}{\text{Date of registration of 1st patient}} > 16 \text{ weeks} 
\] |
| • **Threshold** for Signal detection: 16 weeks after first patient registered (consider only sites with at least one report) |

<table>
<thead>
<tr>
<th>Risk Indicator Value</th>
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<tr>
<td>Centers with <strong>no</strong> Monitoring Visit after 16 wks</td>
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<table>
<thead>
<tr>
<th>Data Source</th>
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<tr>
<td><strong>Source:</strong> Central CRF Tracking Database</td>
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<tr>
<td><strong>Data:</strong> Date of registration of first patient per site</td>
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<tr>
<td>Date of first and second monitoring visit per site</td>
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<td>Cut-Off-Dates for Data Retrieval</td>
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<table>
<thead>
<tr>
<th>Raw data</th>
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<tr>
<td><strong>Extract</strong></td>
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<td><strong>Country- Center #</strong></td>
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<td>A - 01</td>
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<td>C - 03</td>
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<td>G - 01</td>
</tr>
</tbody>
</table>

| Legend: |
| Date of registration of first patient |
| Date of first Monitoring Visit |

Source: Booz Allen Hamilton
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QA Program – Today & the Future

• According to the new FDA guidelines, Risk Assessment activities entail
  – Risk Identification
  – Component analysis: What factors might contribute to the identified risk
  – Assessing relative risk: (Nature) x (Severity) x (Incidence)
  – Prioritization
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QA Program – Today & the Future

• Increased EMEA emphasis on Quality Monitoring

  – Provisions for penalties up to 10% of turnover (for failure to ensure patient safety)
  – Use of risk action plans throughout development (these require quality monitoring)
  – Emphasis on risk minimization
  – Measures of effectiveness of communication to healthcare professionals
  – Focus change in compliance from responsibility to accountability
Ensuring Compliance

**QA Program – Today & the Future**

- QRM is the new approach for quality oversight

- Enables detection of systemic quality issues
  - *Continuous* evaluation of many / all entities and risk areas (vs. sample analysis)
  - *Focused* sets of information on many / all entities (vs. individual functions / sites)
  - Identification of *systemic quality issues* based on comprehensive set of information (vs. fragmented fact base)
Conclusion

• Sponsor ensures GCP Compliance in clinical trials by implementing **Quality Control and Quality Assurance**

• Monitoring and audits are intended to increase subject protection and integrity of data, with **Quality Risk Management** as the new QA approach

• Conducting effective quality clinical trials is impossible, unless **EVERYONE’S** in it!