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Sponsor Oversight

Nelle Stocquart and Trev Simmons

Agenda Day 1

- Review of Sponsor responsibilities following ICH-GCP E6 (R3)*
- What does mean oversight?
  - Quality management
    - Quality by Design
    - Risks management
      - Workshop: Risk identification, analysis, response, monitoring and controlling
    - Issues and Non-compliance
    - Auditing
      - Why auditing as oversight strategy?
      - Whom could be audited?
      - how to set-up audits?
    - Risk Based Monitoring and critical to quality factor
- Q&A

Agenda Day 2

- Q&A Day 1
- What does mean oversight?
  - Resources management
    - Roles and responsibilities
    - Finance
      - Workshop
  - Subcontractor management
    - Agreements
    - Documentation
      - Workshop: oversight plan content
    - Communication
  - Essential records management
  - Q&A

Agenda Day 3

- Quiz Day1 and 2
- What does mean oversight?
  - Site selection and management
    - Feasibility tips and tricks
  - IMP/MD management
    - Drug accountability
    - IRT
- Record management and data governance compliance – *Trev Simmons*
  - Data life cycle
  - Computerised system
    - Buy, Build, Configure, Software-as-a-Service

Agenda Day 4

- Q&A Day 3
- Computerised system validation
  - Lifecycles
  - Risk Management
  - Artificial Intelligence
- Training and user management
- Q&A
- Conclusion

Who is this lady?

Solutionelle

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Who is this man?

What about you?

Who are you?

- Who?
- Education/Experience?
- Expectations?

Introduction

What is a sponsor?

ICH-GCP E6 R3 definition: "An individual, company, institution or organisation that takes responsibility for the initiation, management and arrangement of the financing of a clinical trial. A clinical trial may have one or several sponsors where permitted under regulatory requirements. All sponsors have the responsibilities of a sponsor set out in this guideline. In accordance with applicable regulatory requirements, sponsors may decide in a documented agreement setting out their respective responsibilities. Where the documented agreement does not specify to which sponsor a given responsibility is attributed, that responsibility lies with all sponsors."

Sponsor responsibilities

Sponsor Responsibilities

Reports

Sponsor oversight

Resources

quality management

Financing

Select investigators

Data and records

Quality Assurance and Quality Control

investigational products

Allocation of activities

Safety assessment and reporting

Communication with IRB/IEC and regulatory authorities

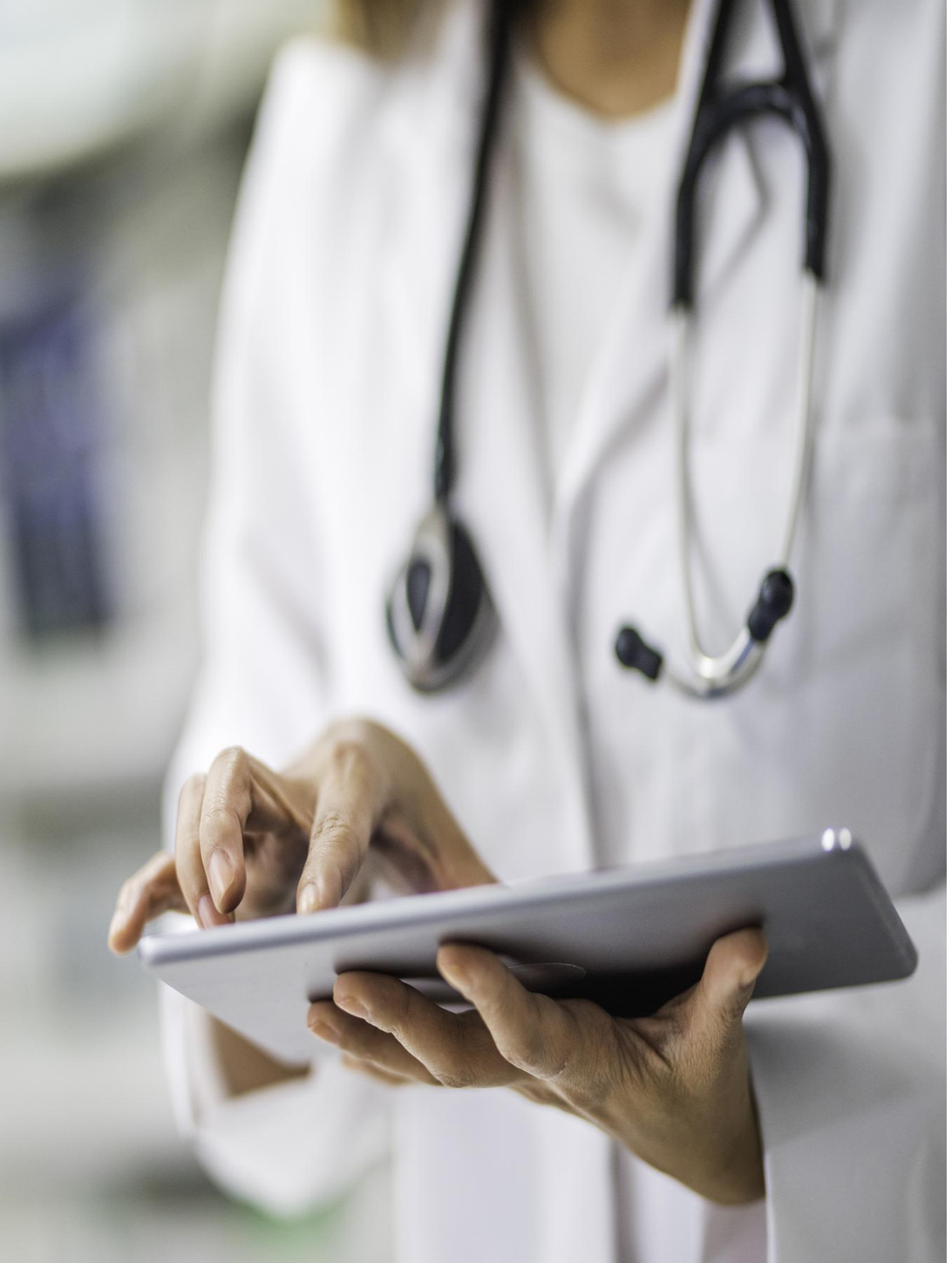
Non-compliance

Agreements

Design trial

Insurance/idemnification/compensation to participants and Investigators

Qualification and training



What are the Sponsor responsibilities?

ICH-GCP E6 R3 : "The responsibility of the sponsor entails the implementation of risk-proportionate approaches to ensure the rights, safety and well-being of the trial participants and the reliability of the trial results throughout the clinical trial life cycle."

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What is risk proportionality?

Definition

Risk proportionality is assessing and implementing controls and mitigations that are balanced with the potential impact the risk may have on the rights, safety, well-being of trial participants, and/or reliability of trial results.

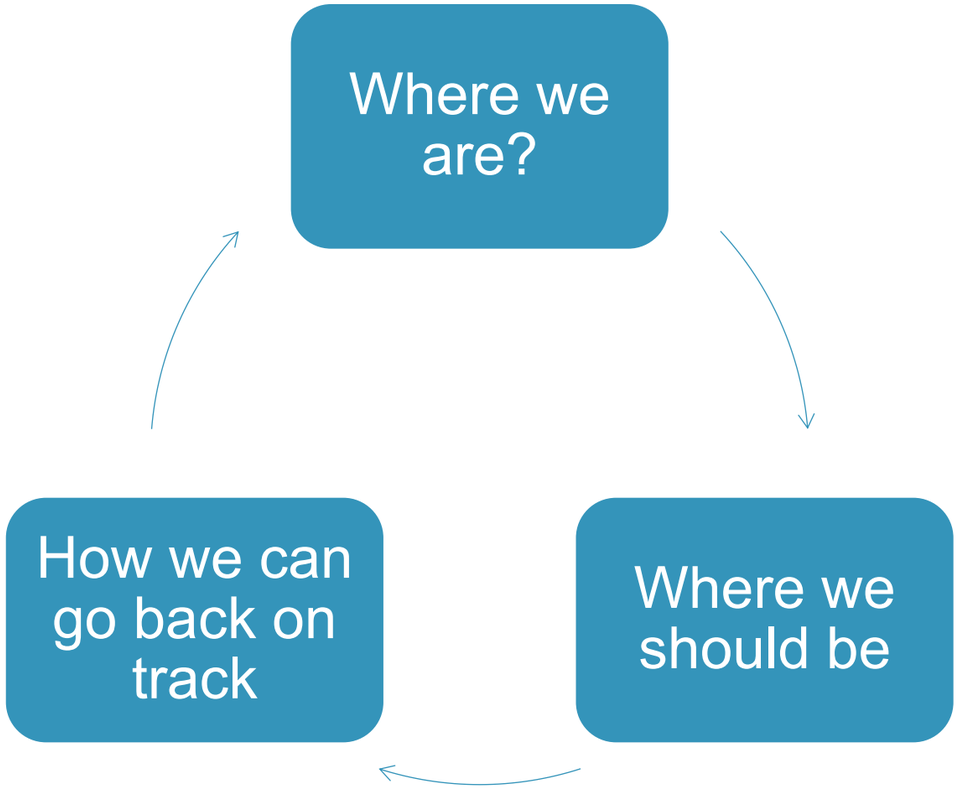
Application

As such, risk proportionality is ideally applied in development planning, trial design, trial conduct and reporting of trial results with the ultimate intent to have a fit for purpose approach that focuses on what matters most.

"Risk proportionality" is synonymous with "proportionate to risk" and "risk-based approach".

What does mean oversight?

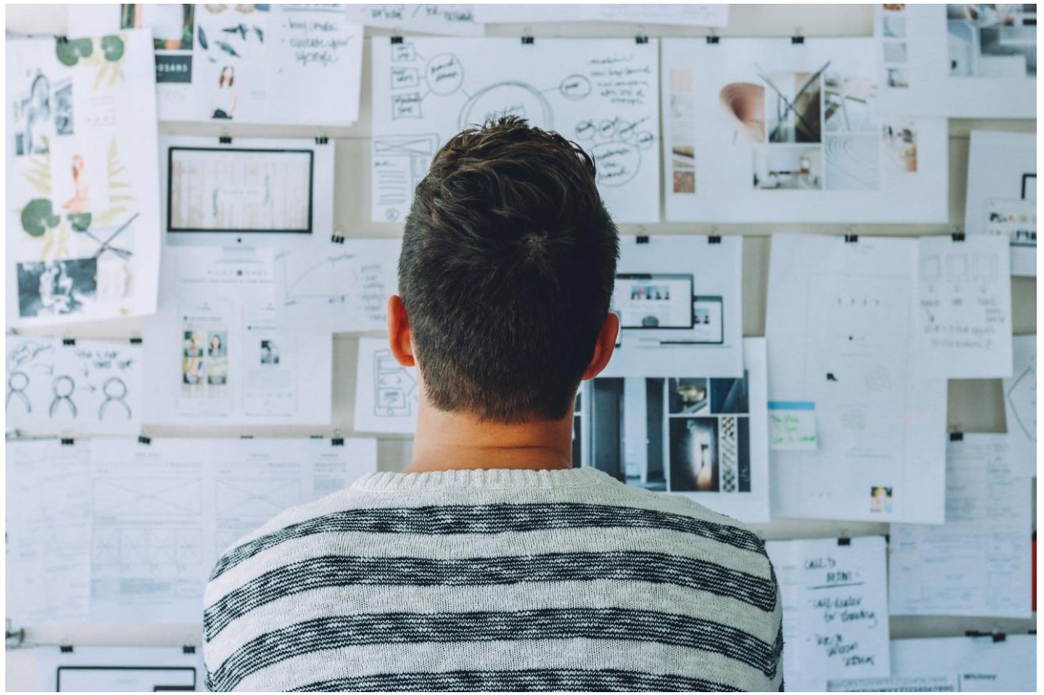
Oversight mean that sponsor should have processes in place to ensure that it is always informed about where we are in comparison with what has been planed (where we should be) and knowing how to come back on track if needed.



And of course, always ensure that participants wellbeing, safety and confidentiality are protected.

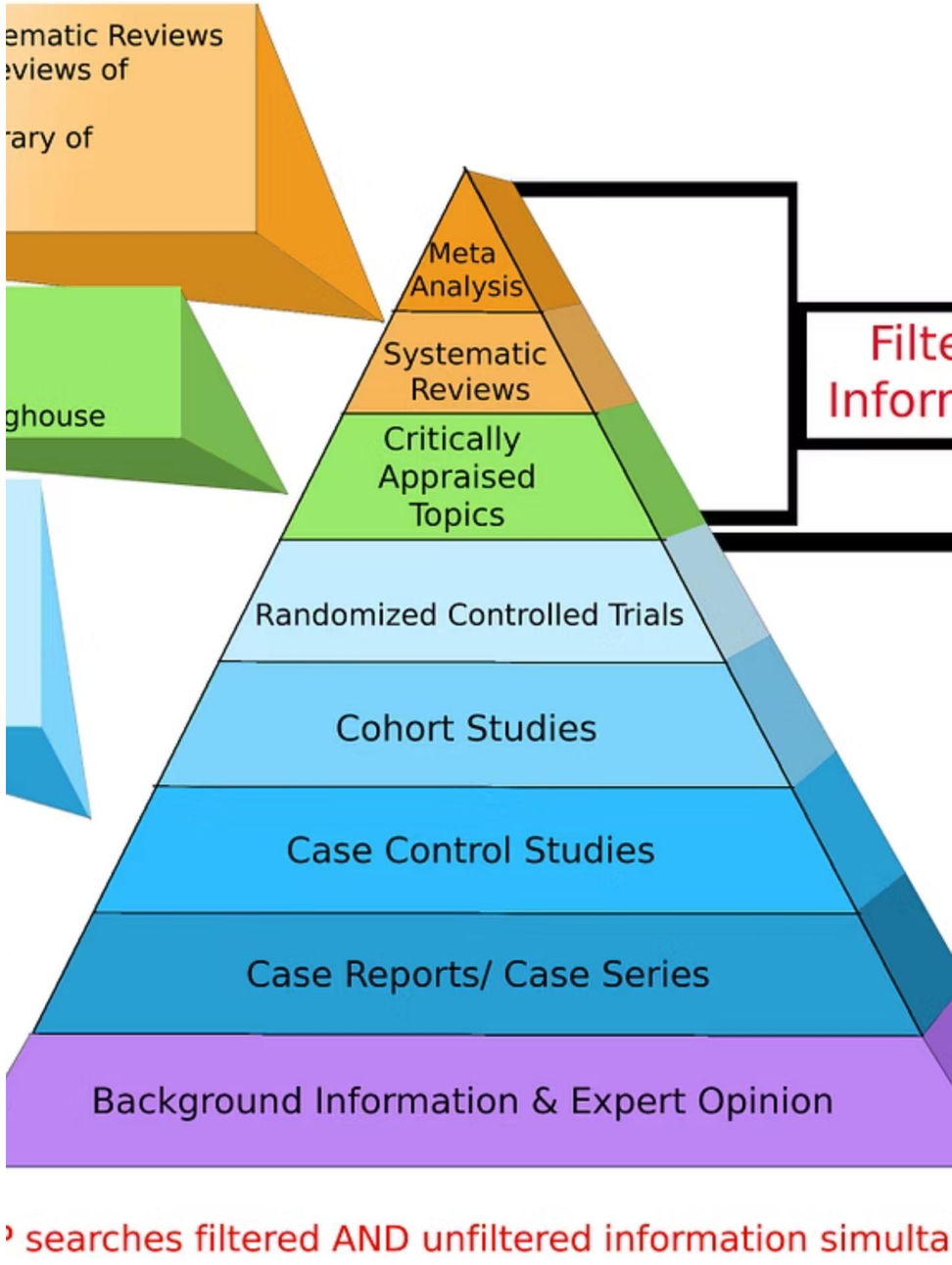
Workshop:

- Please list what are the tools you can use to keep a good study oversight?



Fit for Purpose Oversight

> ICH-GCP E6 R3 "3.9.5 The range and extent of oversight measures should be fit for purpose and tailored to the complexity of and risks associated with the trial. The selection and oversight of investigators and service providers are fundamental features of the oversight process. Oversight by the sponsor includes quality assurance and quality control processes relating to the trial-related activities of investigators and service providers."



ICH-GCP E6 R3: Key Requirements

01

Quality Assurance

"3.9.1 The sponsor should ensure that the trial design and trial conduct, the processes undertaken and the information and data generated are of sufficient quality to ensure reliable trial results, trial participants' safety and appropriate decision making."

02

Compliance

"3.9.2 The sponsor should ensure that trial processes are conducted in compliance with the trial protocol and related documents as well as with applicable regulatory requirements and ethical standards."

03

Risk Management

"3.9.4 Decisions related to the trial should be appropriately assessed for their impact on participant's rights, safety and well-being and the reliability of trial results. Risks related to such decisions should be suitably managed throughout the planning, conduct and reporting of the trial."

04

Issue Escalation

"3.9.6 The sponsor should ensure appropriate and timely escalation and follow-up of issues to allow the implementation of appropriate actions in a timely manner."

Tailoring Oversight to Project Needs

Sponsors most of the time have system in place but it put a lot of burden on the sponsor team and sites. So, it is clear that the oversight measure put in place should be in accordance with project needs/risks.

Phase-Specific Considerations

Indeed a phase I will request a lot of safety and per patient FU, a phase III will need different type of oversight since they are most of the time a lot of sites, multinational and a lot of participants. A phase IV with a marketed product will not request the same oversight measure regarding IMP management, site training etc.

Fit for purpose which means a risk analysis upfront

CRO & Vendor Relationships

It will also depend on if you involved CROs and vendors, and the historical relationship you have with. The oversight might be lighter with a well known CRO or if you have a partnership agreement than with a CRO with whom you work for the first time.

Quality management

Quality Management: QA and QC

The first toolkit for the oversight is to have a quality system in place with quality assurance and quality control process in place.

> **ICH-GCP E6 R3:**
>
> **3.11 Quality Assurance and Quality Control**
>
> The sponsor is responsible for establishing, implementing and maintaining appropriate quality assurance and quality control processes and documented procedures to ensure that trials are conducted and data are generated, recorded and reported in compliance with the protocol, GCP and the applicable regulatory requirement(s).

What is the difference between QA and QC?

Quality Assurance

ICH-GCP E6 R3 "3.11.1 Quality Assurance

Quality assurance should be applied throughout the clinical trial and includes implementing risk-based strategies to identify potential or actual causes of serious noncompliance with the protocol, GCP and/or applicable regulatory requirements to enable their corrective and preventive actions.

Then quality start with quality by design (ICH E8 General consideration for clinical trial) but it also includes the design and implementation of efficient clinical trial protocols, including tools and procedures for trial conduct (including for data collection and management), in order to ensure the protection of participants' rights, safety and well-being and the reliability of trial results."

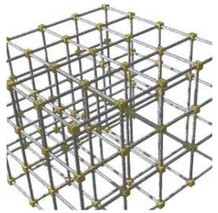
Quality Control

3.11.3 Quality Control

Quality control should be applied using a risk-based approach to each stage of the data handling to ensure that data are reliable and have been processed correctly. Within clinical trials, monitoring and data management processes are the main quality control activities. Where appropriate, quality control activities may also be applied to facilities outside of investigator sites (e.g., central image reading facilities)."

Quality Management System

Quality Management System

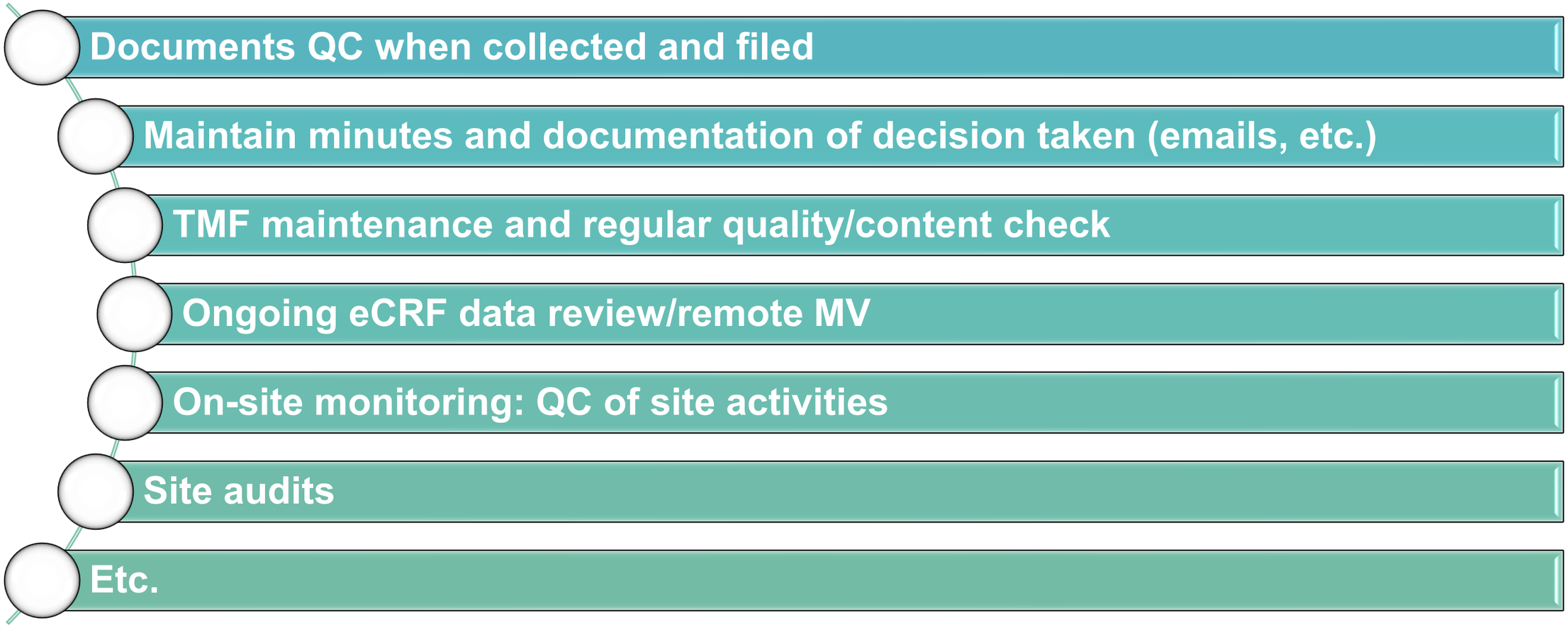


Assuring Quality

Controlling Quality

Managing Risk

What does mean Quality Control?

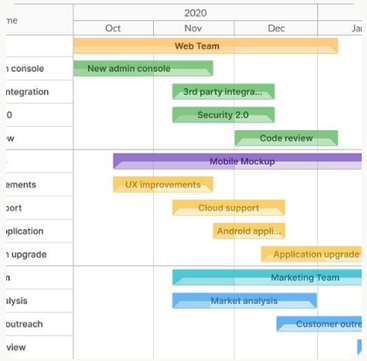


→ **Inspection readiness**

KEY TAKEAWAY

Integrated Quality Management: Resources and Oversight

Resource management forms the cornerstone of successful project delivery. Effective project managers orchestrate multiple resource categories—human capital, budget, investigational medicinal product, and external suppliers—through dedicated planning frameworks.



Project Planning

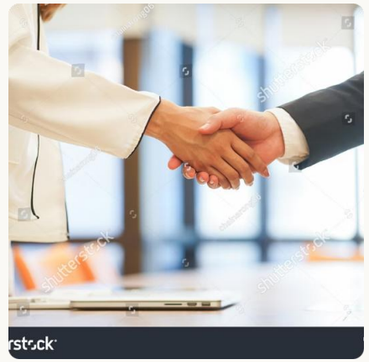
Comprehensive timelines, milestones, and deliverables with clear accountability

Budget Planning

Cost forecasting, allocation, tracking, and variance analysis throughout trial lifecycle

IMP Management

Supply forecasting, distribution logistics, temperature monitoring, and accountability



CRO Oversight

Performance metrics, quality reviews, communication protocols, and relationship management

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The Auditing Imperative

Auditing provides independent quality verification, examining quality management systems at investigational sites and external suppliers. Properly planned audits conducted by independent auditors offer objective assessment of compliance, process effectiveness, and risk control implementation. Together with comprehensive resource management, auditing completes the oversight framework that safeguards trial integrity from initiation through to database lock.

ICH E8 General consideration for clinical studies

- 3.1 Quality by Design of Clinical Studies

Quality is a primary consideration in the design, planning, conduct, analysis, and reporting of clinical studies and a necessary component of clinical development programmes. The likelihood that a clinical study will answer the research questions while preventing important errors can be dramatically improved through prospective attention to the design of all components of the study protocol, procedures, associated operational plans and training.

…

ICH E8 General consideration for clinical studies

3.1 Quality by Design of Clinical Studies

…Good planning and implementation of a clinical study also derive from attention to the design elements of clinical studies as described in Section 5, such as:

- the need for clear pre-defined study objectives that address the primary scientific question(s);
- selection of appropriate participants that have the disease, condition, or molecular/genetic profile that is being studied;
- use of approaches to minimise bias, such as randomisation, blinding or masking, and/or control of confounding;
- endpoints that are well-defined, measurable, clinically meaningful, and relevant to patients.
- Operational criteria are also important, such as ensuring a clear understanding of the feasibility of the study, selection of suitable investigator sites, quality of specialised analytical and testing facilities and procedures, and processes that ensure data integrity.

Quality by Design concept* (QbD)

- Build quality into the scientific and operational design and conduct of Clinical trials.
- Focus on what matters
- Critical data AND Critical processes that impact on:
  - Patient safety
  - Data integrity
- GCP/Regulatory Compliance

Identify risks at the study, and site level in order to employ the appropriate level of monitoring:

- Map the risk to appropriate monitoring plans
- Employ mechanisms to monitor important parameters (inclusive of central monitoring activity)
- Smarter use of technologies that enable effective oversight
- Targeted on-site interventions

Risk-Based Quality Management

ICH-GCP E6 R3 "3.10. The sponsor should adopt a proportionate and risk-based risk-based approach to quality management, …."

Risk Based Monitoring approach*

*Transcelarate Position Paper: Risk-Based Monitoring Methodology Final 30May2013

FOUNDATION

Understanding Risk Management Fundamentals

To establish fit-for-purpose oversight and appropriate quality measures, project teams must systematically identify, analyse, respond to, and monitor project risks throughout the trial lifecycle. This proactive approach forms the foundation of risk-based quality management (RBQM), enabling teams to focus resources where they matter most whilst maintaining robust quality standards.

Effective risk management requires clear understanding of risk categories, stakeholder engagement, and a structured four-phase process that adapts to emerging challenges throughout trial conduct.

Why Risk Management Matters

- Protects participant rights and safety
- Ensures data reliability and integrity
- Optimises resource allocation
- Enables proportionate oversight
- Supports regulatory compliance

Project Risks vs Study Risks: Understanding the Distinction

Study Risks

Protocol-Level Concerns

Study risks operate at the protocol level, encompassing critical elements directly affecting trial participants and scientific integrity. These include participant safety considerations, investigational medicinal product (IMP) management, data collection procedures, and protocol compliance issues. Study risks focus on the clinical and scientific aspects of the trial design and execution.

Project Risks

Operational-Level Concerns

Project risks exist at the project management level, relating to the infrastructure and resources supporting trial delivery. These encompass sponsor team capacity, site performance variability, contract research organisation (CRO) dependencies, process effectiveness, and system functionality (such as eCRF platforms, interactive response technology, and other digital tools). Project risks affect operational efficiency and delivery timelines.

What Constitutes a Risk?

Risk = Event + Probability + Impact

A risk represents a specific event with a measurable probability of occurrence and a potential impact on your project objectives. Unlike issues, which are current problems requiring immediate resolution, risks are prospective challenges that may or may not materialise.

Understanding this distinction is crucial: risks allow for proactive planning and mitigation strategies, whilst issues demand reactive problem-solving. Effective risk management transforms potential crises into manageable challenges through early identification and strategic response planning.

Risk Characteristics

- Future-oriented and preventable
- Quantifiable probability
- Measurable potential impact
- Responsive to mitigation strategies

Issue Characteristics

- Present and requiring action
- Actual occurrence (100% probability)
- Tangible current impact
- Demands immediate resolution

FOUR PHASES

The Risk Management Process

Risk management follows a structured four-phase cycle that creates a continuous improvement loop throughout the clinical trial lifecycle. Each phase builds upon the previous one, creating a comprehensive framework for quality management.

Risk Identification

Discover and document potential risks across all trial processes and systems

Risk Analysis

Evaluate likelihood and impact to prioritise risk response efforts

Risk Response

Develop and implement strategies to avoid, mitigate, accept, or transfer risks

Risk Monitoring

Track effectiveness and adapt controls as new information emerges

Phase 1: Risk Identification

> "The sponsor should identify risks that may have a meaningful impact on critical to quality factors prior to trial initiation and throughout trial conduct. Risks should be considered across the processes and systems, including computerised systems, used in the clinical trial."
>
> — ICH-GCP E6 R3, Section 3.10.1.1

Risk identification demands comprehensive examination of all trial elements, from design through to data handling. This includes participant selection, informed consent processes, randomisation procedures, blinding mechanisms, investigational product administration, and service provider activities.

The identification phase should cast a wide net, documenting all potential risks regardless of perceived severity. Subsequent analysis will prioritise these risks, but premature filtering during identification may overlook critical vulnerabilities.

Trial Design

Protocol complexity, endpoint selection, statistical assumptions

Informed Consent

Process clarity, comprehension, documentation completeness

IMP Administration

Supply chain, storage conditions, accountability, compliance

Participant Selection

Eligibility criteria, recruitment challenges, retention risks

Randomisation & Blinding

System functionality, unblinding procedures, allocation concealment

Data Handling

Collection methods, system integration, quality checks, security

Stakeholder Engagement in Risk Identification

Who Should Participate?

All stakeholders should be actively involved in the risk identification process. Each function brings distinct expertise and perspectives that enrich the risk register and prevent blind spots.

Multidisciplinary Input

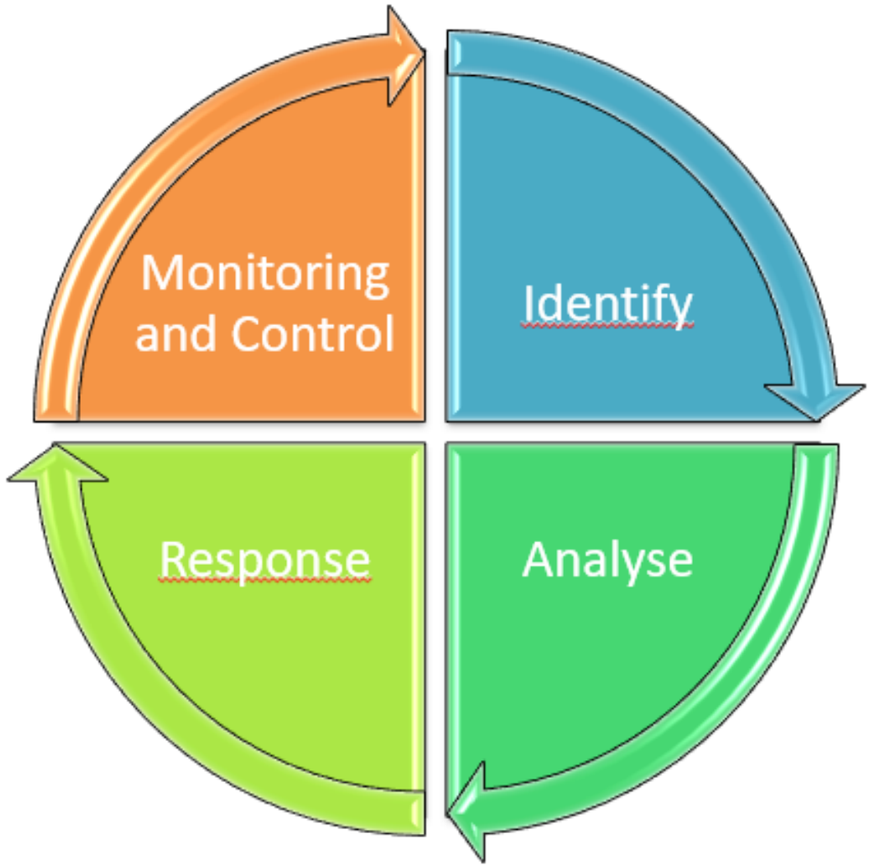
Clinical operations teams identify site-related risks, data management specialists flag system vulnerabilities, statisticians highlight analytical challenges, and pharmacovigilance experts assess safety reporting concerns. Regulatory affairs, quality assurance, and project management contribute further perspectives on compliance and delivery risks.

Comprehensive Risk Cataloguing

There is no upper limit to the number of risks that should be identified. Embrace a comprehensive approach that produces an extensive initial list. Whilst this may seem overwhelming, the subsequent analysis phase will stratify these risks by severity, enabling teams to focus resources on the highest priorities. A thorough identification process is preferable to overlooking critical risks that could compromise trial integrity.

Risk Identification

- How to write a risk statement:
  1. An IF - THEN type of risk statement.
  2. A CONDITION - CONSEQUENCE risk statement.
     Given the “condition”, there is a probability that “consequence” will occur.



Workshop step 1

- Define hazards that can cause harm in a study
- Use the format IF-THEN

Sponsor Code:
CRO Code:

RISK LOG	SAMPLE	Workshop 4, steps 1 - 3						
[complete according to study-specific risks]								
	Step 1	Step 1	Step 2	Step 2	Step 2	Step 3	Step 3	Step 3
Category	Risk identified (If)	Effect (then)	Risk Probability	Risk Severity	Risk Score	Risk Response (incl. "due date" if time-sensitive)	Responsibility	Action taken (incl. date)
SPONSOR								

Phase 2: Risk Analysis and Scoring

Risk analysis employs a systematic scoring methodology to evaluate and prioritise identified risks. By assessing both impact and likelihood on a five-point scale, teams create a quantifiable risk matrix that guides resource allocation and response planning.

The Scoring Process

Each risk receives two scores: **impact** (the potential severity of consequences) and **likelihood** (the probability of occurrence). Both dimensions use a scale from 1 (very low) to 5 (very high). Multiplying these scores produces a risk rating between 1 and 25.

High Risk

Score: 10–25

Red Zone

Requires immediate response and ongoing monitoring

Medium Risk

Score: 5–9

Yellow Zone

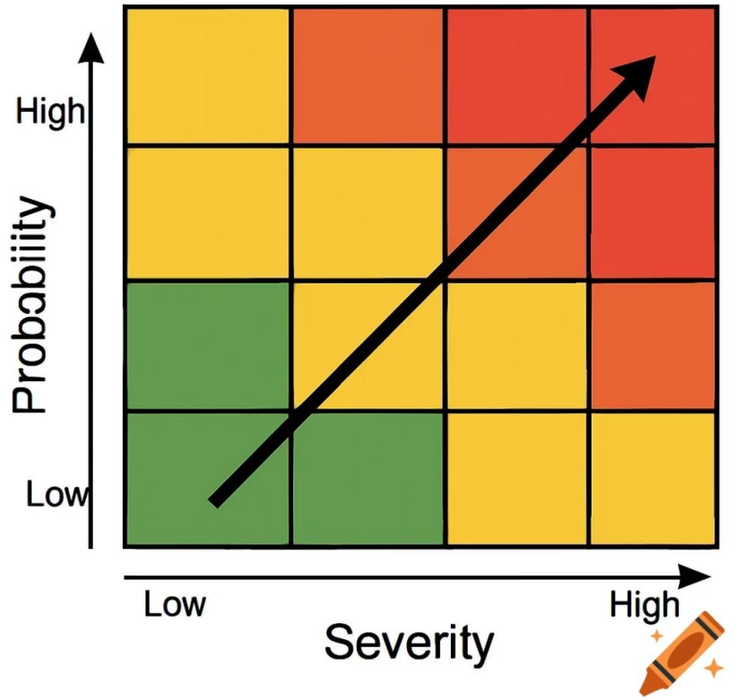
Team discussion needed to decide response or acceptance

Low Risk

Score: 1–4

Green Zone

Generally acceptable; monitor periodically



Enhanced Analysis: Detectability

Risk-based monitoring incorporates a third dimension: **detectability**. This factor assesses how readily a risk manifestation can be identified. For example, informed consent form issues at sites are difficult to detect remotely, whilst missing data values are easily identified through electronic case report form (eCRF) edit checks. ICH-GCP E6 R3 recommends using a three-point detectability scale, where 1 represents easily detectable risks and 3 indicates difficult-to-detect risks.

ICH-GCP E6 R3

Regulatory Framework for Risk Evaluation

> "The sponsor should evaluate identified risks and existing controls in place to mitigate the risk by considering: (a) The likelihood of harm/hazard occurring; (b) The extent to which such harm/hazard would be detectable; (c) The impact of such harm/hazard on trial participant protection and the reliability of trial results."
>
> — ICH-GCP E6 R3, Section 3.10.1.2

This regulatory guidance emphasises three critical evaluation dimensions that balance participant protection with data integrity. When incorporating detectability as the third factor, ICH-GCP recommends adopting a three-point scoring system aligned with the Risk Assessment Categorisation Tool (RACT) methodology.

1

Likelihood Assessment

Evaluate probability based on historical data, trial complexity, and environmental factors

2

Detectability Evaluation

Consider monitoring capabilities, data transparency, and system alerting mechanisms

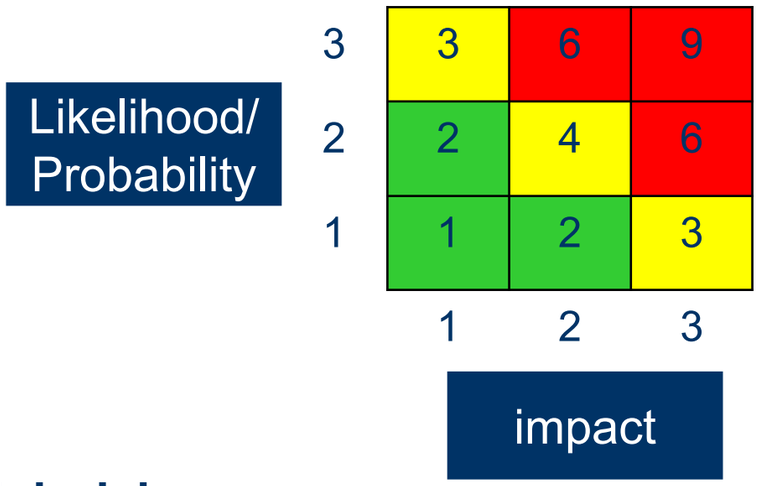
3

Impact Analysis

Assess consequences for participant safety, rights, well-being, and result reliability

Workshop 1 Step 2

- Rate the risks using a 3 point scale:



High risk

Medium risk

Low risk

Risk Analysis

- Take the time to score all risks identified – the list can be very long
- Don’t spend too much time in discussions if the risk zone will not be impacted

Category	Risk identified	Effect	Risk Probability	Risk Severity	Risk Score
SPONSOR	If the results of our main efficacy trial are negative	the whole portfolio for product X will be interrupted	1	5	5
PROJECT TEAM	If we don't hire a PM before end February	Study start will be delayed	4	5	**20**
SITES	If Germany does not open more sites	the registration of the product can be rejected in Germany	3	5	**15**

Phase 3: Risk Response Strategies

An effective risk response should migrate risks from the high-risk (red) zone to the low-risk (green) zone through strategic interventions. Four primary response categories provide a framework for addressing identified risks, each appropriate for different risk profiles and resource constraints.

Avoid

Eliminate the risk entirely by removing the risk source or changing the approach. This is the most definitive response but may require significant protocol or operational modifications.

Mitigate

Reduce either the impact severity or occurrence likelihood through preventive measures. Mitigation includes enhanced training, additional monitoring, improved processes, or technological solutions. Most high risks require mitigation strategies.

Transfer

Shift the risk responsibility to a third party through contracts, insurance, or service agreements. This approach is particularly relevant when specialised expertise or resources are required.

Accept

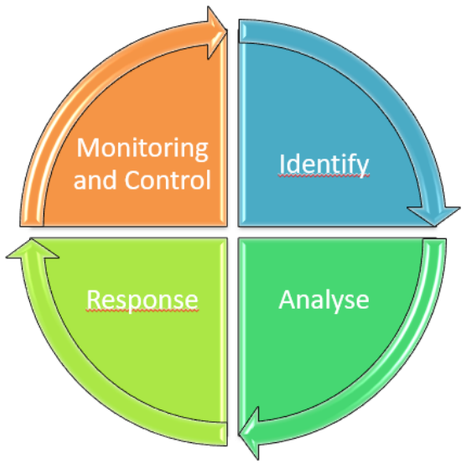
Acknowledge the risk and prepare contingency resources without active prevention. Typically applied to low-probability or low-impact risks where response costs exceed potential consequences. Maintain contingency budget for accepted risks.

Workshop 1 Step 3

- Define which risk handling strategy will be used to respond to the risk: avoid, mitigate, accept, transfer

- Describe the response in more detail & group/person responsible

Risk Response



A response can introduce new risks or influence other previously identified risks.

Always cross-check the risks to obtain a final response list without red items left.

Risk Response

If the strategy is not to accept the risk identified then each risk response should:

- Always define the owner of the action/risk (Stakeholders Vs functional plan)
- Define clear timelines for execution
- Define review timing for following up.

Phase 3: Risk Control Implementation

> "Risk control should be proportionate to the importance of the risk to participants' rights, safety and well-being and the reliability of trial results."
>
> — ICH-GCP E6 R3, Section 3.10.1.3

Risk mitigation activities should be embedded throughout the trial infrastructure, from protocol design through to operational implementation. Control measures may be incorporated into monitoring plans, inter-party agreements defining roles and responsibilities, training programmes, and quality tolerance limits.

Where relevant, sponsors should establish pre-specified acceptable ranges—quality tolerance limits at the trial level—that reflect thresholds beyond which participant safety or data reliability may be compromised. When deviations exceed these ranges, systematic evaluation determines whether corrective action is necessary.

Risk Control Integration Points

01

Protocol Design

Build risk controls into study procedures and visit schedules

02

Monitoring Plans

Define risk-proportionate oversight and trigger thresholds

03

Contractual Agreements

Clarify risk ownership and accountability across partners

04

Training Programmes

Ensure stakeholders understand and can execute controls

05

Critical to Quality Factor

Establish measurable thresholds for acceptable variation

Phase 4: Risk Monitoring and Control

Risk management delivers value only through continuous review and adaptation. The monitoring phase ensures that implemented controls remain effective and relevant as trials progress and new information emerges.

> "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."
>
> — ICH-GCP E6 R3, Section 3.10.1.5

Regular Review Cadence

Risk reviews should be integrated into routine project governance, whether through dedicated risk review meetings or as standing agenda items in team meetings. Contract research organisations (CROs) must participate actively in this process, incorporating risk management updates into their regular reporting cycles.

Additional risk control measures may be implemented as circumstances evolve. This adaptive approach acknowledges that clinical trials are dynamic environments where new risks emerge and existing risks may escalate or diminish based on operational realities.

Monitoring and Control

RISK MANAGEMENT METRICS

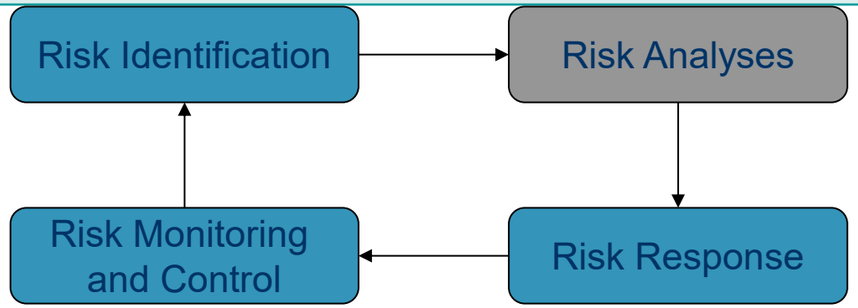
Track risk handling in metrics and evaluate against risk management plan & updating Risk Log

Review the Risk management plan regularly (i.e. during study team meeting)

Important to document:

Lessons learned spread to other projects

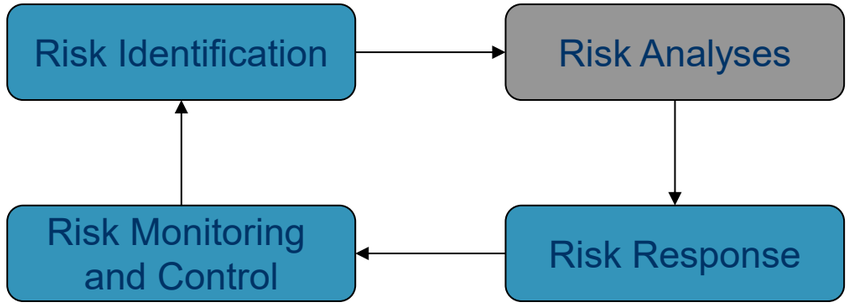
Monitoring and Control



The frequency of review is to be defined for each project, for example:

- Red zone: monthly review during team meetings
- Yellow zone: quarterly review during team meetings
- Green zone: no follow-up mandatory but advisable to evaluate the risk in this zone when large changes occur / yearly review during team meetings

Monitoring and Control



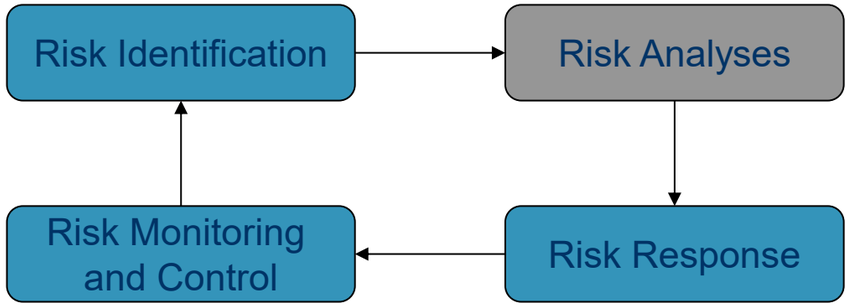
If risk is in the red zone: the response should bring in the yellow/green zone.

If the response is confirmed to act as expected: frequency of FU can be updated (reduced).

If the response did not have the risk moving out of the red zone: a new response is to be considered.

If new risk: analyse and decide on response

Monitoring and Control



Risk	Reduce likelihood	Action	Cost
Site(s) do(es) not perform all assessment as per protocol	Training	Send CRA for training	+ 12 hours
	Closer follow-up	Increase visit time	+ 2 x hours/visit
	Do nothing	No action	+ 0 hours

Total study budget

Risk Management Plan

What is the risk management plan?

- Tool set-up to facilitate risk assessment and risk mitigation discussion
- Tool where all risk identified will be listed, classified and actions to be taken described.
- It is a living tool all along the project (regularly reviewed)
- It is either program or protocol specific
- It is version controlled

Risk Management

Key Changes in Good Clinical Practice [ICH E6(R3)]

	As described in ICH E6(R2)		As described in ICH E6(R3) draft		Summary of Impact
Risk Identification	Limited to processes and data at the system and trial level	→	Clarified that any type or level of risk may have meaningful impact	→	Focus on risks that have a meaningful impact
Risk Evaluation	Used the term error, which implies any mistake should be evaluated	→	Harm/hazard terminology introduced to prioritize risks that may have a meaningful impact	→	Change in terminology to demonstrate the importance of a proportional approach focused on impact
Risk Control	Controls applied based on significance of risk to subject safety and reliability of trial results. Concept of Quality Tolerance Limit (QTL) introduced	→	Concept of Acceptable Ranges introduced, which expands the QTL concept	→	Acceptable Range terminology allows for a broader range of control measures to be applied

Issues, Non-Compliance, and Protocol Deviations

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Understanding Issues

Issues represent events that have already occurred and require immediate resolution. Unlike risks (potential future events), issues demand reactive problem-solving and rapid corrective action to minimise consequences and prevent recurrence.

Protocol Deviation Classification

Sponsors must establish trial-specific criteria for classifying protocol deviations as "important." Important protocol deviations represent a subset that may significantly impact data completeness, accuracy, or reliability, or that may significantly affect a participant's rights, safety, or well-being (ICH-GCP E6 R3, Section 3.9.3).

Deviation Assessment Framework

Not all protocol deviations warrant the same level of concern. Teams must distinguish between minor administrative variances and significant departures that compromise trial integrity. This classification system enables proportionate response—minor deviations may require documentation and corrective action, whilst important deviations trigger comprehensive investigation, impact assessment, and potential regulatory reporting.

Minor Deviations

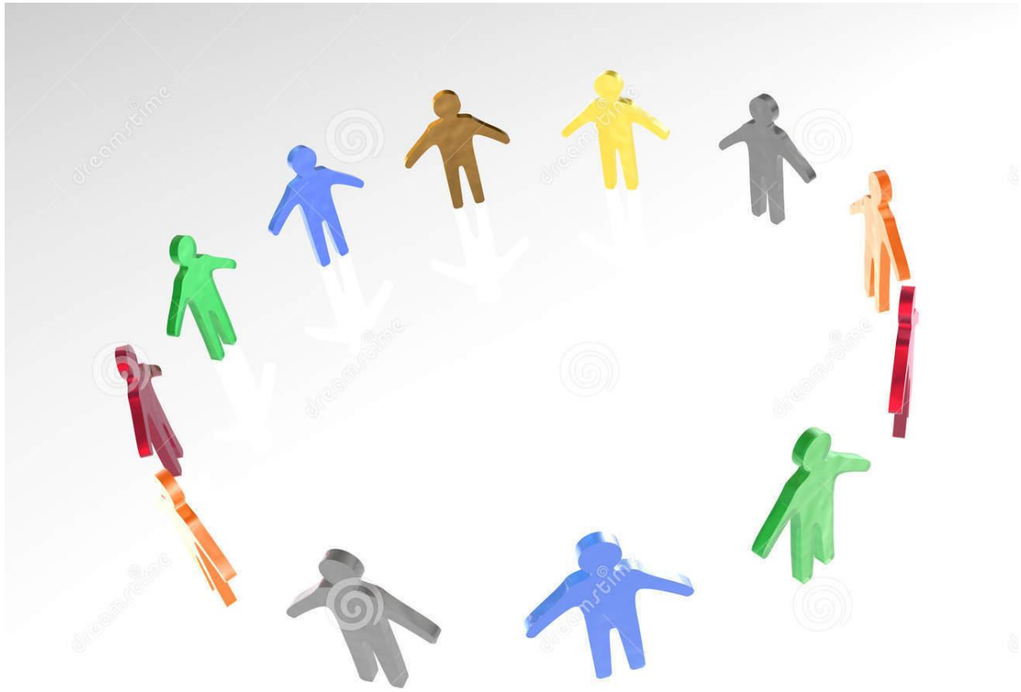
Administrative errors with no material impact on data or participant safety (e.g., documentation timing discrepancies, minor protocol clarifications)

Important Deviations

Significant departures affecting critical quality factors (e.g., eligibility violations, missed safety assessments, informed consent deficiencies)

Issue tracking

- Beside risks proactively identified and mitigated some issues can raise.
- What would you do?



Issue tracking

- Issues tracker:

Issue #	Issue description	Root cause analysis	Resolution action	Owner	timelines

- It needs to be linked with the RMP and then kept in the lessons learned.

Correctice Actions and Preventive Actions (CAPA)?

- All issues do not require a CAPA
- CAPA created following issues should be referenced in the issues log.
- Issues log can be added to lessons learned with the RMP
- Issues will become risks for new studies

Summary

Risks form a situation that can be planned and solutions can be provided to reduce impact or likelihood

Issues are unplanned situation that needs to be resolved immediately

Corrective Action and Preventive Action (CAPA) is developed following an issue that requires root cause analysis and preventive action plan

Issues and CAPA should be logged during a project and will be part of the lessons learned.

Issues discovered during a project can become a risk in future project

Audits

Auditing

Auditing is another tool to keep the oversight by checking the quality management at sponsor, sites and external suppliers.

3.11.2 Audit

When performed, audits should be conducted in a manner that is proportionate to the risks associated associated with the conduct of the trial (see section 3.10.1.1).

> The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or monitoring or quality control functions, is to evaluate whether the processes put in place to manage to manage and conduct the trial are appropriate to ensure compliance with the protocol, GCP and the GCP and the applicable regulatory requirements.

It should be properly planed and done by independant auditors.

3.11.2.2 Auditing Procedures

(a) The sponsor should ensure that the auditing of clinical trials/processes is conducted in accordance with the sponsor's documented procedures on what to audit, procedures on what to audit, how to audit (i.e., on-site and/or remote), the frequency of audits and the form and content of audit reports.

(b) The sponsor's audit plan, program and procedures for a trial audit should be guided, for example, by the importance of the trial to submissions to regulatory submissions to regulatory authorities, the number of participants in the trial, the type and complexity of the trial, the level of risks to the trial participants and any participants and any identified problem(s).

Documentation et Rapports d'Audit

Documentation

(c) The observations and findings of the auditor(s) should be documented.

Regulatory access

(d) To preserve the independence and value of the audit function, the regulatory authority(ies) should not routinely request the audit reports. Regulatory authority(ies) may seek access to an audit report on a case-by-case basis (i.e., when evidence or suspicion of serious GCP noncompliance exists or in the course of legal proceedings).

Audit Certificate

(e) When required by applicable regulatory requirements, the sponsor should provide an audit certificate.

Different types of audits

System audit

External supplier audit

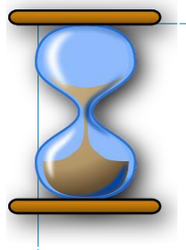
Site audit

What is a System Audit?

- The goal is to assess if the system and supporting processes are fit for purpose:
  - Assess the risks to consistent and acceptable delivery associated with the relevant trial processes and procedures
  - Assess compliance with Regulatory requirements and company standards
  - Assess compliance with the process and consistency of approach
  - Assess staff roles, responsibilities, experience and training to enable them to conduct the required tasks

The Challenges with System Audits

System audits are big cumbersome audits



Take too long to conduct and report

Cut across several different studies so not sure how to report out results

Can identify serious systematic failures or omissions, but issues too complex so no-one wants to deal with it

Need a deep understanding of the process and the regulatory requirements – I don't feel qualified

I don't know where to start

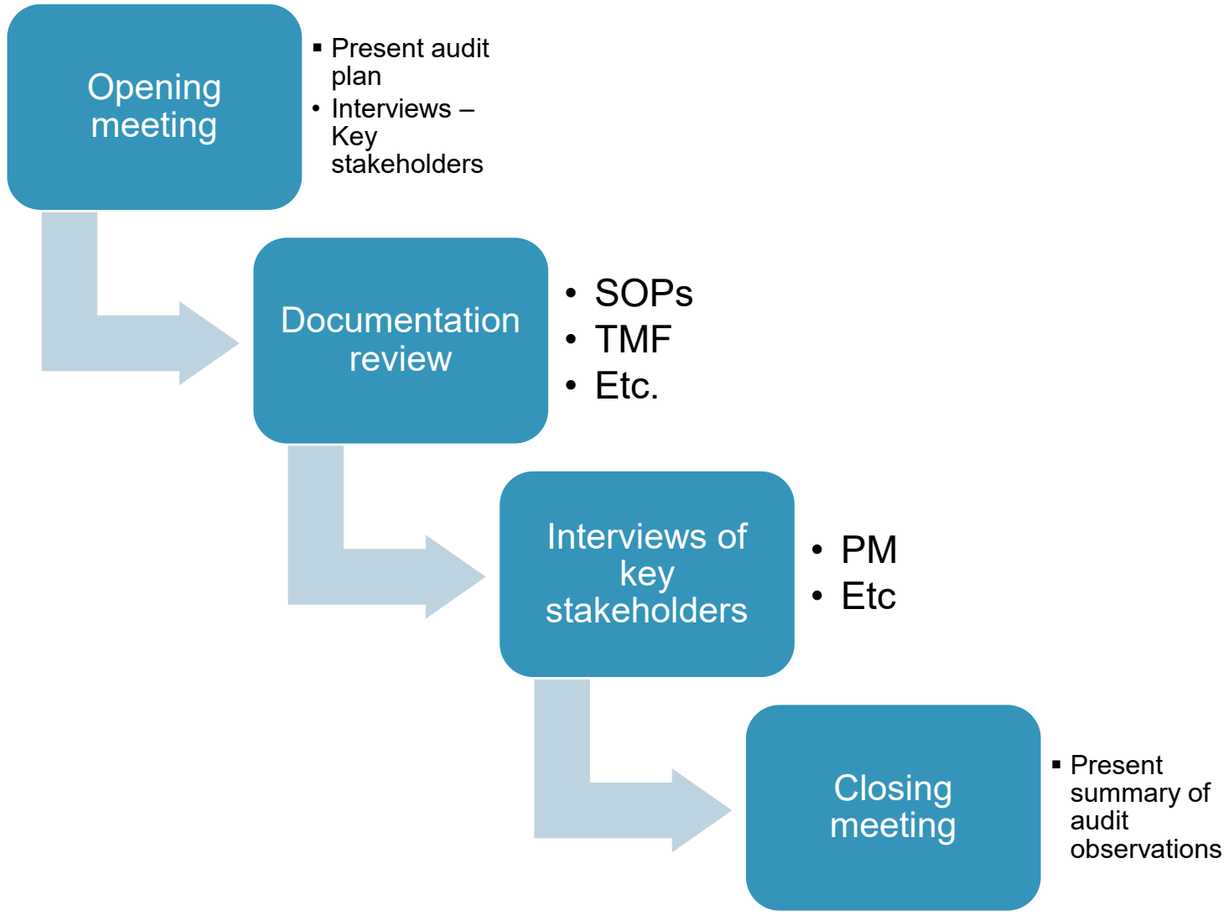
Successful System Auditors

- Understand the Regulatory Environment
- Aware of the Business Environment
- Solicit stakeholder engagement and buy-in
- Adopt a risk managed approach to system audit selection
- Understand the system to be audited (process mapping)
- Adopt a risk managed approach to the scope, design and conduct of the audit
- Deliver timely and user friendly system audit reports

Stakeholder Engagement and Collaboration

- Effective engagement with influential stakeholders is the key to a successful system audit
  - Keep the QA team connected with business
  - Help validate the audit risk managed approach
  - Advocate for quality and compliance
  - Drive process improvement

Conduct of a system audit



Site Audit Programme

- Establish principles (e.g. frequency / number / timing / resources)
- Annual – but update as necessary
- Requires input from Operational Groups

Investigator Site Audits are key element of programme

Site Audit: Selection Criteria

- Aim for +/- 15% of sites
- Number of subjects enrolled
- Rate of enrolment
- Geographic location

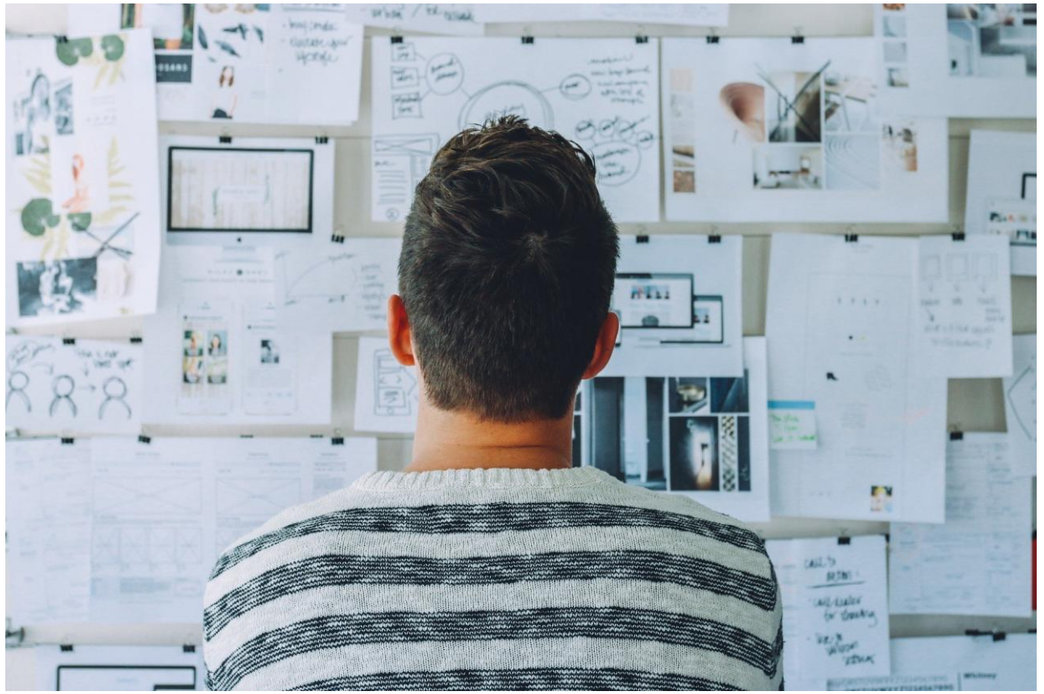
- Experience of site staff
- Experience of monitor
- (S)AE profile
- Discontinuations / withdrawals
- Known GCP issues

Site Audits - Timing

- Best after first 4 to 5 patients entered
- Do not inform site too early (3-8 wks in advance)

In Europe, site contacts often via monitor

Why is it needed to audit sites?



Why is it needed to audit sites?

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01

Ensure data quality and patient safety

02

Identify potential fraud and/or misconduct

03

Improve sites processes

Risk Based Monitoring

Modern Monitoring in RBQM

Monitoring represents a critical quality toolkit for ensuring data quality, reliable results, and participant safety. Within risk-based quality management (RBQM), monitoring transcends traditional site visits to encompass comprehensive oversight across all trial elements.

Expanded Monitoring Scope

Contemporary monitoring is no longer the exclusive domain of clinical research associates (CRAs). It represents a shared responsibility across functions: data management, biostatistics, pharmacovigilance, and quality assurance all contribute surveillance expertise. This multidisciplinary approach identifies issues that single-function monitoring might overlook.

> "The monitoring approach should consider the activities and services involved, including decentralised settings, and be included in the monitoring plan. Monitoring may include site monitoring (performed on-site and/or remotely) and centralised monitoring, depending on the monitoring strategy and the design of the clinical trial."
>
> — ICH-GCP E6 R3, Section 3.11.4

Centralised Data Surveillance

Risk-based monitoring prioritises data surveillance—in-depth transversal analysis conducted regularly to identify trends and outliers. This approach moves beyond per-patient, per-visit review towards statistical pattern recognition that reveals systematic issues earlier and more efficiently. Clinical trial management systems (CTMS) support this helicopter view, though well-designed spreadsheet trackers remain valuable oversight tools.

ICH E8 R1

- 3.2 Critical to Quality Factors
- A basic set of factors relevant to ensuring study quality should be identified for each study. Emphasis should be given to those factors that stand out as critical to study quality. These critical to quality factors are attributes of a study whose integrity is fundamental to the protection of study participants, the reliability and interpretability of the study results, and the decisions made based on the study results. These quality factors are considered to be critical because, if their integrity were to be undermined by errors of design or conduct, the reliability or ethics of decision-making based on the results of the study would also be undermined.

ICH-GCP E6 R3 Principles

- **Principle 6: Quality should be built into the scientific and operational design and conduct of clinical trials.**
- **6.2. Factors critical to the quality of the trial should be identified.** These factors are attributes of a trial that are fundamental to the protection of participants, the reliability and interpretability of the trial results and the decisions made based on those trial results. Quality by design involves focusing on the design of all components of the trial in order to maximise the likelihood of trial success (i.e., that the trial will answer the research question).

ICH E8 R1

- 3.3 Approach to Identifying the Critical to Quality Factors
- A key aspect of a quality approach to study design is to ask whether the objectives being addressed by the study are clearly articulated; whether the study is designed to meet the research question it sets out to address; whether these questions are meaningful to patients; and whether the study hypotheses are specific and scientifically valid. The approach to the identification of the critical to quality factors should consider whether those objectives can be met, well and most efficiently, by the chosen design and data sources. Patient consultation early in the study design process can contribute to this approach and ultimately help to identify the critical to quality factors. Study designs should be operationally feasible and avoid unnecessary complexity. Protocols and case report forms/data collection methods should enable the study to be conducted as designed and avoid unnecessary data collection.

Critical to quality factor

Critical data:

Support primary and secondary objectives

Critical to subject safety: AE, SAEs, ADE, SADE, etc.

Critical processes:

Underpin data quality: eCRF review, ePRO validation or data transfer etc.

Underpin subject safety: blood sampling, IMP/MD storage condition

Support ethical and GCP compliance

Informed consent process

Trial Monitoring

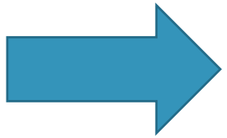
Trial monitoring strategy should include components that ensure trial participant protection and reliability of trial results. Resulting integrated risk-based monitoring strategy should reflect at least the following:

- Defined critical to quality (CtQ) factors specific to the clinical trial and their associated risk
- Other features of trial and site-related factors dictating usability of monitoring components and activities
  - Early engagement with investigators, and other site staff, when designing the monitoring strategy may help identify trial-specific site-related factors and their potential impact.
- Typical monitoring activities that reflect well known approaches for clinical trials

Per ICH E8, the extent and nature of trial monitoring should be tailored to the specific trial design and objectives and the need to ensure participants' safety and data reliability. The monitoring strategy should be flexible and responsive to changes identified through continuous risk reassessments, in accordance with the principles outlined in ICH E6.

Types of Monitoring - oversight

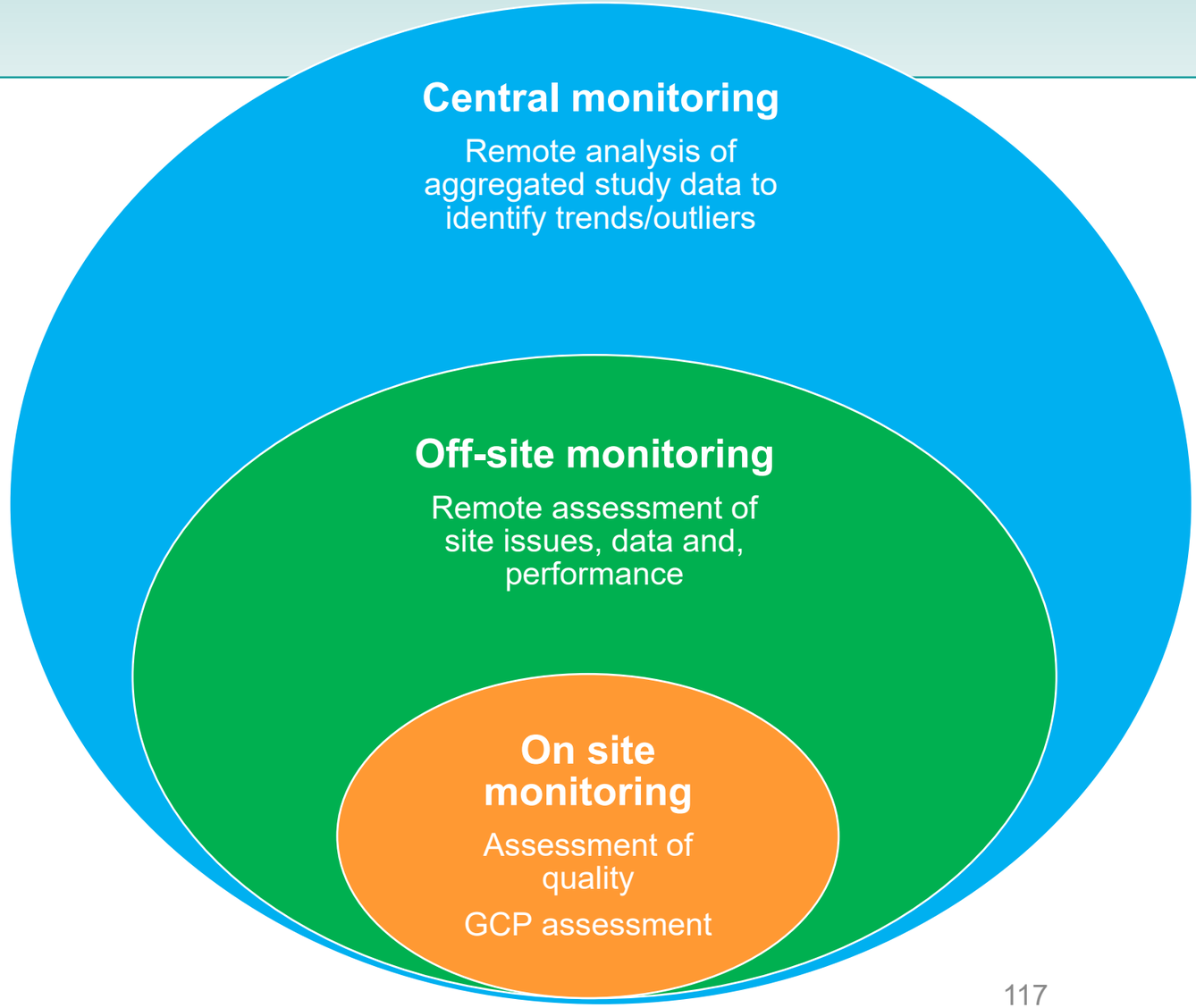
- Term “Monitoring” is used in different ways in the clinical trial context
  - Site Monitoring
  - Safety Monitoring
  - Medical Monitoring
  - Quality Control monitoring by Sponsor internal processes and systems
  - Quality Control mechanisms at site



Monitoring is no longer for CRA only

Monitoring in RBM

- Monitoring defined by risk
- Ongoing central and/or off-site monitoring
- Triggered on-site monitoring
- Monitoring is cross-functional



How Does RBM Differ from "Traditional" Monitoring?

- Monitoring is customized to sites/trials needs
- Schedule is flexible to comply with sites' needs
- Identifies risks proactively
- Leverages technology for centralized surveillance
- Shares monitoring responsibilities across many functional areas
- Relies more heavily on central and off-site monitoring

ICH GCP E6 R3

3.11.4. …« Monitoring involves a broad range of activities including, but not limited to, communication with investigator sites, verification of the investigator and investigator site staff qualifications and site resources, training and review of trial documents and information using a range of approaches including source data review, source data verification, data analytics and visits to institutional facilities undertaking trial-related activities. **Some of these monitoring activities (e.g., centralised monitoring) may be conducted by different methods and persons with different roles (e.g., data scientist).** However, monitoring should be performed by persons not involved in the clinical conduct of the trial at the site being monitored. The monitoring approach should consider the activities and services involved, including decentralised settings, and be included in the monitoring plan. Monitors and other trial staff should adhere to data protection and confidentiality requirements in accordance with applicable regulatory requirements, institution policy and established data security standards.

Monitoring may include site monitoring (performed on-site and/or remotely) and centralised monitoring, depending on the monitoring strategy and the design of the clinical trial.

The sponsor should determine the appropriate extent and nature of monitoring based on identified risks. Factors such as the objective, purpose, design, complexity, blinding, number of trial participants, investigational product, current knowledge of the safety profile and endpoints of the trial should be considered.

ICH GCP E6 R3

- 3.11.4.1 Investigator Site Monitoring

  (a) Monitoring may be performed in relation to the clinical trial activities at the investigator sites (including their pharmacies and local laboratories, as appropriate). The frequency of monitoring activities should also be determined based on identified risks. Monitoring activities and their frequency should be modified as appropriate using knowledge gained.

  (b) This monitoring activity may be performed on-site and/or remotely depending on the nature of the activity and its objectives.

  (c) Monitoring may include remote and secure, direct read-only access to source records, other data acquisition tools and essential record retention systems.

ICH GCP E6 R3

- 3.11.4.2 Centralised Monitoring

  (a) Centralised monitoring is an evaluation of accumulated data, performed in a timely manner, by the sponsor's qualified and trained persons (e.g., medical monitor, data scientist/data manager, biostatistician).

  (b) Centralised monitoring processes provide additional monitoring capabilities that can complement and reduce the extent and/or frequency of site monitoring or be used on its own. Use of centralised data analytics can help identify systemic or site-specific issues, including protocol noncompliance and potentially unreliable data.

  (c) Centralised monitoring may support the selection of sites and/or processes for targeted site monitoring.

Centralised monitoring

- Comparison of data and information (across studies, sites, patients etc.) may include:
  - Protocol deviation rate
  - Data entry and query resolution metrics
  - Adverse event trends or outliers
  - Subject discontinuation trends
  - Unusual data trends or patterns
  - Error rates in critical data/processes

This activity should be done by DM and Statisticians (IA?) based on report extracted from your eCRF

Remote monitoring activities

- Off site monitoring may include:
  - Confirm timeliness and quality data entry
  - Review query resolution
  - Review CRF to check protocol compliance
  - Confirm site's completion of previously identified actions
  - Review essential documents
  - Assess site recruitment and enrolment
  - Monitor investigational product
  - Monitor for changes in site staff
  - Monitor delegation of responsibility
  - Conduct training

→ IA May help in this review

RBM on-site monitoring

Focus on critical data and issue identified by centralised and off-site monitoring (SDR):

SDV/SDR critical data only	Review of subject source documents in a holistic sense in order to ensure critical processes and source documentation are adequate to ascertain investigator involvement	ICF review	IMP accountability, if applicable	Essential documents review (ISF)

There may be less focus on SDV and more focus on the process of data collection

ICH-GCP E6 R3 Sponsor responsibilities

3.11.4.3 Monitoring Plan

The sponsor should develop a monitoring plan that is tailored to the identified potential safety risks, the risks to data quality and/or other risks to the reliability of the trial results. Particular attention should be given to procedures relevant to participant safety and to trial endpoints. The plan should describe the monitoring strategy, the monitoring activities of all the parties involved, the various monitoring methods and tools to be used, and the rationale for their use. The monitoring strategy should ensure appropriate oversight of trial conduct and consider site capabilities and the potential burden. The plan should focus on aspects that are critical to quality. The monitoring plan should reference the sponsor's applicable policies and procedures.

Monitoring of important data and processes (e.g., those related to primary endpoints and key secondary endpoints and processes intended to ensure participant safety) performed outside the investigator site (e.g., central image reading facilities, central laboratories) should be addressed in the monitoring plan.

FDA recommendation 2023

Monitoring plans should explain how the sponsor intends to address the risks that could affect the clinical investigation:	A description of the investigation design, including the blinding and randomization procedures, if applicable
	Processes for confirming that randomization is performed according to the protocol and investigational plan or plans
	The sampling plan or plans that will be used to identify the specific records and data that will be monitored, including (1) the rationale for how the sampling plan provides a representative picture of the overall information and (2) how the sampling plan will be implemented
	A description of the types of issues identified through monitoring that would trigger immediate issue escalation
	An approach for determining whether (1) an important issue that is detected at a clinical site may also be present at other clinical sites; and (2) the finding suggests a systemic problem with the protocol or associated investigational plans that requires remediation

Risk proportionate approaches in clinical trials 25 April 2017:

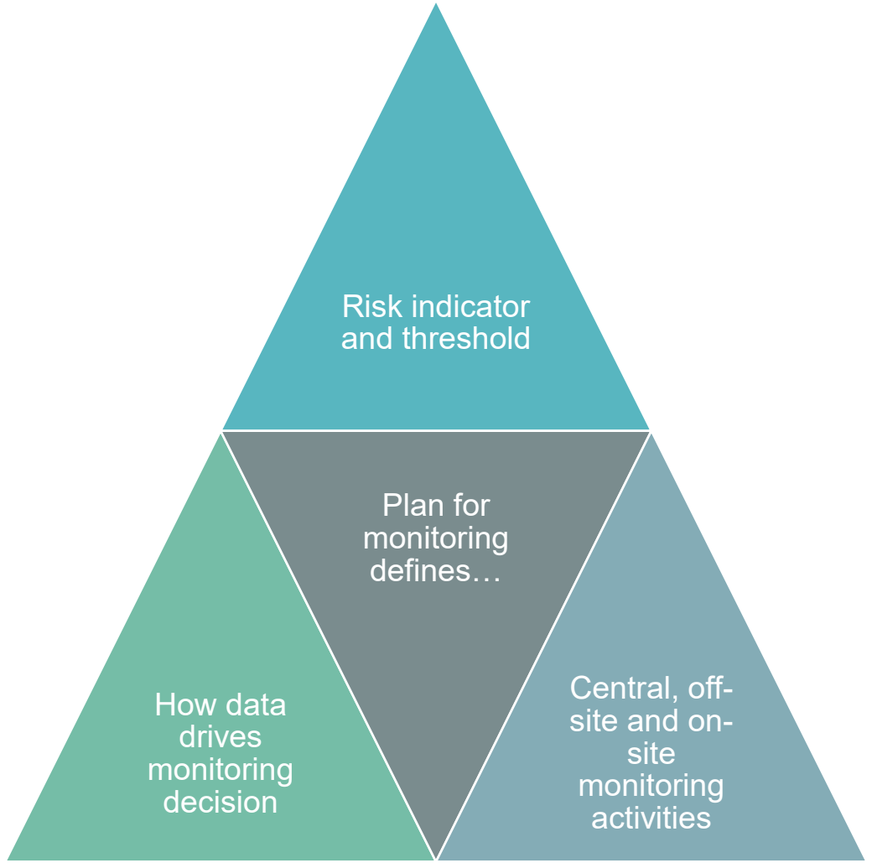
The documentation on risk assessment and mitigation activities (e.g. the risk assessment and mitigation plan) should contain the identified risks that are mitigated by monitoring and the type and intensity of monitoring undertaken. This includes a description of critical data and processes, as well as the quantity and type of source data that needs to be verified against the CRF and corroborated against other records.

Based on the outcome of the risk identification and evaluation, the sponsor should develop a monitoring plan that describes the monitoring methods, responsibilities, and requirements for the trial to be monitored. The monitoring plan should include a brief description of the study, its objectives, and the critical data and study procedures, with particular attention to data and procedures that are unusual in relation to clinical routine and require training of study site staff. The plan should be communicated to relevant parties (e.g. monitors, project managers, data managers, statisticians etc.) and should provide those involved in monitoring with adequate information to effectively carry out their duties.

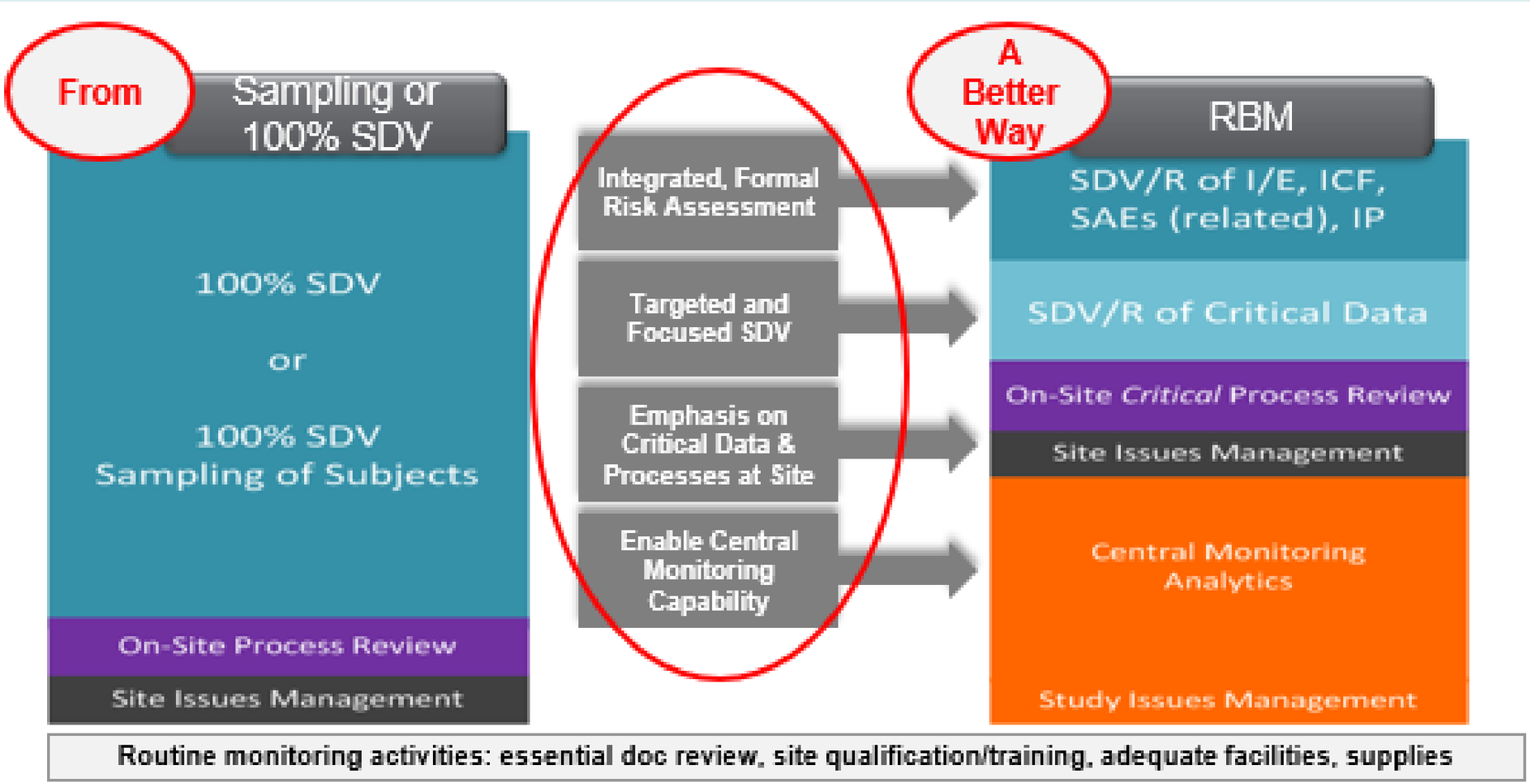
Sponsors should consider what events would indicate a need for review and revision of the monitoring plan and establish processes to permit timely updates where necessary. For example, a protocol amendment, change in the definition of significant protocol deviations, or identification of new risks to study integrity could result in a change to the monitoring plan

Monitoring Plan

- Monitoring plan will have to reflect all monitoring activities



Understanding the Change: Operating Differently



Transcelerate : Risk-Based Monitoring Overview

Risk Proportionality Framework*

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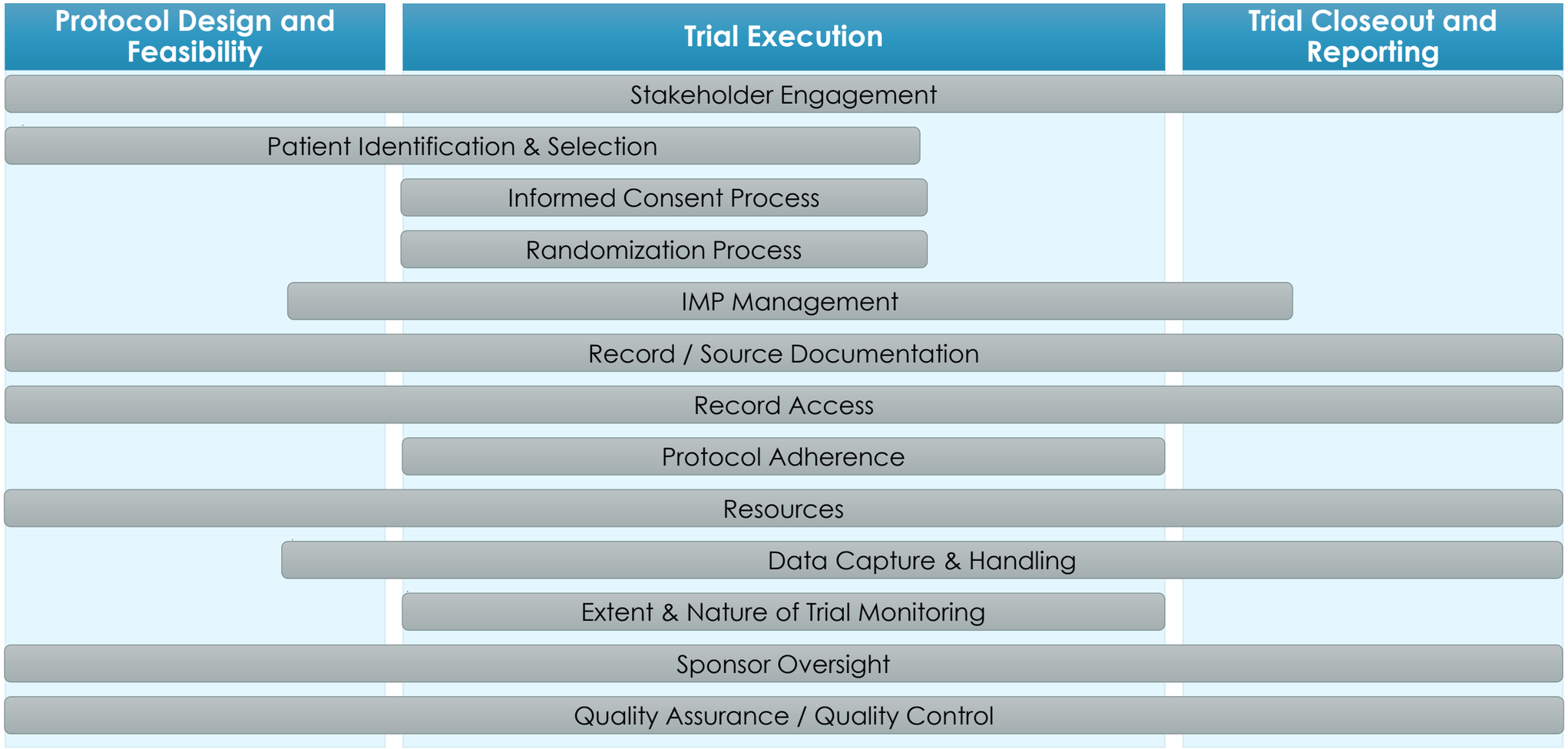
Sample Critical to Quality Factors



*Transcelerate tool kit

Risk Management

Key Changes in Good Clinical Practice [ICH E6(R3)]

	As described in ICH E6(R2)		As described in ICH E6(R3) draft		Summary of Impact
Risk Communication	Documentation and communication of quality risk management	→	Communication of quality management activities as needed for effective control	→	Proportional management of risk drives communication and documentation
Risk Review	Periodic review of risk controls	→	Language unchanged	→	Risk reviews should continue to ensure risk assessments are up to date and implemented control measures are relevant and effective
Risk Reporting	Reporting of the quality management approach and QTLs	→	Summarize risks and remedial actions taken in response to Acceptable Ranges	→	Emphasizing the risk-based quality management approach in the Clinical Study Report

*Transcelerate tool kit

Questions?

Sponsor Oversight

Day 2

Any Question?

Agenda Day 2

- Q&A Day 1
- What does mean oversight?
  - Resources management
    - Roles and responsibilities*
    - Finance
      - Workshop
  - Subcontractor management
    - Agreements
    - Documentation
      - Workshop: oversight plan content
    - Communication
  - Essential records management
  - Q&A

Resources management

ICH-GCP E6 R3

3.3 Allocation of Activities

Prior to initiating clinical trial activities, the sponsor should determine the roles and allocate their trial-related activities accordingly.

Trial Team

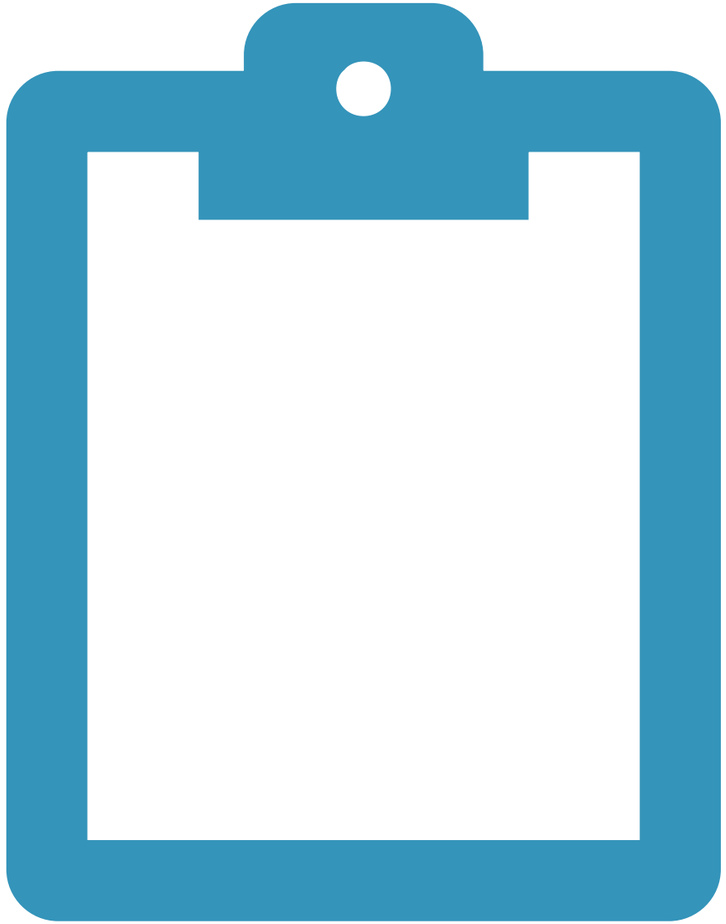
- Describe number & type of people needed for the project.
- Identify the name of individuals & vendors with a leading role in the project.
- For each describe roles & responsibilities in the project.
- For each resource detail start dates, estimated duration
- Create a single sheet containing this information.

Microsoft Word Document

Human resource plan

- Define RACI for each task:

R – **R**esponsible for completing the work
A – **A**ccountable for ensuring task completion/sign off
C – **C**onsulted before any decisions are made
I – **I**nformed of when an action/decision has been made



Human resource plan

The RACI chart shows the relationship between project tasks and team members.

	Project Manager	CTA	DM	QA	Lead CRA	CRAs
Write monitoring plan	R, A	I	C	C	C	I
Review Monitoring plan	A	C	R	R	R	I
Create monitoring forms	A	R	C	C	C	I
Prepare Annotated CRF	C		A, R	C	C	I
Review annotated CRF	A		R	R	R	I

Any proposed changes to project responsibilities must be reviewed and approved by the project manager. Changes will be proposed in accordance with the project's change control process. As changes are made all project documents will be updated and redistributed accordingly.

The Project Plan

Task Allocation Matrix (TAM)

- Who does what?
- Related to the budget

Task Allocation Matrix

- As per ICH-GCP 3.6.4 Any of the sponsor's trial-related activities that are transferred to and assumed by a service provider should be documented in an agreement. The sponsor's trial-related activities that are not specifically transferred to and assumed by a service provider are retained by the sponsor.

Microsoft Word Document

TAM:

- Part of Request For Proposal (RFP)
- Part of Contract ~ Budget
- List all tasks to be done in the trial
- Define who is doing what
- Ensure all needed tasks are listed when they are delegated to a vendor
- List which SOP is applicable for the task

Task Allocation Matrix

- Responsibility SOP-training of team members
- Documented on SOP reference forms:
  - Sponsor SOP list
  - CRO SOP list
  - Study specific SOPs

Microsoft Word Document

- Sponsor's SOPs are kept in TMF,
  as well as SOP up-dates/ new versions/…

Team management

Create a structure in which people can work independently

=

Making clear “who is going to do what, when, where and how”

Team management

- Remind the people on regular basis of the objectives that need to be achieved
- Establish realistic due dates with team members/stick to them
- Maintain organization and communication plan
- Defines roles and accountability for each member
- Handle conflict
- Make decision
- Meet effectively

Team management

- Stimulate cooperation between the team members
- Train the team adequately
- Provide support, remain open to discuss any item
- Celebrate important milestones and achievements

Team management

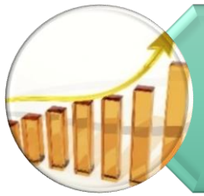
- Project Management ≠ telling people what to do
- Project Management = facilitating others' ideas with an effective plan that completes the project, within budget and resources

Budget Management and Timeline Oversight for Clinical Project Managers

Effective budget and timeline management forms the cornerstone of successful clinical trial oversight. As a project manager, your ability to maintain rigorous financial control directly impacts trial outcomes, sponsor confidence, and regulatory compliance.

Budget Allocation

Projects are by definition unique, and therefore to a degree unpredictable



Variance -10% to + 20% in general project management is considered realistic

Tasks never performed before, are usually under-estimated by a factor 4!

Many companies don't just budget, but want forecast of budget spent as well

FINANCIAL OVERSIGHT

Budget Management: The Foundation of Project Success

Why Budget Control Matters

Budget and timeline oversight represent the most critical responsibilities in clinical project management. Financial discipline ensures trial continuity, maintains sponsor trust, and prevents costly delays or scope compromises.

Essential Budget Management Steps

01

Initial Budget Preparation

Develop comprehensive budgets accounting for all trial phases, personnel costs, site expenses, and contingencies

02

Regular Review Cycles

Establish monthly or quarterly review schedules to track actual versus planned expenditure

03

Forecasting and Adjustment

Continuously forecast future spending based on current trends and adjust allocations proactively

Static budgets become obsolete quickly in dynamic clinical environments. Implementing robust forecasting mechanisms enables early identification of potential overruns, allowing for timely corrective actions. Regular stakeholder communication about budget status prevents surprises and maintains alignment between operational reality and financial expectations.

Cost driver

- Main driver of study budget are:
  - Site fees
  - Monitoring

Budget Allocation

For the Sponsor (with/without help of CRO)

1. Project design and Set-up
2. Regulatory Requirements
3. Project Monitoring
4. Project Management
5. Investigational Medicinal Product
6. Data Management
7. Safety
8. Quality Control
9. Statistics/IRT
10. Report Writing
11. Audit
12. Archiving
13. Central Lab/ Image Readers

By Site

- Staff costs
- Patient care costs
- Fixed costs
- Procedures/tests
- Administrative costs

Budget Allocation

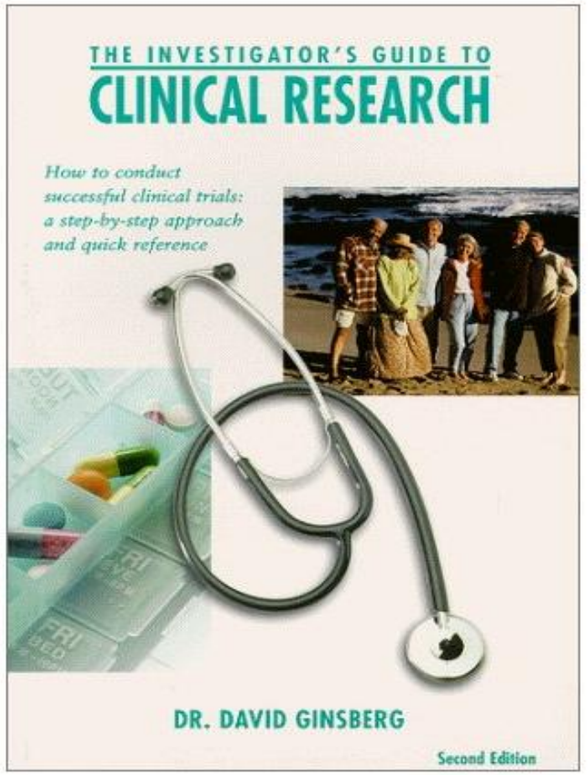
Study Costs vs Standard of Care

- Principle investigator and coordinator must carefully identify usual and customary care procedures vs. research specific procedures
- Usual and customary care procedures would probably be performed if the patient were not on the study
- Research specific procedures would probably not be performed if the patient were not on a study
- Standard of care tests and results may be used for research but are <u>not invoiced to the sponsor</u>

Budget Allocation Site – Procedures

‘In Clinical Research, a site needs to anticipate that the time & effort for successfully completing a study will be *significantly greater*, than it would be for treating a similar number of regular-practice patients.

The site must calculate a budget that provides reimbursement for that extra time and effort.’



Payment schedule

1. **Start-up fee**
   - Non refundable
   - Time for reviewing the protocol, covers EC fees, set up of the trial
2. **Advance payment**
   - Refundable
   - Up-front payment before the first 1 or 2 payments
3. **Regular payments with realistic milestones**
   - Per subject payment : after 3 subjects randomised
     after 2 subjects completed
   - Monthly / quarterly
   - Achievement of milestones – most current

! Site payment will only be executed after visit completion confirmation

Don't forget screening failures and early termination patients !!

Payment schedule (con't)

4. **Final payment**
   - After all CRFs are completed & clean
   - After all sites closed
   - After delivery of Final Study Report (incl. sending to sites)

5. **Invoicing permitted for other costs or unexpected events**
   - Pass-through costs
   - CRA Meetings

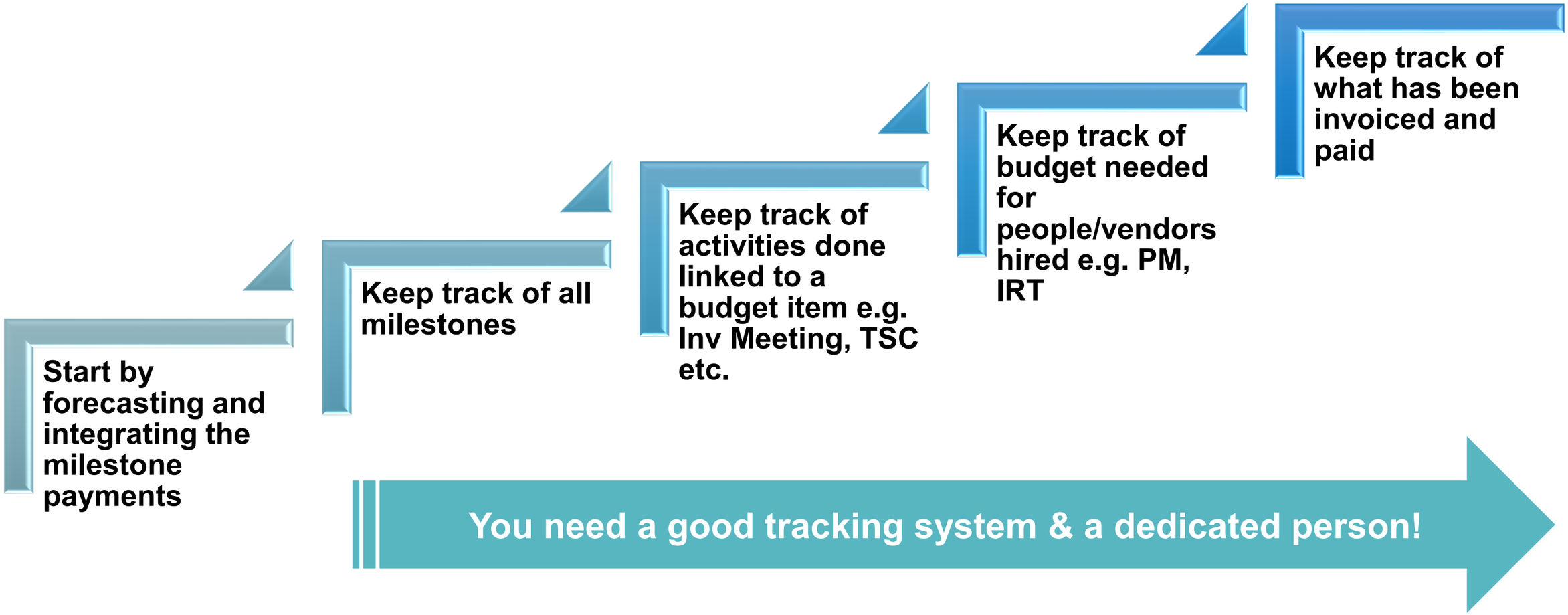
Budget Forecast

As soon as you have your final budget you need to define how and when it will be spent

A forecast is taking into account:

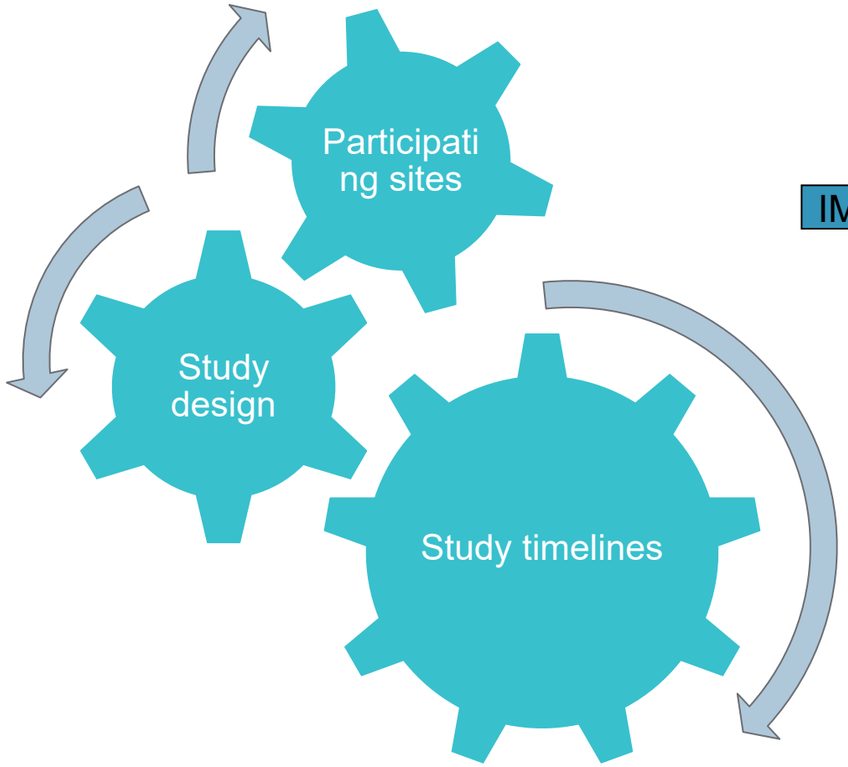
- Sponsor FTE
- External partner cost
- Site costs

How to handle a global study budget?



Monitoring and Control

- Tracking of Sponsor, CRO team budget depends on the possible changes within the study parameters



IMPACT

- Workload
- Study duration
- IMP/MD management

Monitoring and Control

Tracking of Sponsor budget:

No changes in study workload and study duration:

keep track on work efficacy and workload of study team

Changes in study duration (e.g. recruitment period increases) but no changes in study workload:

Re-organize FTE according to the new timelines

Changes in study duration and study workload (e.g. recruitment period increases, and additional sites added)

Reassess study budget

Monitoring and Control

- How to follow your global budget?
  - You need good tools:
    - Tools for time spent recording (Clockify, Toggl, Avaza, etc.)
    - Good excel knowledge (Pivot table, formulas etc.)
    - CTMS
  - You need a dedicated person (PM) and finance department support
  - Finance department should be able to provide you with a status of what has been paid and what not.

Monitoring and Control

! **Finance metrics** for actuals versus planned budget

- Review monthly: spent budget versus the forecast
- Follow-up of the invoices to receive/ paid
- Quarterly estimate updates
- Budget amendments for out-of-scope
- Update the forecast when timeline changes occur

Why so many tracking?

- Error is human!
- Avoid cash flow issues
- Being able to conduct the trial until the end (CSR)!
- Being able to pay the whole team until the end!

Vendors and oversight plan

CRO oversight: ICH-GCP E6 (R3) 3.6

- 3.6.4 Any of the sponsor's trial-related activities that are transferred to and assumed by a service provider should be documented in an agreement. The sponsor's trial-related activities that are not specifically transferred to and assumed by a service provider are retained by the sponsor.
- 3.6.6 A sponsor may transfer any or all of the sponsor's trial-related activities to a service provider in accordance with applicable regulatory requirements; however, the ultimate responsibility for the sponsor's trial-related activities, including protection of participants' rights, safety and well-being and reliability of the trial data, resides with the sponsor. Any service provider used to perform clinical trial activities should implement appropriate quality management and report to the sponsor incidents that might have an impact on the safety of trial participants or/and trial results.
- 3.6.9 The sponsor should ensure appropriate oversight of important trial-related activities that are transferred to service providers, including activities further subcontracted by the service provider.
- 3.6.10 Trial-related activities performed by service providers should be conducted in accordance with relevant GCP requirements, which may be fulfilled by a service provider's existing quality management processes that were not designed specifically to be GCP-compliant but are fit for purpose in the context of the trial.

The basics of any agreement

- What is the contractor supposed to be doing
- Who is doing exactly what
- When it needs to be done by, delivery dates
- How much will it cost

And do not forget GCP and quality statements….

More detail

Exactly what you want them to do in very specific fashion, if this went to court is the level of detail provided sufficient?

It must be very clear who is doing what and there must be no potential confusion due to shared responsibilities. Look at the task matrix and split all lines that are shared.

How will you know that something is done when it is done, is it unambiguous? A clearly defined endpoint that can be independently assessed. Definitions are important

Detail that allows any change in what is done, when it is done, or who is doing it (i.e. anything covered in the points above), can be tracked, assessed and checked against reality.

Vendors Contracting

Detailed contract:

- Roles & involvement (well described services)
  - Prices per country (may differ)
  - Price per activity unit
  - Price for specific duration of activity (ex. duration of monitoring, travel, reporting)
- Is contract clear and understood in the same way for all?
- What in case of turn-over? Training of new members?
- Long term project: inflation increase?
- Pass-through costs? travels of monitors

Clinical
ership Managemen

Invoicing:

- Define invoicing timelines & details (need timesheet?)
- Track invoices & check against budget

Regulatory basis for oversight

Proactive & ‘up front’ determination of the levels of oversight needed for a study.	• Study level quality plans • Relationship level activities
Justified rationale for levels of oversight. Documentation justifying approach	• Risk Management plans • Quality plans • Study level contracts
Flexible to permit changes	• Change Management within plan
What are the risks of minimal/reduced oversight in certain areas?	• Conduct risk management activities to assess
Study teams to work with their sponsor Regulatory contact	• Complete a “Transfer of Sponsor Obligations” document (Roles and Responsibilities matrix)

Regulatory basis for oversight

Assessment activities	Comprehensive Contractual detail & effective contract maintenance	Escalation processes for vendor/site issues	Documentation
• Study team level • Relationship level by Quality and Risk Management (Audits, SOP Review)	• Transfer of obligations (TOO) • 3rd party vendor contracts – selection, set-up and ongoing monitoring	• Develop at study level and confirm escalation path • Centrally through Operational Effectiveness Committee, etc.	• Well organized and complete study files • Decision making activities, etc. (meeting minutes)

Level of oversight needed?

Oversight is the process that a sponsor implements to ensure that CRO contract obligations are fulfilled

Micro management Vs hands-off approach, you need to find the correct balance

What will impact the level of oversight you need to implement?

- Existing relationship with suppliers
- Level of confidence in a supplier
- History of specific issues (sloppy monitoring, lack of correct PM oversight,…)
- Amount of internal sponsor resources available
- Importance of the project
- Phasing of the project
- Type of activities outsourced
- Volume of work outsourced

Sponsor: Volunteered Challenges in Providing Oversight

Turnover, involvement of senior staff, not fully dedicated to one project

"Staff turnover and many employees not experienced enough to provide requested services."

"Junior staff making major decisions and no oversight or thought of checking with the Sponsor."

Metrics, proper measurement

"Defined metrics & systems to track/manage/control."

Alignment on SOPs, avoiding redundancy

"Too many hand-offs between functional groups between both the Provider and organization. Messages get diluted or miss the appropriate audience completely. A lack of flexibility toward processes both from the Provider and the organization which usually leads to gaps in delivering on expectations."

Openness

"Working on the relationship to facilitate transparency; and ensuring that as a Sponsor we are aware of all relevant issues – this takes time and very often there are resource constraints that make it extremely challenging to find the time needed."

Communicating effectively, clearly, responsiveness

"Ensuring we are speaking the same language. Terminology can mean different things to different companies."

Q: What do you feel is the biggest challenge you face when providing oversight to your Clinical Service Providers?

Avoca® THE AVOCA GROUP

Provider: Volunteered Challenges in Providing Oversight

Too much/too little oversight

"Lack of understanding of how to, and benefits of, outsourcing. Either trying to dictate detailed process and micromanage, or on the reverse end, having complete lack of oversight and involvement.

Unclear, not aligned to process/SOPs

"Many different voices on the Sponsor side (sometimes not aligned) or unclear expectations/processes."

"They do not partner and fail to communicate needs and expectations clearly."

AVOCA group survey 2019

CRO - Sponsor Relationship

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Objectives

- Define ways to establish the partnership
- Discuss measuring CRO performance
- Identify key factors to problem solving
- Define framework of a governance board
- Define rationale & factors for conducting an end of project meeting

Workshop: Oversight Plan Content?

Oversight plan

1. DOCUMENT PURPOSE
2. CRO OVERVIEW
3. CLINICAL STUDY MEETINGS
   - Kick-Off Meetings
   - Study Oversight Meetings
   - Study Close-Out Meetings
4. STUDY-SPECIFIC PROJECT PLANS
5. OVERSIGHT ACTIVITIES
   - Site Management / Monitoring Oversight
     - Review of Site Visit Reports
     - Co-Monitoring
     - Protocol Deviations
     - Progress Reporting
   - Data Processing Oversight
     - Quality Checks
     - Progress Reporting
     - Medical Oversight
     - Progress Reporting
   - Clinical Study Supply Oversight
     - Progress Reporting
     - Regulatory Oversight
     - Regulatory Authority Submissions, Questions & Answers
     - Progress reporting
   - Etc.
6. ISSUE ESCALATION
   - Root Cause Analysis and Corrective Action
   - Co-Monitoring Visit(s)
   - For-Cause Audit
   - Issue Escalation Meetings
7. AUDITING
   - Sponsor Audits
   - CRO Audits

Why should it be so detailed?

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Risk management!

- Define sponsor expectation for each activity outsourced
- Describe oversight activities
- Explain how to ensure quality through the study
- Outline risk mitigation activities

Basics

Communication is fundamental to the **success** of an outsourcing relationship. All stakeholders having a vested interest in the outcome of the outsourcing assignment should be identified. This will include both internal and external stakeholders and communication should be considered during the planning stages of outsourcing activities or a project.

Key communication responsibilities and activities need to be recorded in the **contract**, including communication with Third parties. This is formalised in a Communication Plan.

In summary…

"A good communication plan is the scaffolding on which the successful delivery of a project hangs.

The backbone of the overall project plan, it is the code book to explain how a diverse and disparate team unites to deliver"

Carl Emerson, Dec 2007

How to keep the oversight?

- You do **not** need to track everything yourself but you need to know the global picture
- AVOID MICROMANAGMENT
- Good collaboration with all stakeholders is key.
  - Communication plan
  - Escalation path
- Team meeting and status reports are essentials

Vendor management

Consequences of micro-management

- Trust blocker
- Lack of use of CRO expertise
- Money wasted
- Ineffective use of resources
- Decrease CRO empowerment level and rely on Sponsor with minor matters
- Limits innovation from CRO
- Decrease CRO motivation

Good communication and status report is KEY

Priority settings

What do you need to know?

- Serious GCP breaches
- Safety alerts
- Issues in Data entry/Cleaning
- Protocol deviations trends
- Monitoring issues
- Budget changes/issues
- Timelines changes (Site activation, FPI, recruitment, database lock etc).
- Staff changes

Oversight benefits

- ✓ Oversight should be a cure to minimize the risks of …
  - Late delivery of a project
  - Quality & safety issues
  - Changes In Scope
- ✓ And also to
  - Provide updates to management on status
  - Give assurance on the well-being of the relationship

Change management

"Change always takes place; it is how they manage this change that will make the difference."

Companies that effectively manage accruals are also partnering with vendors effectively. Quarterly reconciliations are taking place with their larger trial vendors.

Plan for changes

Part of your project plan (communication plan?)

What changes should be accepted?

- Related to patient safety and/or well-being
- Related to data quality
- To improve study performance
- Minor changes that do not impact timelines and budget

Which ones can be refused?

- Additional scientific research for nice to have
- Budget increase for non-anticipated cost

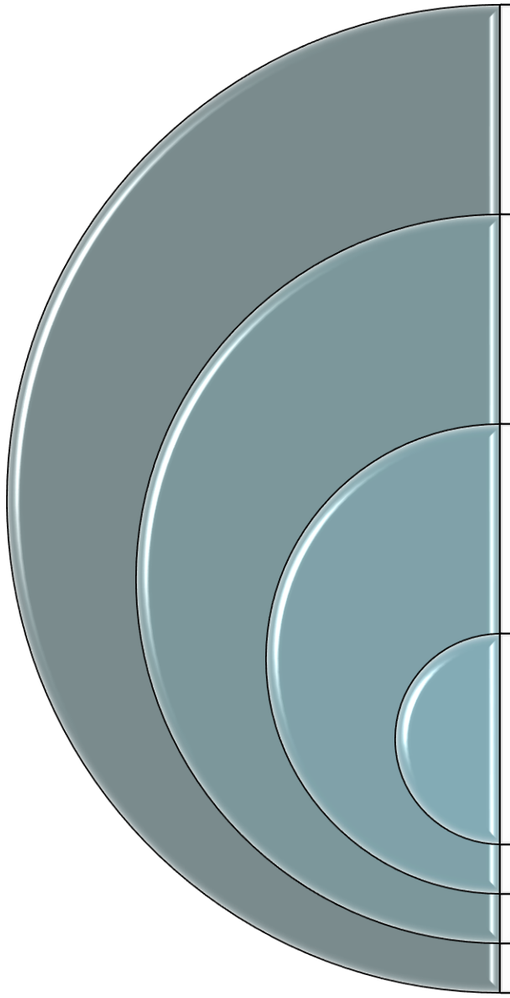
Escalation process

Approval process

Monitoring and Control
Change Control

Requirements:		
Identify change control triggers	Define which changes need upper management/sponsor agreement	Outline a mechanism to: • Update all elements of the plans to reflect approved changes • Communicate approved changes to all areas/functions impacted • Record and track changes over time (change log)

Scope control



Avoid Scope creep: Uncontrolled change in a project's scope which leads to increase risk, time and resource requirement

Keep track of every changes (change log)

Analyse each request, ask for rationale and push back when possible

As soon as a change is approved update budget **and** forecast.

Change in Scope?

The fundamental element to understand in CIS management is the simple but very powerful equation:

=

Budget Control

If delay in a project occurs or a new request is made outside original scope, there is an impact on budget regardless budget type: fee for service; milestone; time & materials

Be proactive to inquire impact on budget

- Delay due to protocol amendment
- What activities are still going on?
- What tasks are put on hold ?

How to manage Change in Scope?

Be clear on initial assumptions and expectations

Make sure the task order is accurate

Make sure you know the task order

Be careful with very low budget proposed

Change orders are a reality so we should discuss upfront the process with your CROs

Detailed	Timely	Communicated in advance	Agreed upon

If you are approach for a Change in Scope…

Don’t make any commitments	Escalate appropriately

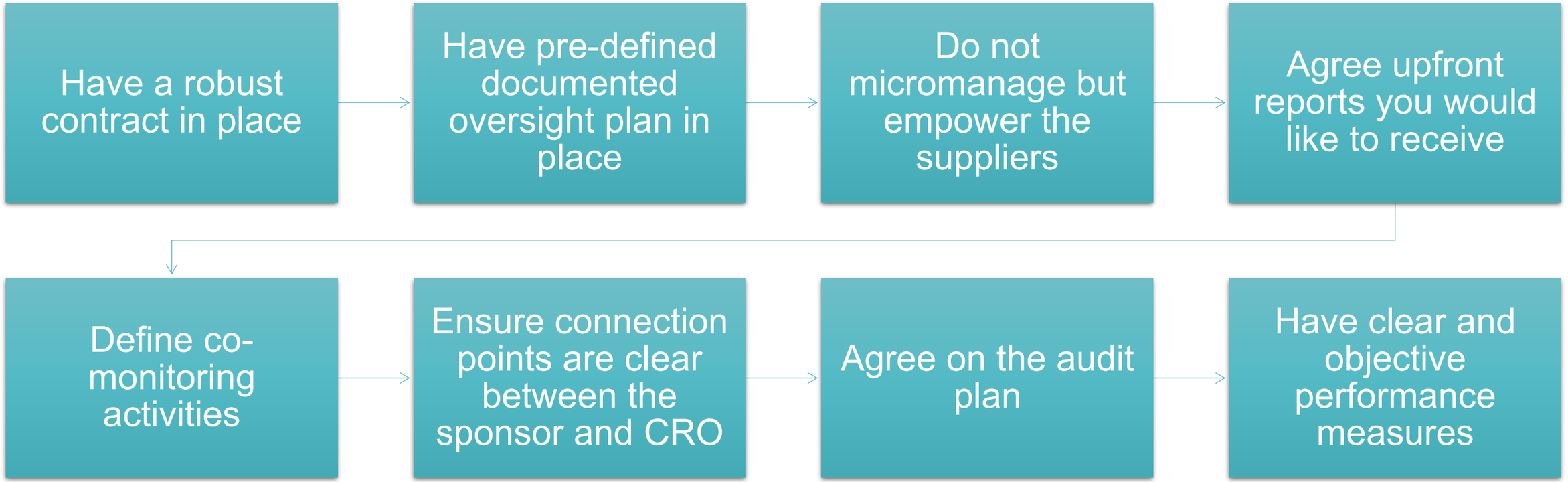
Change Orders

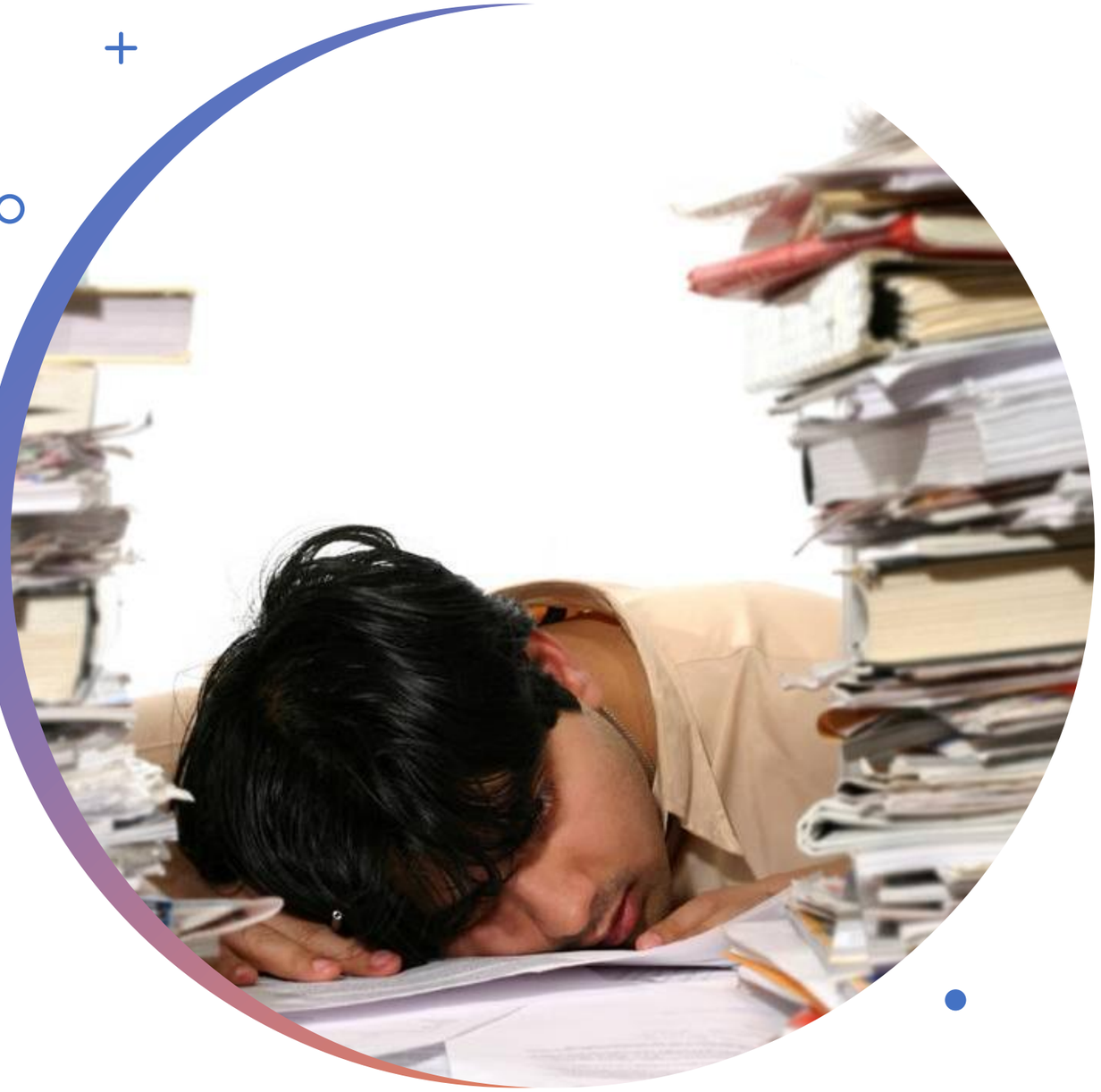
Are change orders necessary?

Sponsor and CRO should have an agreed upon mechanism for managing change in scope

- Detailed
- Timely
- Communicated in advance
- Agreed upon

Effective CRO Oversight





Essential record management

Trial Master File Plan

Archiving plan: Why?

Archiving requirements according to ICH GCP (ICH GCP Appendix C 1.3) and local legislation:

DOCUMENTS

Documents which individually or collectively permit evaluation

- of the conduct of a study and
- of the quality of data produced

Archiving plan
Essential Documents Why?

Purpose: to demonstrate compliance with

- Protocol
- ICH GCP
- Regulatory requirements
- SOPs

by

- Investigator
- Sponsor (Monitor)

Archiving plan
Trial Master File: Why?

- 99% of regulatory requirements (Audit & Inspection) refer to documentation

If it isn't documented,

it did NOT happen!

Overview of documents see:
http://ichgcp.net/?page_id=131

Electronic records management

Electronic records can be documents, data and their relevant metadata

Records management described in the data governance

Documents control

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Audit Trail for traceability & reliability

Changes (paper & electronic) should:

If generated as a direct computer input

- never obscure the previous entry
- indicate the reason for change
- be dated & signed
- ensure full audit trail

ALCOAC++

- Attributable,
- Legible,
- Contemporaneous,
- Original,
- Accurate,
- Complete,
- Consistent, Enduring, Available when needed, and Traceable

Archiving plan - Trial Master File

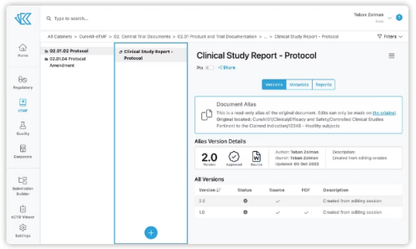
- The CPM is the person finally accountable for the Trial Master File!

- Ensure that the whole team understands the study documentation requirements and the reasons why!

ICH-GCP E6 R3

Understanding Essential Records in Clinical Trials

The ICH-GCP E6 R3 guidelines define Essential Records as comprehensive documentation facilitating trial management and regulatory compliance. These records encompass all documents and data—regardless of format—that collectively enable evaluation of trial methods, influencing factors, and actions taken during conduct.



Purpose and Function

Essential records allow verification that trials were conducted according to GCP standards and applicable regulatory requirements whilst enabling assessment of result reliability

Risk-Proportionate Approach

The nature and extent of records generated depend on trial design, conduct methodology, and the relevance of each record to trial integrity

Oversight and Inspection

Records support sponsor oversight, monitoring activities, independent audits, and regulatory authority inspections to assess trial conduct

Records Management Responsibilities and Compliance Requirements

Investigators and institutions bear critical responsibilities for essential records throughout the trial lifecycle. According to ICH-GCP E6 R3 Section C.1.3, these records serve multiple stakeholders including IRB/IEC committees, sponsor oversight teams, independent audit functions, and regulatory authorities during inspections.

Access and Control

Investigators must maintain unfettered access to all essential records generated at their institution throughout trial conduct

Ongoing Management

Records facilitate continuous trial management, enabling real-time evaluation of methods, factors, and actions affecting trial integrity

Retention Compliance

All essential records must be retained according to applicable regulatory requirements, ensuring long-term availability for verification purposes

Key Takeaway: Proper records management isn't merely administrative—it's fundamental to demonstrating GCP compliance, ensuring data reliability, and protecting trial integrity. Project managers must implement robust systems for record generation, maintenance, and retention that satisfy regulatory expectations whilst supporting efficient trial operations.

Archiving Plan/TMF

Archiving requirements according to ICH GCP and local legislation:

- Structure of the TMF
- Paper/electronic/hybrid TMF?
- Accounts for e-TMF
- Study document locations during the study
- Document flow with coding/timepoints/frequency
- Procedure to send the documents
- **Quality checks and reviews**

→ IA can help to manage your eTMF

Any Question?

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Sponsor oversight

Day 3

Question?

Agenda Day 3

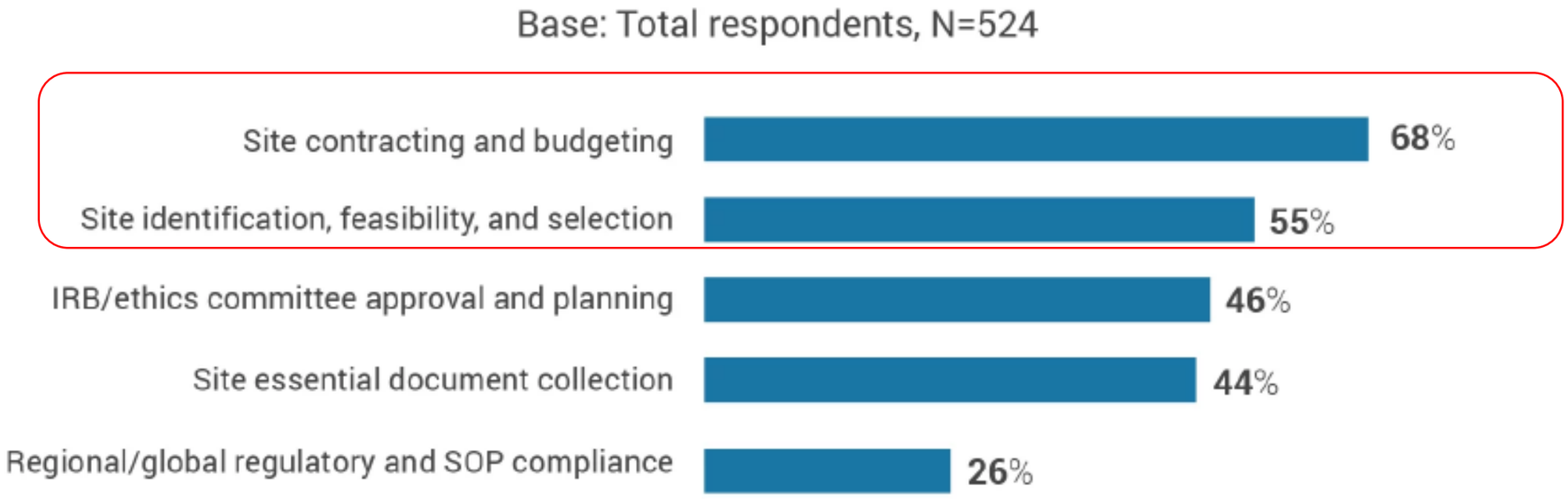
- Quiz Day1 and 2
- What does mean oversight?
  - Site selection and management
    - Feasibility tips and tricks
  - IMP/MD management
    - Drug accountability
    - IRT
- Record management and data governance compliance – *Trev Simmons*
  - Data life cycle
  - Computerised system
    - Buy, Build, Configure, Software-as-a-Service

Site feasibility Tips and tricks

ICH-GCP E6 R3 Sponsor responsibilities

- 3.7 Investigator Selection
  - 3.7.1 The sponsor is responsible for selecting the investigator(s)/institution(s). Each investigator should be qualified by education, training and experience and should demonstrate they have adequate resources and facilities to properly conduct the trial. If a coordinating committee and/or coordinating investigator(s) are to be utilised in multicentre trials, their organisation and/or selection are the sponsor's responsibility, and their roles and responsibilities should be documented prior to their involvement in the trial.

Pharma biggest Challenges with Study Start-up Processes



Fast Tracking Study Start-Up from Site Selection to First-Patient Enrollment. November 18, 2020
Ashley Davidson; **Applied Clinical Trials**, Applied Clinical Trials-11-01-2020, Volume 29, Issue 11

Select investigators

- Having a study ready to start recruitment (SIV done) is time consuming and not easy

Company Type	Variable	N	Average Number of Weeks	P-Value
CRO	Sites Worked With Before	70	21.8	0.007
	Sites Not Worked With Before	69	28.0	<.0001
Sponsor	Sites Worked With Before	161	27.4	0.007
	Sites Not Worked With Before	163	39.0	<.0001

Tufts Center for the Study of Drug Development June 2017

Site activation and recruitment

80% of studies are delayed due to recruitment

Nearly 1/5 investigators do not enrol any patients

1/3 enrol only 5% of evaluable patients.

In most programs, only 1/3 consistently enrol patients

Selecting the right investigators/sites is essentials

Recruitment time has impact on budget!

Site identification

- Site identification :
  - Historical collaboration (internal database)
  - Publications
  - Key Opinion Leaders
  - Patient associations/advocacy groups
  - IA can support in this research
  - Etc.
- Don’t underestimate the community hospitals
  - Less experienced
  - Less studies running
  - Accessibility to specific patients' population (low socioeconomic, etc.)

Site Feasibility

- **for the sites**
  - ❑Selection of sites based on draft protocol
  - ❑Qualification
  - ❑Experience similar clinical studies
  - ❑Recruitment & retention in prior clinical trials
  - ❑Trial-required facilities such as laboratories and pharmacies
  - ❑Regulatory requirements
  - ❑**Concurrent trial workload**
  - ❑Predict subject enrolment
  - ❑Trial-specific equipment e.g. measuring and imaging apparatus

→ Identify potential risks

Decentralised/hybrid study elements

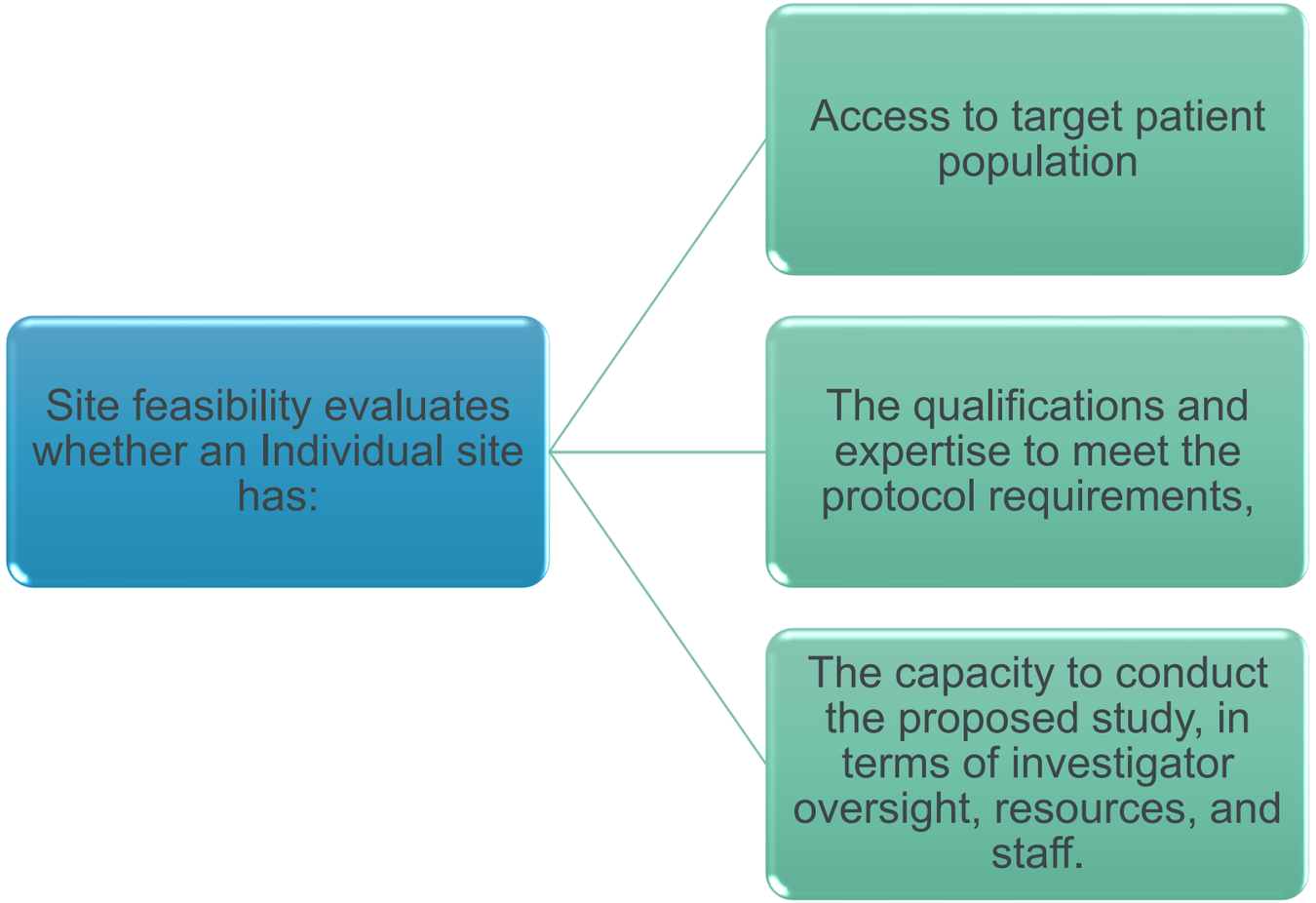
- Flying study nurses – contract requirements?
- eICF – easy to use for the site and patients?
- eCOA and ePRO - easy to use for the site and patients?
- IMP delivery at local pharmacy or patients: is it feasible for site and PI responsibilities?

The Feasibility

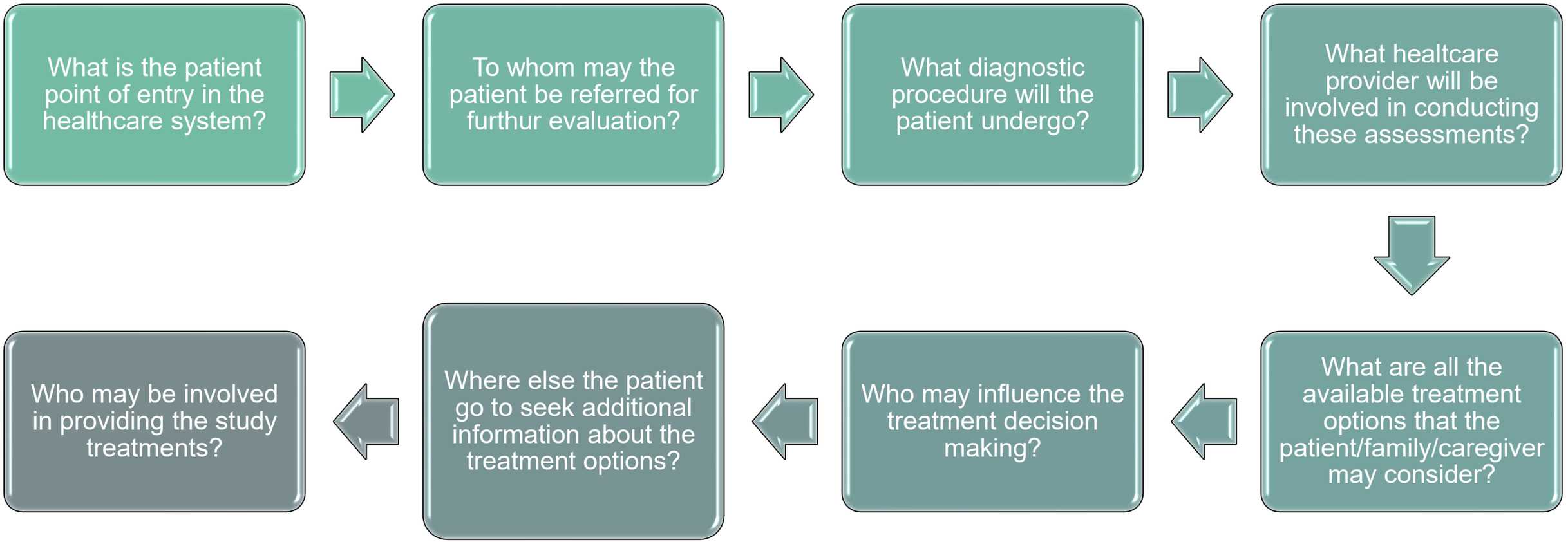
- **<u>Site Feasibility Questionnaire</u>** (SFQ)
  - Questions too long / too many
  - Abbreviations not explained
  - Unnecessary details / irrelevant questions
  - Ambiguous questions/multiple in 1 question
  - Indirect language
  - Lay-out not user-friendly / print too small
  - ……..
- **<u>Feasibility Study Tracker</u>**
  - Rating: 1 Very Good – 2 Good
    3 Acceptable – 4 Unacceptable

feasibility questionnaire

Usual site feasibility considerations



Patient Flow



Despite a long experience there is no magic recipe to select sites

Site management

Understanding The Difference Between Management And Oversight

Site management focuses on execution: coordinating visits, updating logs, tracking training, managing documents, and supporting patient-facing activities. It is essential for day-to-day operations.

Site oversight is strategic. It requires intentional and continuous verification that study activities are conducted ethically, accurately, and according to protocol and regulatory requirements. While management asks, “Was the task completed?”, oversight asks, “Was it done correctly, by the right person, and with documented evidence?”

Key components of site oversight

Consistent, documented PI engagement — Oversight requires meaningful, ongoing PI involvement.

- Routine review of safety data, deviations, and screening logs
- Oversight of informed consent discussions
- Timely review and signoff of critical documents
- Presence during key study procedures

Competency-based delegation — Delegating tasks is not enough; oversight requires validation.

- Training verification and retraining when needed
- Skills assessment for specialized tasks
- Documentation of competency-based delegation decisions

Key components of site oversight

Proactive data review — Oversight includes continuous evaluation.

- Query patterns
- Data inconsistencies
- Timeliness of entry
- Deviation and issue trends

Informed consent oversight — ICH and FDA guidance highlight informed consent errors as a top inspection finding. Oversightensures:

- correct versioning,
- complete signatures and dates,
- proper consent conduct, and
- verification of reconsent, where required.

Key components of site oversight

Preventive QC activities — Instead of waiting for monitors or audits to uncover errors, oversight-driven sites conduct:

- source document QC,
- ICF QC,
- IP accountability QC, and
- visit readiness checks.

Documented decision-making:

- Oversight must be visible in documentation. Decisions, escalations, and rationale should be recorded through notes-to-file, communication logs, or deviation assessments.

How to help site to have good oversight

Build an oversight-oriented culture — Oversight must be understood as a shared responsibility, not just the PI's. SCs,regulatory staff, and leadership should operate under consistent expectations.

Strengthen SOPs around oversight — Well-defined SOPs ensure consistency, such as delegation and competency processes,QC schedules and responsibilities, PI oversight requirements, and escalation pathways.

Implement oversight huddles — Brief, routine meetings support continuous quality, such as PI–SC quality review meetings,monthly deviation and data trend meetings, and risk-mitigation discussions.

Leverage technology — Systems such as CTMS, eReg, and dashboards enable transparent oversight such as real-time performance metrics, query aging reports, training compliance visibility, and IP oversight tools.

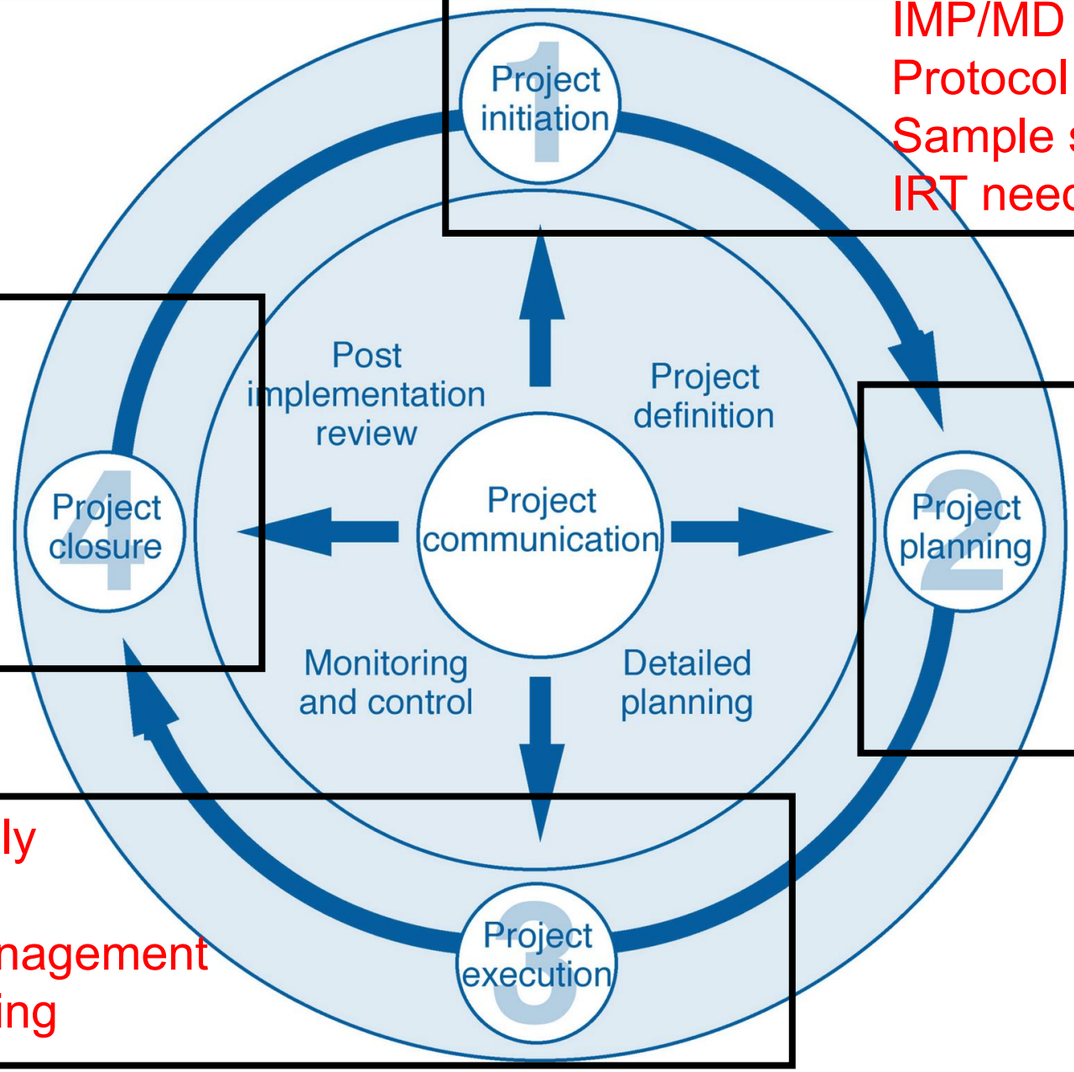
Transform monitoring visits into oversight validation — Monitoring should validate what oversight already ensures, notbecome a cleanup exercise. Sites with strong oversight experience fewer findings and better sponsor relationships.

IMP/MD management

Investigational Product(s)

Section 3.15 — Sponsor responsibilities covering information, manufacturing, packaging, labelling, supply, and handling of investigational products in clinical trials.

Project Life Cycle – drug supply



IMP/MD production
Protocol development
Sample size
IRT needs

IRT selection
Supply strategy
Packaging and labelling
IMP/MD supply

Re-supply
Expiry
date management
Relabelling

Drug return
Drug destruction

3.15.2 Manufacturing, Packaging, Labelling & Coding

Characterisation & GMP Compliance

Investigational product(s) — including active controls and placebo — must be characterised appropriately for the stage of development, manufactured in accordance with applicable GMP, and coded and labelled to protect blinding. Labelling must comply with applicable regulatory requirements.

Storage & Administration

The sponsor must determine acceptable storage temperatures, conditions (e.g., protection from light), shelf life, reconstitution fluids and procedures, and administration devices. All involved parties — monitors, investigators, pharmacists, storage managers — must be informed.

Packaging Integrity

Investigational product(s) must be packaged to prevent contamination and unacceptable deterioration during transport and storage.

PM: Initiation of the study

Clinical Operation and supply manager should be part of the protocol development to define if an IRT will be needed

Production, supply manager and clinical operations should from the initiation phase communicate on:

- Production timelines
- Number of countries and regions
- Number of patients planned

Do we need an IRT and then involve procurement/outsourcing managers?

PM: Risks assessment

- Define risks linked
  - To production timelines
  - Packaging and labelling
  - Supply strategy
  - Expiry dates
  - Regions and country requirements
  - Regulatory requirements
  - etc

Sponsor role?

DEFINE BUDGET FOR IMP PRODUCTION, PACKAGING AND LABELLING

DEFINE BUDGET FOR STORAGE AND SHIPMENT

DEFINE RISKS VS BUDGET

3.15.3 Supplying Investigational Product(s)

1 Sponsor Responsibility

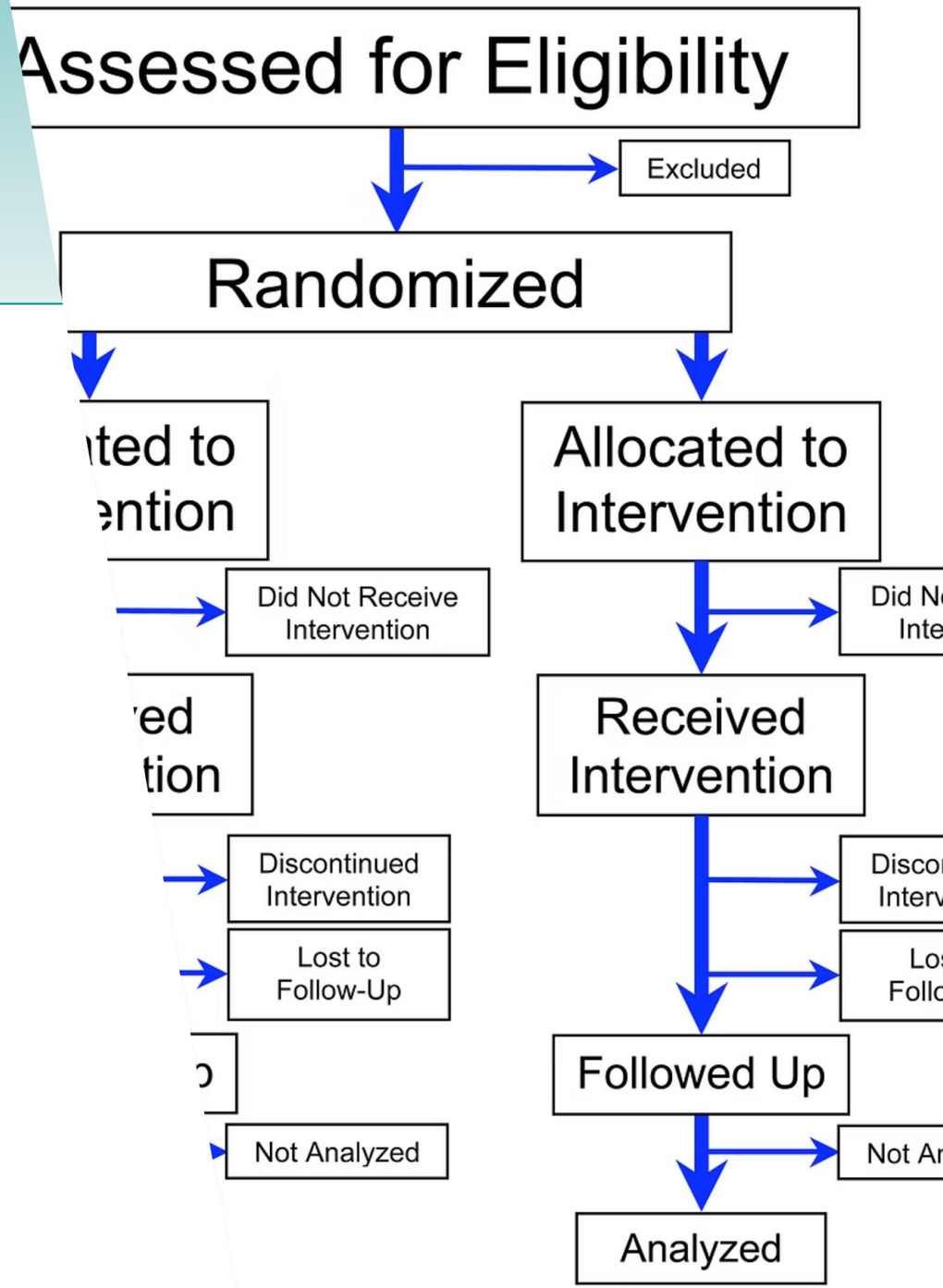
The sponsor is responsible for supplying investigator(s)/institution(s) with investigational product(s). Supply must only occur after obtaining required IRB/IEC and regulatory authority approval. Shipping and dispensing approaches should consider product characteristics, route of administration, and known safety profile.

2 Handling Instructions

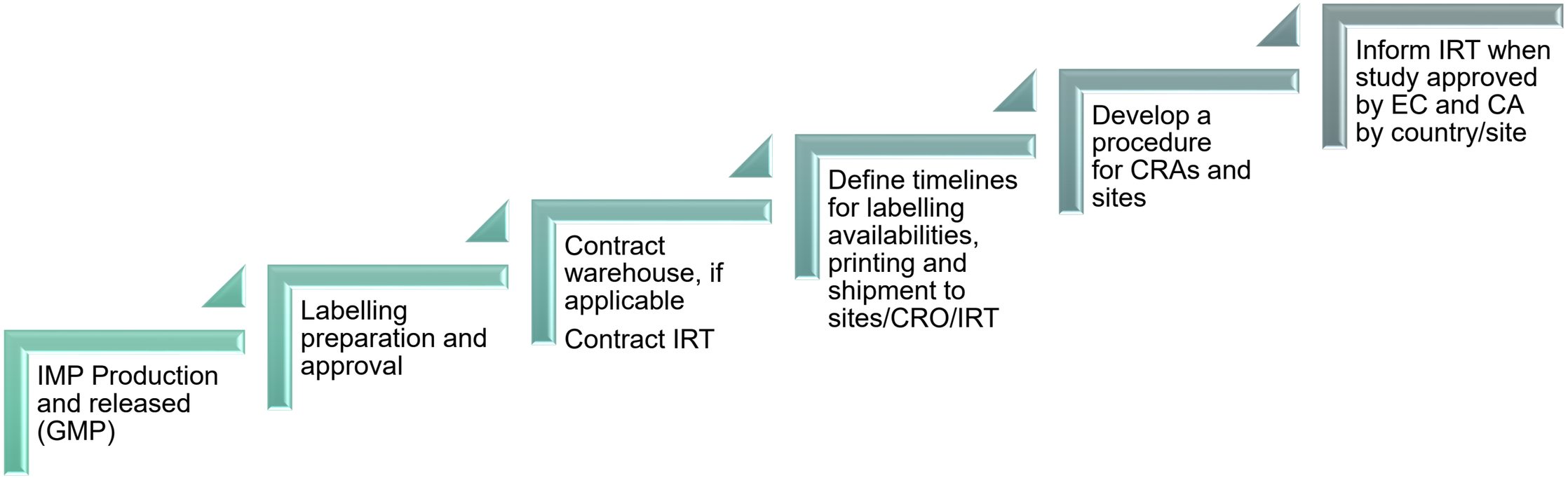
The sponsor must ensure instructions are available for investigators, institutions, or participants covering receipt, handling, storage, dispensing, retrieval of unused product, and return to the sponsor or alternative authorised disposition.

3 Safeguards

Investigational product management must comply with applicable regulatory requirements, with safeguards in place to ensure product integrity, protocol-compliant use, and participant safety.



Sponsor responsibilities



Sponsor Role

DO WE NEED WAREHOUSE? - CONTRACTING?

PROVIDE EXPIRY DATE

PROVIDE PRODUCTION PACKAGING TIMELINES

PROVIDE PACKAGING STRATEGY

PROVIDE NUMBER OF VISITS PER PATIENT

Sponsor Obligations: Supply Management

The sponsor must fulfil the following specific obligations in managing investigational product supply throughout the trial lifecycle.

01

Timely Provision

Ensure timely supply to investigators or participants to avoid trial interruption and support continuation of treatment.

02

Record-Keeping

Maintain records documenting identity, shipment, receipt, return, and destruction or alternative disposition of investigational product(s) (see Appendix C).

03

Retrieval & Disposition

Maintain processes for retrieving and disposing of investigational products — including deficient product recall, post-trial return, destruction, and expired product reclaim — with full documentation.

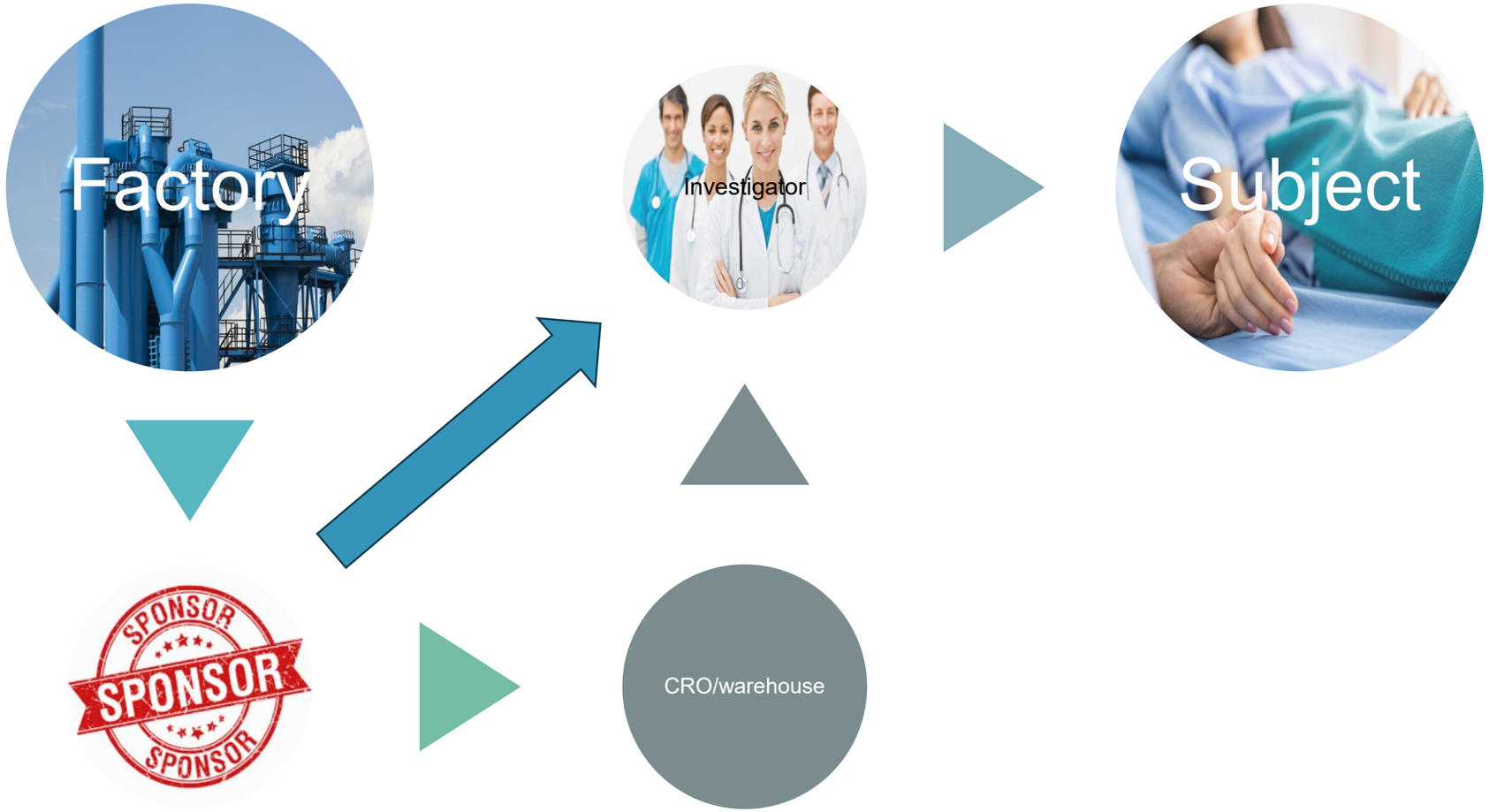
04

Stability & Shelf Life

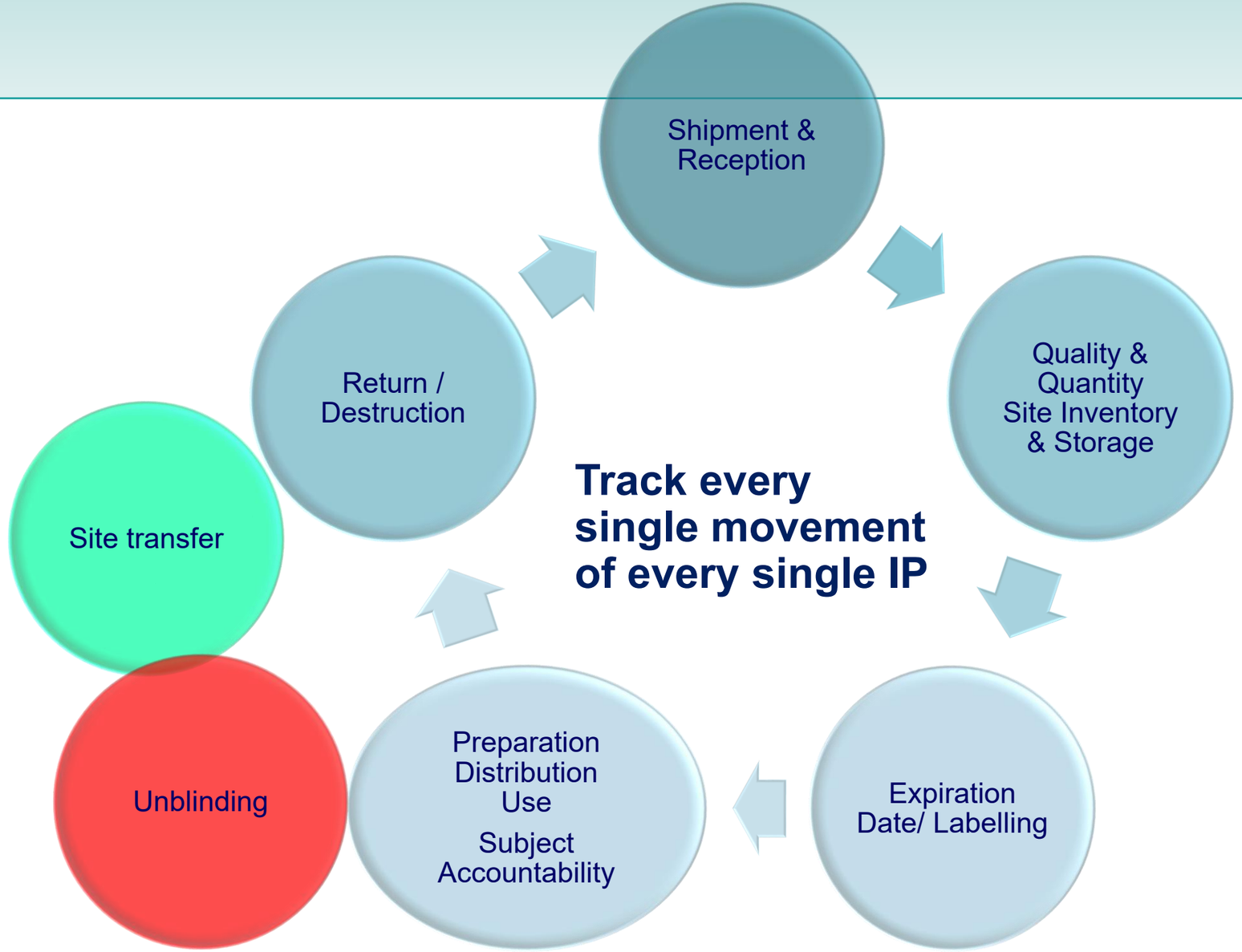
Ensure product stability over the period of use and that product is only used within current shelf life. Retain sufficient batch samples and records of analyses until trial data analysis is complete or as required by regulation, whichever is longer.

For authorised medicinal products used unmodified from their authorised state, batch samples are typically retained by the manufacturer rather than the sponsor, in accordance with local regulatory requirements.

IMP distribution parties involved



IP Accountability



PM during the study - Oversight

- Tracking regularly the number of IMP available in each sites and warehouse
- Ongoing shipments
- Proper use of IMP at sites/by patients
- Expiry dates
- New batch release dates
- Labelling and relabelling
- Randomisation mistakes and misallocation of treatment

How can a Project Manager keep drug supply oversight?

wehive
masterclasses • conferences • in-house training

IRT reports

- Enrolment
- Drug accountability on site and local depot
- Batch recall
- Etc.

eCRF reports

- Drug accountability
- Patients'visits

CRA Monitoring Visit report and Protocol deviation list

Regular communication with production

Etc.

Blinding Requirements

In blinded trials, the sponsor must implement robust processes to protect and manage the blind throughout the trial.

Blinding Process

A process to blind sponsor staff, participants, investigators, and site staff to product identity and assignment, with mechanisms to prevent and detect inappropriate unblinding.

Emergency Unblinding

A procedure permitting the investigator to rapidly identify the product in a medical emergency, whilst protecting the treatment assignment of all other participants.

Safety Reporting

A mechanism protecting the blind where a participant's treatment assignment is unblinded for safety reporting to regulatory authorities and/or IRB/IEC, where appropriate.

→ Sponsor must be informed immediately about any unblinding and the reason for

Record management and data governance compliance