A Sponsor Responsibility

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)

Clinical Trials
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?

Clinical Trials

Today's CT Environment - EXPECTATION

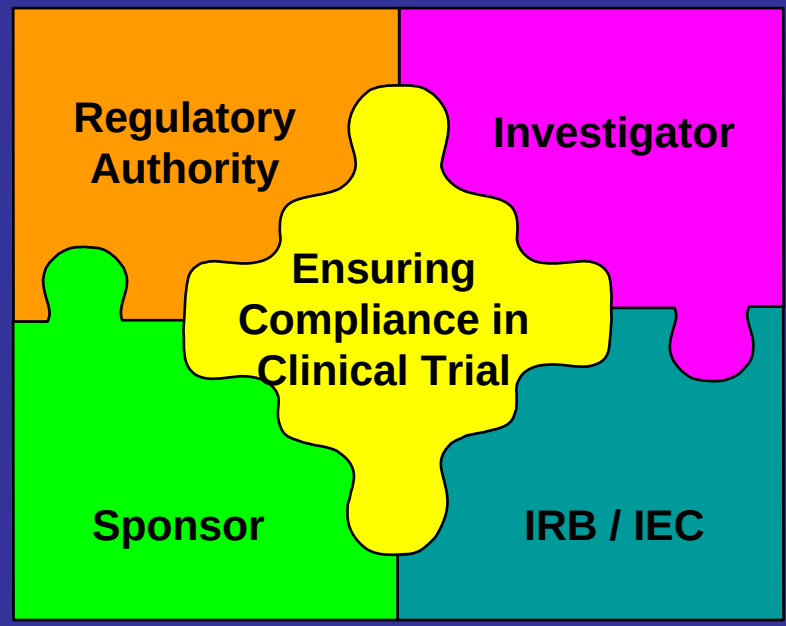
- Never forget the goals of GCP
  - Protecting Research Subjects
  - Subject safety
  - Rights as subjects (research ethics)
  - Ensuring the quality and integrity of research data
  - Assuring the existence and operation of "quality systems"

Clinical Trials

Today's CT Environment - EXPECTATION

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

- Sponsors
- IRB / IEC
- Investigators and site staff
- Regulatory Authority



Clinical Trials

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

Ensuring Compliance
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

Ensuring Compliance
Sponsor Responsibility

QUALITY ASSURANCE / AUDIT

- "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

What	Who (How)	Where
Monitoring	Monitor (CRA)	Site (Investigator) level
Audit	Auditor	Site level and clinical trial systems
New: Quality Risk Management	Automatic analysis for detection of systemic quality issues (for a continuous risk evaluation)	On existing gathered data (safety, clinical trial, clinical info)

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

Ensuring Compliance
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.

Ensuring Compliance
Audit

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

Ensuring Compliance
Audit

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

Ensuring Compliance
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?

Ensuring Compliance
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...

Ensuring Compliance
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

Ensuring Compliance
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

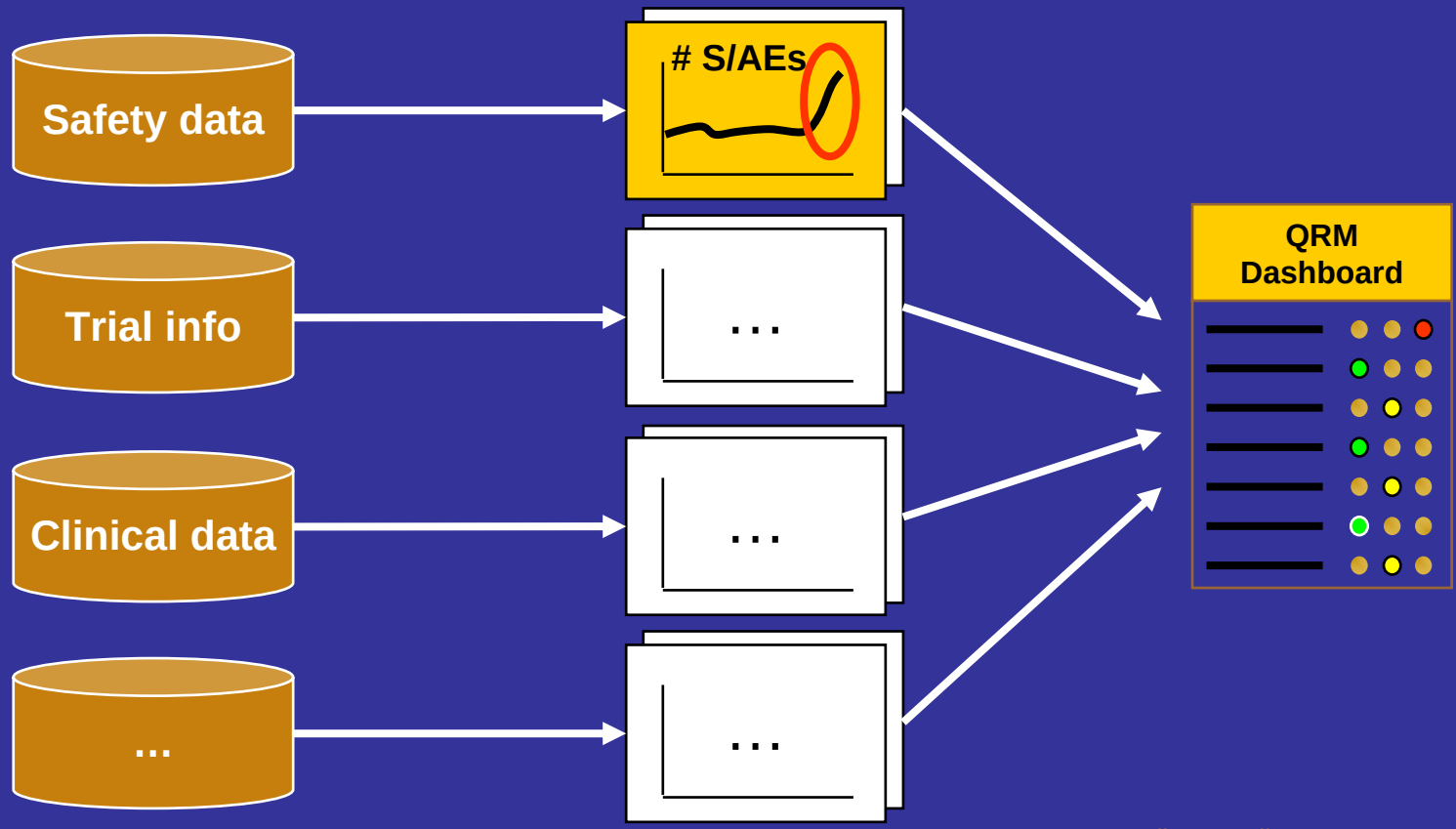
- Protection of human subjects
- Ensuring data quality and integrity
- Compliance with regulations and ICH GCP

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



Source: Booz Allen Hamilton

EXAMPLE: LACK OF MONITORING VISITS EASILY DETECTABLE BASED ON CENTRAL DATA

Definition

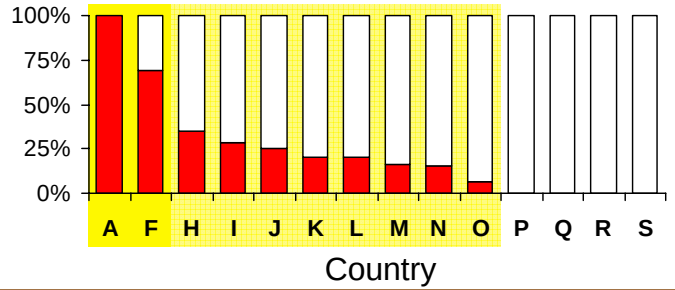
- **Formula**

$$\left[\begin{array}{l}\text{Date of 1st monitoring visit} \\ \text{Date of registration of 1}^{st}\text{ patient}\end{array}\right] > 16 \text{ weeks}$$

- **Threshold** for Signal detection: 16 weeks after first patient registered
  (consider only sites with at least one report)

Risk Indicator Value

Centers with no Monitoring Visit after 16 wks



Data Source

Source: Central CRF Tracking Database

Data: Date of registration of first patient per site

Date of first and second monitoring visit per site

Cut-Off-Dates for Data Retrieval

Raw data

Extract

Country-Center #	Sep-04	Oct-04	Nov-04	Dez-04	Jan-05	Feb-05	Mar-05
A - 01	●						○
B - 05		●		○			
C - 03		●	○				
D - 01		●		○			
F - 01		●			○		
F - 02		●					○
G - 01		●			○		

Legend: ● *Date of registration of first patient*
○ *Date of first Monitoring Visit*

Source: Booz Allen Hamilton

Ensuring Compliance
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

Ensuring Compliance
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!