



Combined CRCS Forum
25 Aug 2017
Presenter – Maggie LIM

Identification of Critical Data and Processes – Risk Based Approach in Clinical Studies

- **Revision of ICH GCP R(2)**
The Addendum - Expectations of Sponsor Responsibilities

- **Risk-Based Approach in Study Management – A Paradigm shift**
 - What : Risk Assessment of Study – Key Risks
 - How : Use of Tools to facilitate the process (thorough review of potential key risks)
 - When : Focus on key risks that can be prevented or managed throughout study duration
 - Who : Central and Local study teams

- **Documentation and Study Plans**
 - Documentation is Key!
 - Risk Identification and development of Study Data Quality Plan
 - Owners to different risk areas & monitoring plan

- **Questions / Comments**





ICH GCP E6 R(2) Guidelines

5. Sponsor

ADDENDUM

5.0. Quality management

The sponsor should implement a system to manage quality throughout all stages of the trial process.

Sponsors should focus on trial activities essential to ensuring human subject protection and the reliability of trial results. Quality management includes the design of efficient clinical trial protocols and tools and procedures for data collection and processing, as well as the collection of information that is essential to decision making.

The methods used to assure and control the quality of the trial should be proportionate to the risks inherent in the trial and the importance of the information collected. The sponsor should ensure that all aspects of the trial are operationally feasible and should avoid unnecessary complexity, procedures, and data collection. Protocols, case report forms, and other operational documents should be clear, concise, and consistent.

~~The quality management system should use a risk-based approach as described below.~~

5.0.1. Critical process and data identification

During protocol development, the sponsor should identify those processes and data that are critical to ensure human subject protection and the reliability of trial results.

5.0.2. Risk identification

The sponsor should identify risks to critical trial processes and data. Risks should be considered at both the system level (e.g., standard operating procedures, computerized systems, personnel) and clinical trial level (e.g., trial design, data collection, informed consent process).

5.0.3. Risk evaluation

The sponsor should evaluate the identified risks, against existing risk controls by considering:

- The likelihood of errors occurring.
- The extent to which such errors would be detectable.
- The impact of such errors on human subject protection and reliability of trial results.

5.0.4. Risk control

The sponsor should decide which risks to reduce and/or which risks to accept. The approach used to reduce risk to an acceptable level should be proportionate to the significance of the risk. Risk reduction activities may be incorporated in protocol design and implementation, monitoring plans, agreements between parties defining roles and responsibilities, systematic safeguards to ensure adherence to standard operating procedures, and training in processes and procedures.

Predefined quality tolerance limits should be established, taking into consideration the medical and statistical characteristics of the variables as well as the statistical design of the trial, to identify systematic issues that can impact subject safety or reliability of trial results. Detection of deviations from the predefined quality tolerance limits should trigger an evaluation to determine if action is needed.

5.0.5. Risk communication

The sponsor should document quality management activities. The sponsor should communicate quality management activities to those who are involved in or affected by such activities, to facilitate risk review and continual improvement during clinical trial execution.

5.0.6. Risk review

The sponsor should periodically review risk control measures to ascertain whether the implemented quality management activities remain effective and relevant, taking into account emerging knowledge and experience.

5.0.7. Risk reporting

The sponsor should describe the quality management approach implemented in the trial and summarize important deviations from the predefined quality tolerance limits and remedial actions taken in the clinical study report (ICH E3, Section 9.6 Data Quality Assurance).

An Ex-EMA inspector comments...



February 21, 2017 | by [Sarah Hand, M.Sc.](#)


On the 14th of June, 2017,* the revised ICH-GCP E6(R2) guidelines will go into effect in the EU. Regulatory agencies around the world – including the FDA, EMA and Japanese Health Authority – are expected to adopt the new Good Clinical Practice regulations.

As this new rule will have an impact on all stakeholders in the clinical trials process – including study sponsors, contract research organizations (CROs), and investigator sites – it's important that the guidelines are fully understood before GCP inspectors begin implementing them. To help investigator sites prepare to comply with the revised guidelines, cloud-based technology company Intralinks, hosted a [webinar](#) on what was changing in ICH-GCP E6(R2), compared to previous versions of the rule.

I had a chance to speak with Gunnar Danielsson, a former GCP Inspector for the Swedish Medical Products Agency and European Medicines Agency, who now helps the industry and academia as an independent consultant.

Danielsson will also be participating in Intralinks' upcoming webinar, "[ICH-GCP E6\(R2\) – Live Q&A with GCP Inspector and Investigator Site Perspectives](#)." Register for this webinar by following the link, and feel free to submit your own questions about ICH-GCP E6(R2) in advance of the event.

Once ICH-GCP E6(R2) takes effect, how do you think it will change the perspective of an inspector when they're doing the GCP audit following these new guidelines?

 If you look at what has been added to the R2, apart from added clarification of the requirements of electronic systems, it stresses the responsibilities of oversight both by investigators as well as sponsors and control of vendors. This includes control of data, study staff, documents and the quality systems that should be implemented. I think that the main purpose of the revised regulation is to ensure that you increase the quality of the study by ensuring that all stakeholders – whether it be the investigator, ethics committee, sponsors or CROs – all jointly take responsibility for study quality.

The pharmaceutical industry is very conservative when it comes to how they interpret regulations and guidance. Do you see these changes as part of encouraging the industry to focus more on what the intention is, and not just on the actual letter of the law?

I really hope so, because the intention of the risk based approach is to encourage sponsors to concentrate on what is important. Having said that, I totally agree with you that the pharmaceutical industry is very often doing their utmost to complicate things, and I worry that some sponsors are going to implement some very complicated risk-based quality management system that is taking away the whole idea of concentrating on the importance.

- Are there *aligned* Central and Regional / Local study teams' approaches towards Risk assessment expectations?
- How do we ensure this alignment? SOPs and guidelines?
- What are doing for Outsourced clinical studies to CROs/ Vendors?
- How do we ensure there is equivalent compliance?
- How does Sponsor access CRO information to test vendors compliance to confirm oversight?





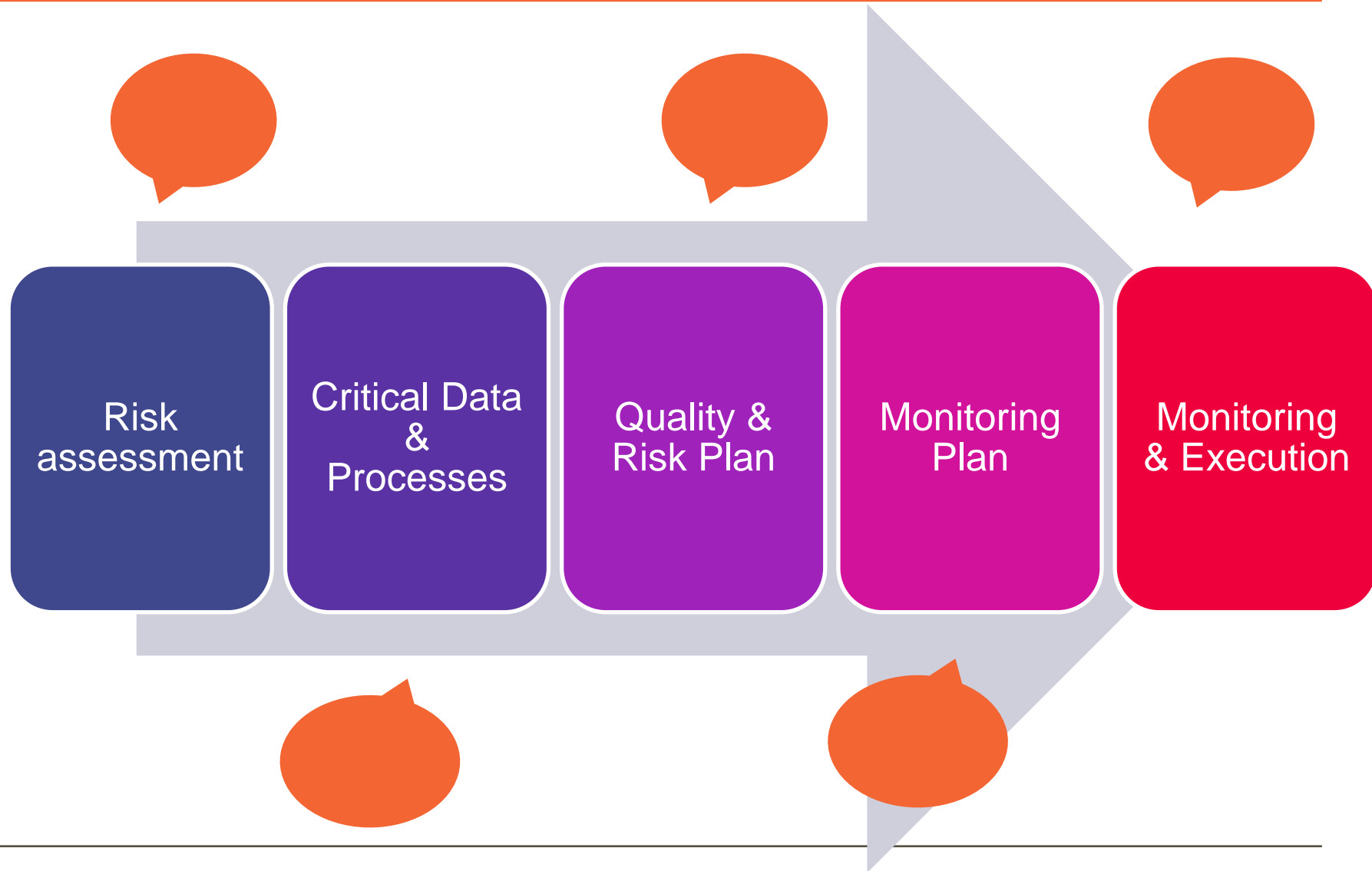
Risk Based Approach – Implications in Study Management

Risk-Based Approach : Key Principles



Increased Quality through Targeted intervention

Risk-Based Approach: Basic Process Overview



Step 1 – Know your Risks

- Each study team will be required to conduct a robust **Risk assessment** & identify study specific risks that can be mitigated through monitoring intervention
- Facilitated process that uses the **Risk Assessment Categorization Tool (RACT)** to ensure a thorough review of potential risk areas
- Focus should be **on study specific risks** that can arise over the course of a study that can either be prevented or managed through pro-active identification
- Ensures **monitoring strategies** are tailored to risks that are focused on Critical Data and Processes

RACT - Discussion Point



When?

During study planning, before functional risk mitigation plans (Monitoring Plan, Data Plan, Safety Plan, etc.) are finalized

Who?

A cross-functional group involving various roles and team members (e.g. Data Managers, Monitors, Clinical Scientists)



Step 2 - Identification of Critical Data & Processes

- ✓ Identification of Critical Data and Processes for the clinical trial is the foundation of the Study Monitoring Plan
- ✓ Consideration should be placed on how to monitor key study processes (Centrally, on-site / off-site)
- ✓ Key to a study-specific SDV/SDR plan

Critical Data

- Support primary and key secondary objectives
- Critical to subject safety
- Support decision-making about efficacy of the IP

Critical Processes

- Underpin data quality
- Underpin subject safety
- Support ethical and GCP compliance

Critical Data & Processes – An Example



Study A

Informed Consent
Inclusion/Exclusion Criteria

Primary and secondary endpoints

Adverse Events of Special Interest
SAEs
Liver Events
ECG
SAE / Endpoint Reporting Time

IP/Compliance
IP Discontinuation

Randomization

Subject Status

Standard of care meds

Study B

Informed Consent
Inclusion/Exclusion Criteria

Primary and secondary endpoints

Events of Special Interest
SAEs/AEs
Haematological & Clinical Chemistry parameters
(incl Liver events)
ECG
Vital Signs
X Rays

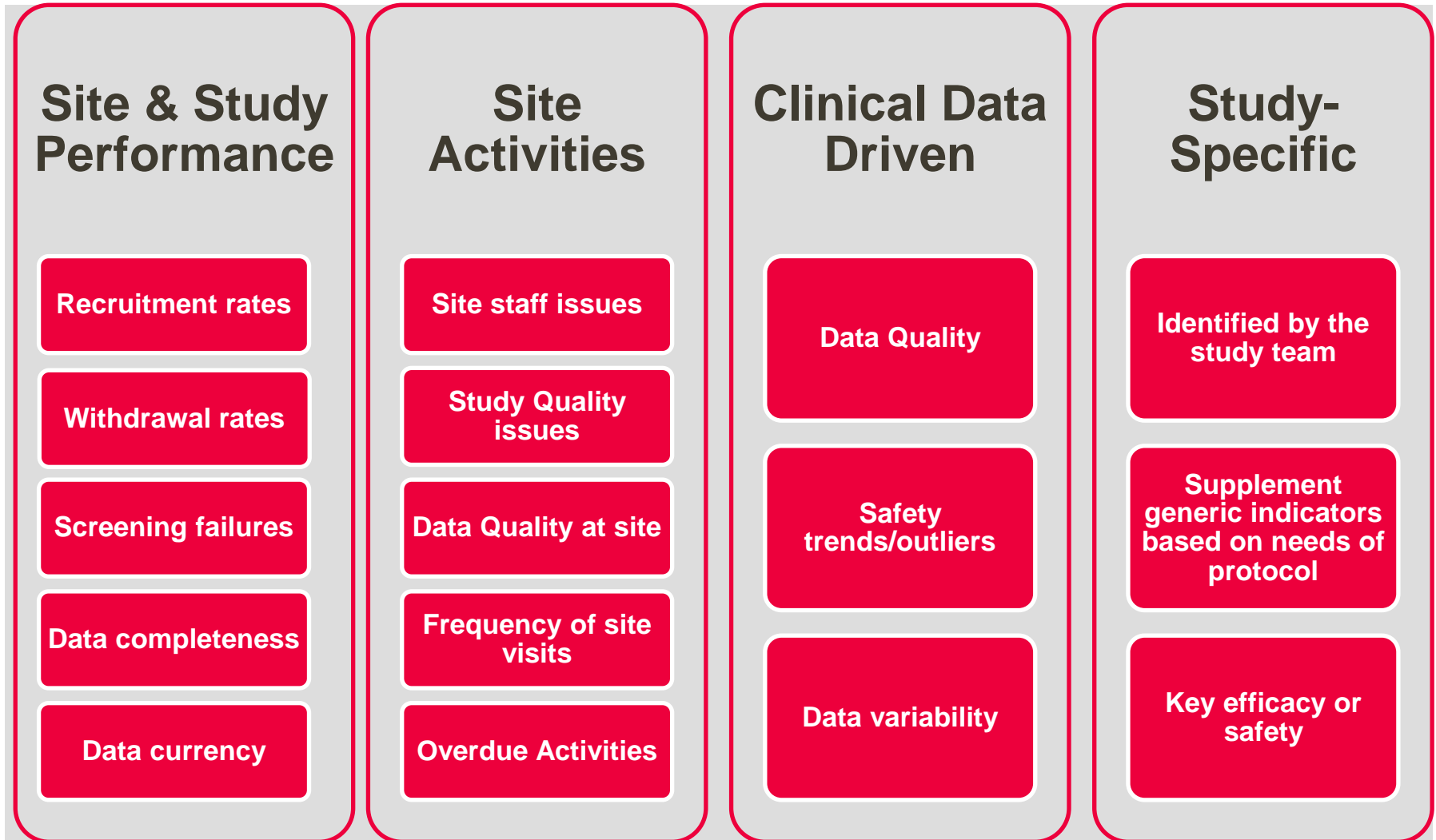
Container numbers / Blinding
SAEs, other events leading to discontinuation of treatment

Step 3 - Focusing on Quality & Risks

- Following the risk assessment & identification of critical data and processes, the team will define how they will **document** the in-stream management of quality
 - The Data Manager will lead the development of the **Study Data Quality Plan**
 - **Assign Accountability** for different risk areas to be managed over the course of the study
 - Build those into associated plans such as the **Study Monitoring Plan**
- Prior to study start, the Study Team determines **the Key Risk Indicators (KRIs)**



What Do We Mean By “Risks”?



Key Risk Indicators

Generic – KRIs

- **Site Performance**
 - Enrolment & Data Volume
 - Data Currency
 - Query Rate
- **Site Issues**
 - Site Staff Issues
 - Site Quality Issues
 - Protocol Deviations
- **Clinical data**
 - Early Withdrawals, Screen Failures
 - Frequency of Safety Events
 - New Critical Safety Data

Study A KRIs

- Incidence of SAEs
- Incidence of outcome events
- Rate of IP Discontinuation
- Rate of IP Noncompliance
- Potential subjects lost to follow-up
- Delay in reporting of SAEs
- Rate of data queries on SAE & outcome event eCRFs

Study B KRIs

- Frequency of X-rays for disease / exacerbations
- Rate of IP discontinuation
- Rate of IP Non-compliance
- Variance in subject Spirometry values
- eDiary compliance

Step 4 - Generating a Robust Monitoring Plan

- Customised Study monitoring Plan (SMP) is the final step to document the mechanism by which the study will be monitored.

It should highlight:

- ✓ The baseline monitoring approach based on risk assessment and critical data & processes:
 - Includes a differentiated SDV/SDR plan
 - Provides instruction on CRA actions in response to risk indicators
 - ✓ Details Central, Off-site, and On-site monitoring activities
 - ✓ Describes triggers for a change to monitoring approach
 - Based on findings at site and/or
 - In response to key risk indicators
-

Generating a Robust Monitoring Plan

Continued...

- Central monitoring is covered by proposed SOPs.
- Need confirmation from vendors that they have confirmed compliance.
- What is Sponsor's ability to access info to test the vendors compliance & confirm oversight?
- Need to compare SOP and MP template to ensure all aspects of the requirements are documented.
Are we confident that documentation of monitoring will provide sufficient detail to verify the requirements of the MP?



-
- RBM studies have **targeted study plans** which will specifically outline the SDV and/SDR criteria.
 - Why do we need to distinguish between SDV and SDR?
 - Address different risks
 - Answer different questions
 - Use according to needs

Objectives of SDR

- Allows holistic monitoring by taking into account the complete picture of what is happening at the site & ensuring the integrity of the data is not compromised
- Allows technology to pick up on data entry errors
- Allows more time to focus on critical data

SDV and/or SDR can be temporarily increased or decreased depending on the type of issues and risks noted at the site, country/region, or study level

Targeted SDV & SDR Strategy



- With targeted SDV and /SDR, not all subjects will have their data reviewed
- Each study will have a specific strategy for conducting SDV and SDR
- The sampling strategy is determined by the study specific algorithm
- Illustrated Table - example of a targeted SDV and /SDR strategy

| Subject # | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|----------------|------|------|------|-----|---|---|------|---|-----|----|-----|------|
| SDV Sampling | SDV | SDV | SDV | | | | SDV | | | | | SDV |
| SDR Sampling | SDR | SDR | SDR | SDR | | | SDR | | SDR | | SDR | SDR |
| Total Sampling | Both | Both | Both | SDR | | | Both | | SDR | | SDR | Both |

General RBM Process Flow

Study Team



Study Team & Managers review Oversight Reports

Study Team prepares Risk Assessment, SDV/SDR Strategy & identifies KRIs

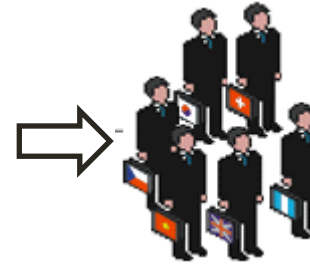
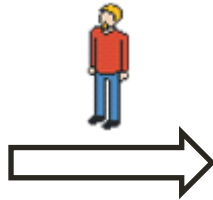
DM Prepares Monitoring Activity Plan

CRA decides how to act based on ALL information

Instream Data



Data Manager



CRA



Sites

Information from Visit Reports read back into system

All actions recorded as per normal practices

Summary



What are we doing?

Why are we doing this?

What does it mean?

