Sponsor Oversight

Advanced GCP Training Course

WEHIVE
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Key course elements

- Defining "sponsor oversight" according to ICH E6 (R3)
- Discussing service provider oversight including service provider selection
- Contract Management
- Challenges including inspection risks
- Risk Management activities
- Improving collaborations between sponsors and service providers
- "Guiding principles" for sponsor oversight and good practices
- Workshops

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Organisations are encouraged to consult additional sources and conduct a thorough review of ICH E6(R3) to ensure a comprehensive understanding of the changes and their implications.

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Defining sponsor oversight

What is meant by "Sponsor Oversight"?

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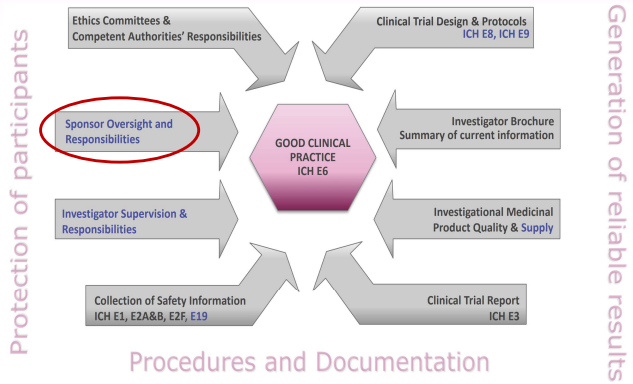
The Essence of Good Clinical Practice

as per ICH E6 R3 Expert Working Group



Source: ICH E6 R3 Expert Working Group Perspectives, Rebecca Stanbrook, 3 June 2020

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Sponsor oversight according to ICH E6 (R2)

ICH E6 R2 stated

The sponsor **should ensure oversight of any trial-related duties and functions carried out on its behalf, including trial-related duties and functions that are subcontracted to another party** by the sponsor's contracted CRO(s)

ICH E6 (R2) mentions the word "oversight" 3 times

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Sponsor oversight according to ICH E6 (R3)

- **According to ICH E6 R3**, the term "**trial conduct**" includes processes from planning to reporting, including planning, initiating, performing, recording, **oversight**, evaluation, analysis and reporting activities" (Section I, Introduction)

and

- **GCP** is defined as "a standard for the planning, initiating, performing, recording, **oversight**, evaluation, analysis and reporting of clinical trials that provides assurance that the data and reported results are reliable and that the rights, safety and well-being of trial participants are protected"

- **Thus, "oversight" is part of the regulated clinical trial conduct**

ICH E6 (R3) mentions the word "oversight" 23 times (this includes investigator oversight) and covers a whole section (3.9) on Sponsor Oversight

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Sponsor oversight according to ICH E6 (R3) "The WHY"

The sponsor must….

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 participant's safety and appropriate decision making (3.9.1)

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 (3.9.2)

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Sponsor oversight according to ICH E6 (R3) "The WHAT"

The **range and extent** of **oversight measures** **must be fit for purpose and tailored** to the **complexity** of and **risks** associated with the trial (3.9.5)

- **Oversight measures must be proportionate to individual trials and must fit the complexity and risks of the service provider/investigational site**
- **Ensure a rational for the oversight measures is documented, i.e. oversight is part of your risk assessment**
- **No more "cut and paste" of oversight plans**

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Sponsor oversight according to ICH E6 (R3) "The WHAT"

The **selection** and **oversight** of **investigators** and **service providers** are **fundamental features** of the oversight process (3.9.5)

➡ not just CRO selection and oversight are vital, also of any other service providers

The sponsor is responsible for **assessing the suitability** of and **selecting the service provider to ensure** that they can adequately undertake the activities transferred to them (3.6.7)

➡ Risk based service provider selection processes are needed

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Sponsor oversight according to ICH E6 (R3) "The WHAT"

The sponsor **must** ensure **appropriate oversight of important trial-related activities** that are transferred to service providers **and further subcontracted** (3.6.9)

➡ You must define what are "important" activities, i.e., the critical to quality factors (ICH E8)

➡ You need to define "appropriate" oversight

➡ You need to know about all subcontractors

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Sponsor oversight according to ICH E6 (R3) "The HOW" (1)

The sponsor must

Appropriately **assess decisions** related to the trial **for their impact** on participant's rights, safety and well-being and the reliability of trial results
and
suitably **manage risks related to such decisions throughout the planning, conduct and reporting of the trial** (3.9.4)

➡ It is essential to document decisions (to keep this in the TMF) and to add impact assessments and justifications throughout the trial activities

➡ Ensure applicable decisions are documented in your risk management logs

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Sponsor oversight according to ICH E6 (R3) "The HOW" (2)

The sponsor must

Determine necessary trial-specific criteria for **classifying protocol deviations** as **important** (i.e., those that **may significantly affect** the rights, safety or well-being of trial participants; and/or **may significantly impact** the completeness, accuracy and/or reliability of the trial data) (3.9.3)

- **Deviation Plans are required defining deviation classification - Terminology now matches ICH E3**
- **Avoid using the term "major" deviations → potential need in change of processes/plans**

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Sponsor oversight according to ICH E6 (R3) "The HOW" (3)

The sponsor must

Have **access to relevant information** (e.g., **SOPs and performance metrics**) for **selection and oversight of service providers** (3.6.8)

- **Ongoing access to service provider SOPs (i.e., all your service providers, not just CROs) means ongoing review of (updated) their processes)**

Ensure appropriate and timely **escalation and follow-up** of issues to allow the implementation of appropriate actions in a timely manner

- **Escalation processes are required (e.g. in project plans)**
- **Clarification of sponsor expectations regarding escalation should be in service provider/investigator contracts/study plans**

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Sponsor oversight according to ICH E6 (R3) "The HOW" (4)

Oversight by the sponsor includes **quality assurance and quality control processes** relating to the trial-related activities of investigators and service providers (3.9.5)

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Quality Assurance and Quality Control

Quality assurance and quality control processes must be implemented in the oversight of investigators and service providers (3.11)

1. 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**. 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 control activities include Data Management and Monitoring. This must also cover service providers (e.g. data reviews, visits (not audits), governance measures, KPI reviews) and Centralised Monitoring** (see 3.11.4.2)

➡ **a Risk Based Monitoring Strategy supports trial oversight**

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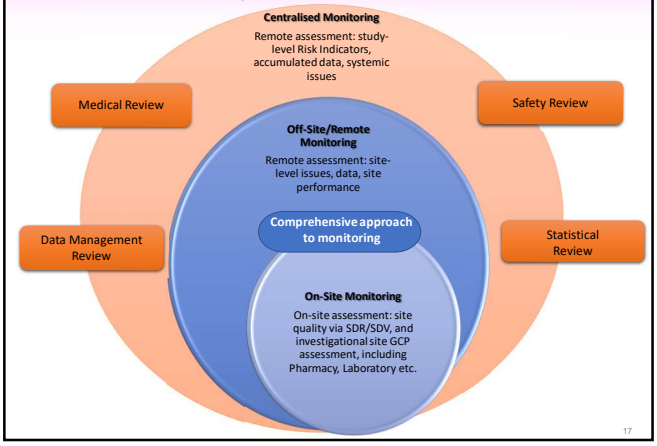
RBM - Monitoring Execution



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Quality Assurance and Quality Control

3.11

2. Quality Assurance (3.11)

- Quality assurance should be **applied throughout the clinical trial**
- QA 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

➡ **QA is not just meant to conduct audits**

➡ **QA requires a strategy how to identify serious non-compliance**

- **Audits should be risk based**

➡ **The "every 3 years" audit approach is no longer appropriate**

- The sponsor's **audit plan, program and procedures** for a trial audit should be guided by level of risks, problems, number of participants in the trial, the type and complexity of the trial

➡ **Audit programme, audit plan and relevant procedures should be trial specific**

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Sponsor oversight according to ICH E6 (R3)

- The sponsor **may consider** establishing an IDMC to assess the progress of a clinical trial, including the safety data and the efficacy endpoints, at intervals and to recommend to the sponsor whether to continue, modify or stop a trial (3.9.7)
- Where appropriate, sponsors **may** also establish an endpoint assessment/adjudication committee in certain trials to review important endpoints reported by investigators to determine whether the endpoints meet protocol-specified criteria (such committees should typically be blinded to the assigned treatments when performing their assessments, regardless of whether the trial itself is conducted in a blinded manner) (3.9.8)

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Sponsor Oversight Summary - MHRA Grey Guide

"The sponsor is responsible that the trial complies with the legislation and GCP.

Trial Management and an effective quality management system provide a means of oversight of all functions, whether undertaken in-house or subcontracted"

https://www.tsoshop.co.uk/product/9780117081079/Medical/MHRA/Good-Clinical-Practice-Guide-Paperback/?TrackID=000039

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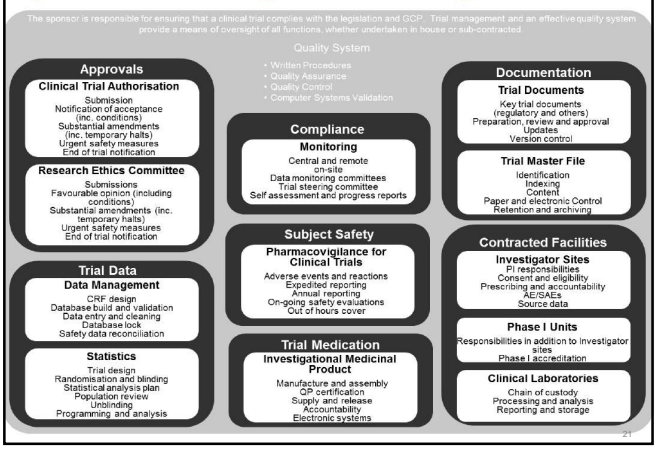
Sponsor Oversight Summary



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What is part of "oversight" in our training?

- Service Provider selection
- Contract Management (set up and review)

- Service Provider oversight
- Quality Management
- Performance and relationship management

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Service Provider Selection

Contract management

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Service Provider Selection

- **Operational Function (Business Owner)**

The business owner must assume responsibility for the prospective service provider relationship management and contractual negotiations

➡ **Define the business requirements**
- What exactly is required from a service provider, what will be done by the sponsor; what are the success criteria

➡ **Identify potential service providers** → relevant sponsor functions to review that service providers have the capabilities/staffing to fulfil the trial requirements

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Service Provider Selection

- **Operational Function (Business Owner)**

The business owner must assume responsibility for the prospective service provider relationship management and contractual negotiations

Initiate requests for information
- Use a RFI template*
- Assessment of expertise and alignment with sponsor and trial needs
  - For example: what is the approach to challenges such as recruitment; access to Key Opinion Leaders; experience in the therapeutic area

Review of service provider processes/SOPs (it is not QA responsibility to assess operational suitability) – see ICH E6 R3 3.6.8 – Sponsor must have access to relevant information (e.g., SOPs and performance metrics) for selection and oversight of service providers
  - For example: does the service provider has their own oversight processes in place regarding subcontractors; what is their risk-based monitoring process, etc.

Discuss how to use/share existing processes and systems

Assessment of service provider criticality and risks

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Example - RFI template

Table of Contents

Table of Contents | Provider Contact Information | KnowledgeExperience Sponsor-CRO | Organization (ORG) | Financial Stability (FNS) | Insurance (INS) | Ethics (ETC) | Privacy (P...

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Example - RFI template - Sample topic

Third Party Management

Please indicate in the Comments if evidence is attached.

		Yes / No	Comments (1200 characters or less)	
TPM1.0	**TPO- ENGAGEMENT DOCUMENTING**			
TPM1.1	Does the business document in writing all activities performed by third parties involved in clinical trials?			0
TPM2.0	**TPO- PREQUALIFICATION AND SELECTION PROCEDURE**			
TPM2.1	Does the business have procedures for the prequalification of external services and materials?			0
TPM2.2	If yes, how does the business document the prequalification of external services and materials?	If Yes, please describe in comment field		0
TPM2.3	Does the business have procedures for the selection of external services and materials?			0
TPM2.4	If yes, how does the business document the selection criteria and decision-makers for the selection of external services and materials?	If Yes, please describe in comment field		0
TPM2.5	Does the business have procedures for purchasing of external services and materials?			0
TPM2.6	Does the business have a maintained approved or preferred supplier list?			0
TPM2.7	If yes, how is this list maintained/checked?	If Yes, please describe in comment field		0
TPM2.8	If yes, how is a qualified supplier removed or retained on the qualified supplier list?	If Yes, please describe in comment field		0
TPM3.0	**TPO- CONTRACTING PROCEDURE**			
TPM3.1	Does the business have documented procedures for the establishment of agreements/contracts for providing clinical services to clients			0

Insurance (INS) | Ethics (ETC) | Privacy (PRV) | Facilities Management (FCM) | Computer Systems (CMS) | Quality Mgt Systems (QMS)

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Service Provider Selection

- **Procurement (or relevant operational function)**
  - Initiate requests for proposals
- **Quality Assurance (based on risk assessment)**
  - Decide on assessment options **based on risk**
    - Due diligence assessment (e.g. website, company background, CVs, phone calls with service providers)
    - Questionnaire
    - Quality survey
    - On-site assessment of compliance with regulatory requirements
  - Review Inspection history if possible (e.g., FDA inspection outcome/ debarment, Health Canada inspection outcome)
- **Legal**
  - Examination of service provider history, financial stability, due diligence, references, adherence to data protection requirements

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Service Provider Selection

→Bid defence process

- Assessment Teams (including Information Security, Data Privacy, Legal, Ethics & Compliance, Quality Assurance, and IT Validation if necessary) evaluate the service provider

→Assessment based on pre-defined success criteria

- Consider using a scoring system* as **evidence of unbiased review**

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Example - Scoring system template

<Name of Technical Service Provider Assessed>		Service Assessed:		Team Member #1 Reported Score <Name>	Team Member #2 Reported Score <Name>	Team Member #3 Reported Score <Name>	Team Member #4 Reported Score <Name>	Team Member #5 Reported Score <Name>	Team Member #6 Reported Score <Name>	Team Member #7 Reported Score <Name>	Team's Summary Score
			Team member active?	Yes	Yes	Yes	Yes	No	No	No	
Scorecard Dimension	Core Standards Explanation	Weight	Comments	Enter Provider Score	Enter Provider Score	Enter Provider Score	Enter Provider Score	Enter Provider Score	Enter Provider Score	Enter Provider Score	Average of Individual Score
Organization		20%		1.5%	0.3%	5.5%	6.5%	0.0%	0.0%	0.0%	5%
Ownership/Chart/ Locations/Employees	Maintains/tracks organizational ownership, chart, business locations and employees by location.	5%		1.0	3.0	18.0	18.0				60%
History	Maintains, tracks and shares history of the organization.	5%		2.0	18.0	1.0	3.0				40%
Financial Stability		5%		2.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1%
Reporting/Solvency/Cash Segregation	Provides 3 years of audited financial reports, financially solvent, is not subject to bankruptcy proceedings, and segregates cash advances funds.	5%		5.0	0.0	0.0	0.0				13%
Insurance		5%		5.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1%
Coverage/Certificates	Has valid insurance policies and will provide certificates and name client company upon request.	5%		18.0							25%
Ethics/ Anti-Bribery/Anti-Corruption (ABAC)		5%		5.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1%
	Business confidence, integrity, impartiality exist and are free from										

Please enter a number from 0 to 10

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Example - Scoring system template

Step 1: Optional 'Weight' column: Adjusting weights is optional. The Weights provided are default and may be edited. If you wish to adjust the weight, change the weight value for each sub-category in the white boxes. **Important**: The total of all category weights should equal 100% at the bottom of the column, which is also calculated automatically.

Step 2: Each team member needs a column to provide a score for each subcategory.

Step 3: To score a service provider on each category, each team member should enter a provider score for each standard or set of standards. To do this, enter a value from 0 to 10, with 10 being the best value indicating the highest level of compliance. The Average of Individual Scores will calculate automatically for each category and sub-category and are shown in the last column;

An associated colour for that score will appear in the box with green indicating higher levels of compliance, yellow are lower levels, and red indicates lowest levels of compliance or non-compliance.

Source: based on the Avoca Quality Consortium Score Card (no link available)

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Service Provider Selection

- Senior leadership oversees governance, compliance, and risk-based decision-making

→**"Approved service provider"**

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Service Provider Selection

→ Note that inspectors expect to see (regarding selection)

- a service provider selection process/SOP
- evidence of selection criteria used for the service provider
- management approval of relevant service provider selection
- a service provider list (general and per study)

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Service Provider Selection (through a CRO)

- CROs often recommend service providers that had been approved/qualified by the CRO
- CROs often manage supplier contracting, performance evaluation, and service provider payments

➡ **It is essential that the sponsor reviews these CRO processes (and documents this review)**

➡ **The sponsor will be expected to confirm approval for the engagement of chosen service providers**

The sponsor always retains full responsibility for all service providers, whether selected by the CRO or not

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Service provider Onboarding

Contracts and Deliverables

- Define the terms of the engagement between Sponsor and Service Provider in detail
- Communicate expectations to all parties involved
- Define the working relationship between Sponsor and service provider
- Reduce the potential for misunderstandings and conflicts
  - Define accountability
  - Define deliverables (time, budget, quality)
- Provide a framework for resolving any disputes

→Aims to ensure that expectations are met and protection of Sponsor interests

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Contracts – should contain at least (1)

- Clear identification of the study or studies to which the contract applies
- Services and Deliverables description
  - Study-level tasks including Study team/Governance meetings, Risk Management, communication plan etc.
  - Budget and Payment Schedules
- Timeframes for mutual provision of information (or may otherwise be agreed in other defined documents e.g. study plans)
- Applicable laws, regulatory standards, SOPs, etc.
- Access arrangements for SOPs
- Service provider training requirements (e.g. GxP; therapeutic indication; study documents)
- Statements regarding precedence between contracts and the trial protocol, i.e. that compliance with the protocol and regulations supersedes the contract and any internal procedures or vice versa as applicable
- Subcontracting clause, i.e., how the sponsor maintains oversight of any service providers subcontracted by the CRO/ service provider

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Contracts – should contain at least (2)

- If electronic systems are used for handling trial data, contracts should state that these must be validated and that records are available for audit and inspection
- Trial Master File details (if managed by service provider)/or detailed TMF plan*
- Records Management/Archiving arrangements/Transfer to sponsor
- Clearly delineated roles and responsibilities
- Granting regulatory bodies and sponsor QA function to inspect/audit
- Notification of quality issues to the sponsor, incl. non-compliance, deviations, potential serious breaches
- Portfolio/Project Performance Metrics (KPIs and KQIs), and Quality/Technical Agreements as necessary

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Contracts (3)

- **Detailed project specific contractual stipulations may also include:**

- **Project Level Governance specification**
- Governance aims to ensure oversight of project milestones, performance management, issue escalations, risk mitigations, budget tracking, and invoicing
  - Governance may involve Steering Committee meetings and regular Commercial and Operational Management Team reviews
- **Quality Alignment clarification**
  - Quality alignment may be maintained through a service provider risk oversight committee that is monitoring supplier risks, Portfolio level Quality Standards, and management of Corrective Action Requests
  - Service provider Project Plans define communication strategies, issue escalations, key milestones, deliverables, and risk-mitigations for effective project management

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Contracts - TMF details

- Structure and indexing of the TMF;
- Access arrangements for all involved parties;
- eTMF - details of the system and change control management;
- Lists of applicable procedures to be followed and training requirements;
- Type of documents that each party should retain;
- Arrangements for managing correspondence;
- How the TMF would be made available to the competent authorities and auditors;
- Arrangements for Quality Control reviews by the service provider;
- Arrangements for oversight of the TMF performed by the sponsor
- Arrangements for when the trial is completed;
- Document/TMF retention times;
- Access to TMF after archiving;
- Procedures in case of an involved party closing down its business.

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Contract reviews

- **Ensure contract review timelines are clarified and reviews are indeed conducted and documented**
  - Amendments/modifications of the protocol occur
  - Regulations may change
  - Responsibilities may change
  - Nature of partnership may change

If service providers subcontract contracted tasks to other service providers, these **subcontracted service providers must be bound to the same**

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Top mistakes in service provider selection (1)

1. **Inadequate Requirement Analysis**
   - Failing to clearly define and document the requirements and expectations before starting the selection process can lead to choosing a provider that does not meet the actual needs
2. **Ignoring Provider Experience and Expertise**
   - Overlooking the importance of the provider's experience and expertise can result in poor service quality. It's crucial to assess their track record
3. **Overemphasis on Cost**
   - While cost is an important factor, making a decision based solely on the lowest bid can lead to subpar services. The focus should be on value for money rather than just cost

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Top mistakes in service provider selection (2)

4. **Lack of Due Diligence**
   - Not conducting thorough due diligence, including background checks, financial stability assessment, and client references, can lead to selecting an unreliable provider
5. **Ignoring Cultural Fit**
   - Overlooking the cultural fit between organisations can create friction. It's important that the provider's work culture, values, and communication style align with those of the sponsor
6. **Poor Contract Management**
   - Neglecting to clearly outline the terms and conditions, service level agreements, and performance metrics in the contract can lead to misunderstandings and disputes

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Top mistakes in service provider selection (3)

7. Insufficient Evaluation of Technical Capabilities

- Not properly evaluating the technical capabilities and resources of the provider can result in inadequate performance

8. Neglecting Post-Selection Support

- Failing to consider the provider's reliable support and plans for continuous improvement can lead to issues in ongoing operations

9. Ignoring References and Reviews

- Not checking references or ignoring feedback can provide a misleading picture of the provider's capabilities and reliability

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Top mistakes in service provider selection (4)

10. Failure to Plan for Transition and Integration

- Overlooking the complexity of transitioning and integrating the service provider's operations with existing processes can cause disruptions

11. Inadequate Communication and Collaboration

- Not establishing clear communication channels and collaboration frameworks can lead to misunderstandings and project delays as effective communication is key to a successful partnership

12. Underestimating the Importance of Security and Compliance

- Not thoroughly evaluating the provider's security measures and compliance with relevant regulations can lead to vulnerabilities

13. Not being familiar with providers processes

- Not assessing provider's processes (SOPs etc) can lead to gaps in integration, not documenting the assessment will become a regulatory inspection risk

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Challenges in service provider oversight

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Challenges Overseeing CROs: Sponsor (1)

- Avoiding excessive oversight and micromanagement while ensuring quality and meeting timelines
- Lack of clarity of staff roles, leading to duplication of effort
- Distrust of CROs, difficulty empowering CROs to make decisions
- High turnover at CRO
- Lack of desire or budget to train staff on tactics to oversee CRO
- Lack of standardization of oversight processes and procedures
  - Varies by CRO: variations in SOPs/internal processes.

Challenges Overseeing CROs: Sponsor (2)

- Budget management: balance of cost and quality
- Communication and Transparency
  - Within sponsor/ between CRO functions
  - Ensuring that CROs provide sufficient updates and information on study progress, timelines, risks and issues to sponsor
  - Appropriate communication between the strategic partner and sponsor regarding realized risks, deviations and response to issues
  - Lack of face-to-face communication

Challenges Overseeing CROs: Sponsor (3)

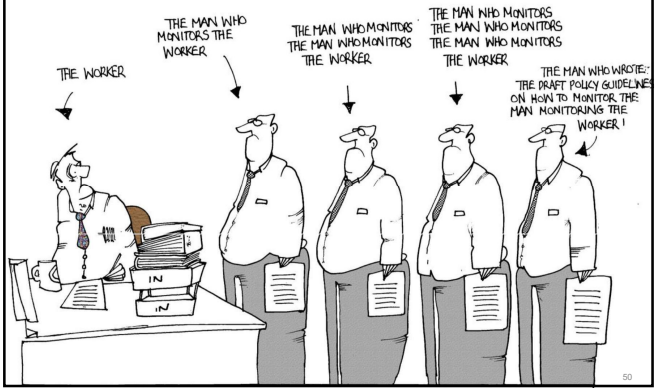
- Failure to make use of lessons learned
- Need for proactivity
  - CROs taking ownership of activities, thinking critically, and proactively taking initiative to identify/mitigate risks
- Quality issues- CROs prioritize time over of quality
- Lack of effective use of metrics for strategic oversight
  - Transparency and visibility into performance data across all CROs

Challenges Overseeing CROs: Sponsor (4)

- Setting of expectations- Understanding of milestones and deliverables
- Insufficient resources- Insufficient sponsor staff to appropriately manage CRO
- Management of multiple functional service providers
- Technology and reporting
  - Quality systems needed on both sides of relationship
  - Incompatibility of systems; lack of access to each others systems
  - Systems not user friendly

Challenges in overseeing service providers?

Are sponsors using resources efficiently?



Challenges in CRO Oversight: CRO (1)

- Micromanagement by sponsor; inefficient use of resources; Duplication of effort; Sponsors do not listen to or trust project team staff; Sponsor's failure to delegate ownership of decisions to CRO
- Communication, internal and between sponsor and CRO
  - Irregular communication flow; Poor responsiveness by sponsor
  - Miscommunication when sponsor communicates directly with site staff
  - Lack of feedback from sponsor on initial deliverables provided

Challenges in CRO Oversight: CRO (2)

- Inadequate escalation pathway, involvement of senior CRO management
- Setting common expectations; agreement on resources; lack of clarity
- Inconsistent level of oversight: Some sponsors micromanage; others are hands-off
- Committing to unrealistic deliverables under short timelines
- Sponsor representatives make conflicting decisions; provide inconsistent feedback; changes to agreed upon decisions
- Sponsor does not allow time and budget to allow for training on quality

Other challenges in overseeing service providers

The Challenge:

● Project Pressures ● Quality vs. "please the street with speed" ● CRO attempts clarification with questions – slows things down ● "You should know this already" ● Unclear expectations ● Unclear assumptions lead to shaky foundation ● No transparency ● Poor performance ● Lack of prioritisation ● Lack of knowledge (e.g. subcontractors)

● Service provider contracts with "subcontractors" may be for multiple sponsors, thus not willing to share ● Sponsor approval requests slow things down ● Sponsor micromanagement ● "we can't change our SOPs for each sponsor" ● "our SOPs are confidential"

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Other challenges in overseeing service providers

- Oversight practices vary by:
  - Experience and skill set of project manager
  - Capabilities of individuals at both the sponsor and CRO
  - Phase of projects
- Other issues
  - Performance variations
  - Availability of systems to provide transparency into performance data

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Inspection observations regarding oversight

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…recurrent inspection observations…

MHRA GCP INSPECTION METRICS REPORT issued 12Feb2021: "critical and major findings are still due to lack of documented evidences demonstrating sponsor oversight"

- Trial-related **duties and function were not defined, established, and allocated** before trial initiation
- **Sponsor did not ensure that personnel responsible for the execution of trial related duties were qualified by education, training, and experience** to assume responsibility for the proper conduct of the study
- **Sponsor did not ensure personnel was thoroughly familiar with the appropriate use of the investigational product** as described in the study protocol
- **Sponsor did not ensure personnel was aware of and remained in compliance with GCP and applicable regulatory requirements**

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Other common and related Inspection Observations

- **Lack of information and documentation in contracts and agreements with service providers**
  - Not clear in agreements that compliance with the protocol and regulations is required which would supersede any internal processes and procedures
  - Subcontracting is not mentioned in the contract and how the sponsor maintains oversight of any further subcontracting performed
  - Sponsor has not agreed to the use of subcontractors
  - Delegation of duties is not clearly documented
  - Key legislative requirements are missing from contracts such as reporting of urgent safety measures and serious breaches

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Some sample findings

- **Review of the sponsor trial master file for a selected trial demonstrated insufficient oversight of the conduct of the overall trial**
  - There was insufficient documentation present within the sponsor trial master file to demonstrate appropriate oversight
  - There was a lack of oversight of SUSAR reporting by the CTU management. Trackers used to log SAEs in this trial were incomplete therefore it was not possible to have oversight of reporting timelines
  - Sponsor research governance staff had at least two opportunities to identify significant issues existed with this trial yet failed to take appropriate action including the notification of a serious breach

Source: GCP_inspection_metrics_2019-2020.pdf

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Some sample findings

- The Trial Master Files (TMF) was found to impede the inspection with the inspection having to be performed primarily with document requests. This was a major finding at the previous inspection of this organisation and was therefore escalated to a critical finding. **There was insufficient documentation present within the sponsor trial master file to demonstrate appropriate oversight**
  - The TMFs were incomplete or inaccurate, which resulted in an inability to reconstruct the trial or procedural conduct to enable the verification of GCP compliance.
  - Several documents being filed outside the core electronic TMF (eTMF). Whilst the TMF master list did state that these were filed across various locations, it did not index exact locations and direct access could not be provided to inspectors.
  - "Data" files were classified as non-essential and filed outside the eTMF, including SAE data listings. Such data files, however, were essential for demonstrating key safety processes and **sponsor oversight** and thus should have been held in the eTMF.

Microsoft Word - GCP inspection metrics 2018-2019 (12-02-21)

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Some sample findings – my favourite….

- There was no clear audit programme in place or periodic review of the eTMF system audit trial to demonstrate oversight and quality assurance of completeness and accuracy of the TMF systems in place

Microsoft Word - GCP inspection metrics 2018-2019 (12-02-21)

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Potential Inspection risks

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Potential inspection risks

Contract Management

- Do you know the content of the relevant contracts?
- Are duties (responsibilities/accountabilities) clearly defined to identify clear expectations, efficiencies and synergies between sponsor and service provider? E.g., use of task ownership matrix, RACI matrix
- When have you last read relevant contracts – how often are they reviewed against compliance and regulatory changes?
- Do you know gaps in content of contracts (for example process for document management as required by EMA TMF guidance; computer system validation, Serious Breach management)?

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Potential inspection risks

Service provider selection (1)

- Have you got awareness of subcontractors? Did you approve use of subcontracting?
- Is there evidence of documented review of service provider SOPs (to assess suitability of service provider processes and gap analysis)?
- Do you have access to service provider SOPs including an agreement how to access updates to SOPs?

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Potential inspection risks
Service provider selection (2)

- Do you have documentation available to show evidence of Service provider Selection activities:
  - Rationale for selection (e.g., set of skills, services, previous performance)
  - Evidence of assessment performed (from both a compliance (audit) and operational perspective)
  - Results of the assessments performed
  - Have you filed relevant records in the TMF?

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Potential inspection risks
Training

- Do you have evidence of study specific training for all relevant team members (including the service providers), e.g., for protocol, IB etc. ?
- Are (study specific) service provider training records accessible to you?
- Does the service provider have evidence of regulatory training for the study teams (e.g., EU directive/ regulation/ country requirements/GXP) ?
- Is there availability of up-to-date CVs to check competencies?
- Can you access documentation of team handovers?

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Potential inspection risks
Computer System Validation

- Do you know the computer systems used for each study (including service provider systems used for your trial)?
- Can you explain how computer system validation review is conducted for each system used and do you have the evidence?
- Are all computer system records in the TMF?

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Potential inspection risks
TMF

- Sponsor Oversight Files – defined content per function (what goes in the oversight files?)
- TMF index (are you aware what's in the TMF, do you have access)
- Does TMF index contain "signpost" to all outside storage location – do you know these locations?
- Evidence of consistently documented QC of the TMF (& Process for this)

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Potential risks
Study Management

- Documented evidence of internal document review
- Co-monitoring process
- Monitoring report review process and evidence thereof
- Reporting the outcomes of any centralized monitoring review of clinical data or justification for not conducting centralized monitoring
- Medical Monitor CRO interaction
- Serious Breach/urgent safety measure management
- Escalation procedures
- Knowledge and access to service provider SOPs

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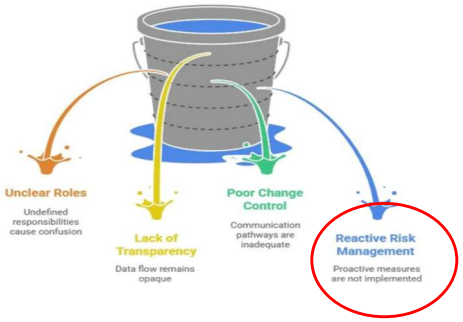
Inadequate Service provider oversight



Source: LinkedIn: Dr Karin Koehler-Hansner

Risk Management ….

Identify your study's most important data and critical to quality success factors to get to the right level of oversight for your staff, your service providers and sub-contractors

ICH E6 R3 Section 3.10

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Risk Management Steps

1. Critical Process/System and Data Identification
2. Risk Identification – **During protocol development**
3. Risk Evaluation
4. Risk Control – **predefined thresholds for quality**
5. Risk Communication
6. Risk Review
7. Risk Reporting – **report deviations from the predefined thresholds**

Based on ICH E6 R3 Section 3.10

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1. Critical Process/System and Data Identification

- **During protocol development**, the sponsor should
  - identify processes/systems and data that are critical

to assure **human subject protection and the reliability of study results (Critical to Quality Factors)**

3.10.1.1

→ **Highlighting the need for assessing processes/systems as well as data and determine if they are critical**

→ **Defining, rationalizing and documenting those critical processes/systems and data (Critical to Quality Factors)**

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Critical data and processes

Critical Data	Critical Processes/Systems
What are the data which are critical to program and/or protocol success? **What Critical Data must be collected in order to satisfy the objectives?**	**What are the Critical Processes that must be done correctly to ensure subject safety, data quality, and GCP/regulatory compliance?** **Are there any Critical Processes and Systems in the program and/or protocol which are vulnerable to error?**

Data that support primary & key secondary objectives
• Rationale: why is it critical?
  • Endpoint - primary or secondary
  • Safety - SAEs, events leading to discontinuation of treatment
  • Other (specify)
	Processes that underpin safety or quality
	• Rationale: why is it critical?
	  • Safety/ethical treatment - seeking appropriate medical consultation, investigating clinically significant findings
	  • Data quality – blinding, event adjudication, controlling inter-rater variability
	  • Compliance – GCP, local regulations, protocol

Example: 1) AEs/SAEs 2) Laboratory results	Example: 1) Collection and reporting of AEs/SAEs 2) Collection, storage, shipment of labs

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Critical to quality factors ?

If their integrity were to be undermined by errors of study design, data sources or conduct, the reliability or ethics of decision-making would also be undermined

Fundamental to
- protection of study participants,
- reliability and interpretability of study results,
- decisions based on study results

Should be considered holistically so that dependencies among them can be identified

Successful application may minimize the need for modifications of the protocol and make adherence throughout the study more likely

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ICH E8(R1) Guideline

ANNEX 3: SELECTED EXAMPLES OF CRITICAL TO QUALITY FACTORS

Selected Examples of Critical to Quality Factors	E1	E2A-E2F	E3	E4	E5	E6	E7	E8	E9	E10	E11	E12	E14	E15	E16	E17	E18
Protocol Design																	
Eligibility Criteria						√	√	√	√		√	√	√	√		√	
Randomisation				√		√		√	√	√		√	√			√	
Blinding/Masking						√		√	√	√							
Types of Controls	√			√				√		√			√			√	
Data Quality	√						√	√	√					√			
Endpoints				√	√			√	√	√	√	√				√	
Procedures Supporting Study Endpoints and Data Integrity					√	√		√	√	√	√	√				√	
Investigational Product (IP) Handling and Administration						√							√				
Feasibility																	
Study and Site Feasibility																√	√
Accrual									√		√		√				
Patient Safety																	
Informed Consent						√					√						√
Withdrawal Criteria and Trial Participant Retention			√			√					√		√				

Note: This Annex was available in the DRAFT version of ICH E8 (R1), not in its final version

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ICH E8(R1) Guideline

Selected Examples of Critical to Quality Factors	E1	E2A-E2F	E3	E4	E5	E6	E7	E8	E9	E10	E11	E12	E14	E15	E16	E17	E18
Signal Detection and Safety Reporting		√ (B)	√			√						√	√				
Data Monitoring Committee (DMC)/Stopping Rules						√			√	√			√				
Study Conduct																	
Training						√							√			√	√
Data Recording and Reporting		√ (B,C,F)	√	√					√		√		√		√	√	√
Data Monitoring and Management		√ (A,B,D)	√						√						√	√	√
Statistical Analysis			√	√	√				√				√			√	
Study Reporting																	
Dissemination of Study Results		√ (D,F)															√
Third-Party Engagement																	
Delegation of Sponsor Responsibilities						√											
Collaborations						√											

Note: This Annex was available in the DRAFT version of ICH E8 (R1), not in its final version

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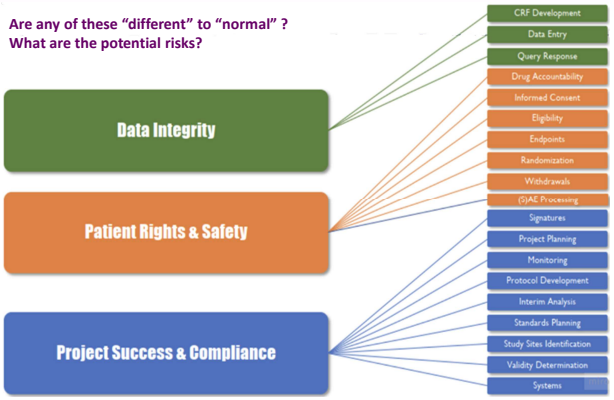
Other Examples - Critical to Quality Factors

Are any of these "different" to "normal" ?
What are the potential risks?



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2. Risk Identification (ICH E6 R3)

- The sponsor should **identify risks** that may **have a meaningful impact on critical to quality factors** (3.10.1.2)
- Risks should be considered across the processes/systems used in the clinical trial, including computerised systems (e.g., trial design, participant selection, informed consent process, randomisation, blinding, investigational product administration, data handling and **service provider activities**)
  - → **Clarifying the need for assessing processes as well as data**
  - → **Highlighting the need to define ""Prespecified Acceptable Ranges"**

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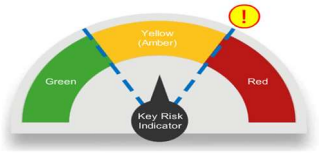
Setting "Prespecified Acceptable Ranges" e.g. quality tolerance limits at the trial level

Risk Indicator	Threshold
Risk indicators are metrics used to monitor identified risk exposures over time	A pre-determined level, point, or value (e.g., number, %, range) associated with a Risk Indicator that indicates the need for a follow-up action



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Quality Tolerance Limits

3.10.1.3: **pre-specified acceptable ranges (e.g., quality tolerance limits at the trial level) to support the control of risks to critical to quality factors**.
These pre-specified ranges reflect limits that when exceeded have the potential to impact participant safety or the reliability of trial results.
Where deviation beyond these ranges is detected, an evaluation should be performed to determine if there is a possible systemic issue and if action is needed.

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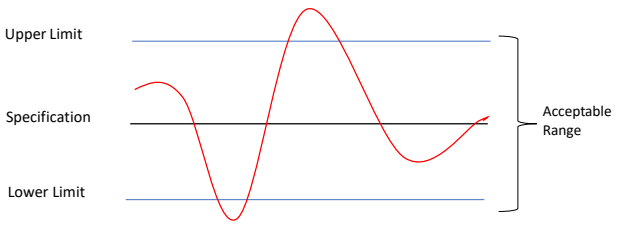
What are QTLs?

- QTLs have historically been required for Good Manufacturing Practice (GMP) activities
- Are inferring limits by which significant actions must be taken to ensure the manufactured product achieves quality and usability limits



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Acceptable ranges (Quality Tolerance Limits)

QTLs are your tripwires – planted so you can act

They are real thresholds based on data…
Someone **actively** monitoring them, not just filing them
If your QTLs don't drive timely action, they are failing their purpose.

QTLs should be living tools, not buried metrics.

Are your QTLs stored away and forgotten?
Or are they part of your weekly dashboards – flashing alerts if the line is crossed?

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Acceptable ranges (Quality Tolerance Limits)

- **The Risk Management Plan and related activities as part of the Sponsor Oversight** should include strategies for monitoring these parameters, determining the root cause, and addressing any deviations
- **QTLs and justification of changes must be documented in the CSR**

→ **Sponsor Oversight includes risk management**

Suggested reading: Risk-Based Quality Management - TransCelerate

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Risk Management Steps

1. Critical Process/System and Data Identification
2. Risk Identification – **During protocol development**

Followed by

3. Risk Evaluation
4. Risk Control – **predefined thresholds for quality**
5. Risk Communication
6. Risk Review
7. Risk Reporting – **report deviations from the predefined thresholds**

Based on ICH E6 R3 Section 3.10

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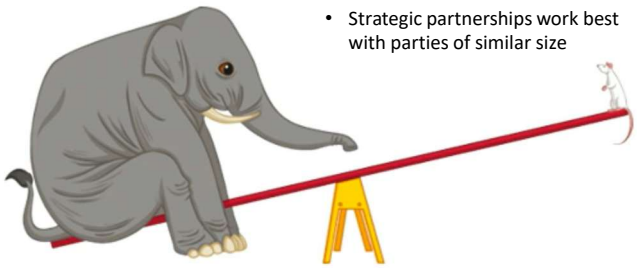
Guiding principles for oversight processes

Guiding principles for oversight processes (1)

- Strategic partnerships work best with parties of similar size



Your ability to influence a service provider is proportional to your importance to the service provider

A collective business model only works if each organisation plans for the other organisation to be successful

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Guiding principles for oversight processes (2)

- Transparent communication with service providers and responsiveness → better alignment, knowledge of expectations
- Improved project plans/communication plans
- A clearly established and documented expectation for quality (e.g., by using "Quality Agreements" and/or clear details in contracts)
  - Containing a precise definition of accountability and responsibility

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Guiding principles for oversight processes (3)

- Comprehensive documentation of the oversight planned and conducted
- Sponsor approval of documents and processes implemented to carry out the delegated functions
- Sponsor awareness of service provider processes

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Guiding principles for oversight processes (4)

- Setting and evaluating metrics and/or key quality indicators (KQIs) and/or key performance indicators (KPIs) and Key Risk Indicators (KRIs)
- Monitoring and measuring trends
- Using “indicators” to determine risk based actions

- Sufficient processes to verify that activities are being conducted appropriately, e.g., monitoring oversight visits, audits

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Guiding principles for oversight processes (5)

- Ongoing identification of deviations, risks and systematic quality issues and appropriate escalation
- Implementation of root cause analysis and CAPAs
- Reviewing and updating of Corrective and Preventive Action (CAPA) Plans
- Checking effectiveness of CAPAs

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Guiding principles for oversight processes (6)

- Transparency of risks identified
- Collaborative addressing of risks
- Frequent and detailed feedback at the beginning of the service provider collaboration and throughout
- Reviewing quality related continuous improvement initiatives
- Implementing consistent "lessons learnt" sessions and sharing of such with service providers
- Ongoing (mutual) training

A risk based concept must be applied throughout the trial

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Oversight tools

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Tools (1)

Ensure appropriate documentation is in place

For example:
- **SOPs/Policies**
- **Service Provider lists**
- **Executive Committee + Charter**
- **Operations Management Committee/Governance + Charter**
- **Business Management Committee + Charter**
- **Quality Agreements**
- **Service Provider Training Plans/Training Matrix**
- **Service Provider Oversight Plans**
- **Risk Management Plans**
- **Evidence of adherence to relevant plans**

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Tools (2)

Develop a communication plan

Containing for example:
- **Clearly articulated Roles (not job titles), Responsibilities and Accountabilities within and between Sponsor and service provider**
- **Methods of information sharing and decision making**
  - **What, When, From whom, To whom, Channels**
- **Activity reviews/timing/detail of reviews**
- **Issue resolution**
- **Escalation steps**
- **CAPA management**
- **Key quality/performance indicators and risk indicators**
- **Metrics/Metrics Dashboard**
- **Evidence of adherence to relevant plan(s)**

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Metrics

Some examples of potential metrics/measures may include the following:

- Predetermined trigger dates or timing and metrics for when a risk should be escalated for decision, for example:
  - Any new, undocumented risk that is uncovered should be documented (and tracked) within 3 business days
  - Any risk that has is considered "high" should be escalated to the next level within 5 business days
  - The risk log will be prepared within 20 business days of new project kick-off meeting
- Cycle time for Issue escalation and resolution
- Number of issues escalated and resolved
- Feedback via survey ratings by both parties for example on
  - Speed and quality of decision making
  - Quality of communication
  - Quality of relationship
  - Overall success of collaboration

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Metrics

Metrics are a management tool
It's not enough just to measure…..

- Which are the "high impact" risks?
- When do risks become issues (tipping point)?
- To which issues should mitigation resources be allocated?
- What are the "trigger levels"?

- Ongoing evaluation of program lessons learned
- Assessment and action plans for recurring risks and issues - Leading practice, effective mitigations
- Ensure assessment by all development teams to allow overall process related enhancements

Knowledge Management:
- Retain and manage knowledge regarding prior programs
  - **risk drivers, risk events, emergent issues, realised risks, consequences**
  - leading practice mitigations and solutions

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Tools (3)

Ensure appropriate training is in place

Covering at least:
- **Relevant SOPs/Policies**
- **Project Plans incl. Risk Management Plans**
- **Regulatory requirements and updates/GCP/regulatory intelligence**

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Tools (4)

Ensure Quality Assurance Plan(s) is in place

- **Discuss service provider risks with QA**
- **Consider service provider audits**
- **Collaborating with QA regarding CAPAs and CAPA effectiveness**
- **Support QA to establish Key Risk Indicators to determine risk based audits**

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Potential Key Risk Indicators (KRI) for service provider management

- Due Diligence Assessment conducted during service provider selection process
- Qualification status (e.g. "fully qualified")
- New service provider and/or new services provided
- Major change in service provider organisation/ QMS/ Processes
- High volume of outsourced activities
- Computerized system or processes used falls under GxP
- Regulatory changes occurred impacting the service of the service provider
- Could service provider performance have an impact on patient safety/rights/ reliability of trial result
- Could service provider SOPs be assessed against sponsor needs
- Service provider uses third parties as part of their services
- Did quality issues occur
- Were quality issues resolved/time for resolution
- Audit history (Last audit/ type + number of findings)
- (Internal) intelligence gathering

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Tools (5)

- Ensure teleconferences, meetings or other appropriate communication with the Service Provider are organised to monitor the progress of the project and address any potential issues as they arise – define nature and frequency of relevant communication
  - Generate and retain meeting minutes as applicable
- Conduct ongoing documented contract reviews to ensure regulatory updates are covered

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Tools (6)

- Review and assess records and results related to the outsourced activities (using a risk-based approach)
- Ensure the services provided are in compliance with the relevant regulations (including SOPs/Plans/Records)
  - Input of a QA or other specialist may be employed as needed
- Ensure service provider training is conducted, review evidence
- Perform documented review of relevant metrics
- Monitor the output of the Quality Agreement

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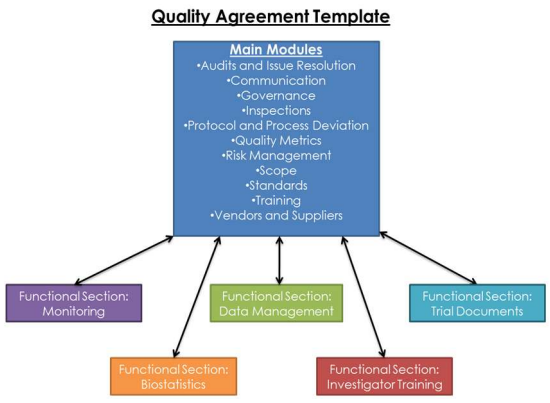
Potential components of a "Quality Agreement"



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Potential components of a "Quality Agreement" (1)

- Scope
- Applicable standards/regulations
- Responsibilities of each party (including subcontractors) (RACI Matrix – responsible, accountable, consulted, informed)
- Handover processes if applicable
- Communication (e.g., meetings, calls – frequency, minutes)
- Agreed timelines for any notifications (e.g., of noncompliance issues)
- Risk Management
- Quality Control

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Potential components of a "Quality Agreement" (2)

- Quality Control
- Protocol/Process Deviations
- Quality Metrics
- Selection/Training of personnel
- Issue Escalation
- Issue Resolution/Process Improvement
- Audits/Inspections
- Performance/Control of Trial Activities
- Governance/Process Improvements/Lessons Learnt
- Document filing/transfer and archiving responsibilities

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Advantages of "Quality Agreements"

- Mechanism to ensure that "best practices" are being adhered to in the conduct of clinical trials
- Cover the "how to implement" clinical trial regulations
- Support Master Service Agreements and Workorders that do not always cover "Quality" elements adequately
- Provide a mechanism to share major and critical audit/inspection findings thus providing information on compliance
- Provide a structure for audit management (e.g.. notification timelines, scope, duration, frequency of audits)

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Challenges for "Quality Agreements"

- Commonly used for GMP operations involving Contract Manufacturing Operations, not required by regulations for GCP
- Regulatory language governing service provider participation in clinical trials is (currently) limited
- Quality Agreements are often modelled after GMP regulation/guidelines and may have significant legal input and tone to them that service providers may resist
- A quality agreement could take a long time to negotiate

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Examples how to demonstrate oversight (1)

- General:
  - Verification that 3rd parties have effective quality systems and governance before engaging them
  - Document rational for selection and decision to select a service provider
  - Contracts to clearly detail all delegated tasks/responsibility matrix
  - Quality expectations explicit in contract or in a stand-alone Quality Agreement – setting standards/boundaries
  - Specified details of planned oversight in contracts with service providers

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Examples how to demonstrate oversight (2)

- General:
  - Formulised handover procedures when activities/responsibilities change hands/change control
  - Plans and reviews of service provider performance/KPIs/metrics
  - Agreement on actions when something goes wrong/escalation procedures
  - Changes in duties appropriately captured in writing
  - Audits (including assessments of service provider QMS and quality control measures)
  - Spot checks (process and documents)
  - Meeting minutes with concerned parties (TC/on-site)

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Examples how to demonstrate oversight (3)

- Clinical operations:
  - Review of monitoring reports
  - Review and approve contracted monitors (documented review of CVs)
  - Co-monitoring visits to assess the conduct of the trial
  - Review/QC of TMFs
  - Review of progress reports
  - Central review of clinical trial data, review of emerging safety data, documents and reports
  - Feedback from questionnaires sent to investigators
  - Regular review meetings with meeting minutes (e.g. sponsor with Contract Research Organisation (CRO)/Chief Investigator)

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Examples how to demonstrate oversight (4)

- Clinical operations:
  - Formal approval of (at least):
    - Study plans for statistical analysis, on-site monitoring, data management, TMF, safety management, communication, etc.
    - Study protocol and final report
    - Review of site regulatory green light IMP forms
    - Documented review for risk management plans and upfront definitions of major protocol deviations
  - Documented participation in study decision-making
  - Documented provision of medical supervision
  - Ongoing review of protocol violations, serious/adverse events and risk registers
  - Centralised monitoring of data
  - Written communication plans and other documents/ plans that define planned service provider/sponsor interactions
  - Sharing issues between functions

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What now ? – Development of the oversight process

Summary

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What now? - Development of the oversight process

Level 1 Initial Oversight
- Few or no policies, standards, process or tools available to provide direction on oversight requirements.
- Oversight informally implemented.
- Inadequate documentation of oversight activities and no internal compliance checks on the process.
- Inconsistent oversight of processes used by third parties.

Level 2 Enabled Oversight
- Oversight policy needs are recognized and prioritized.
- Process owners are assigned to develop oversight standards, processes and tools.
- Informal oversight planning underway.
- Informal approaches for documentation of oversight.
- Initial oversight process checks commence.
- Alignment on business needs for oversight of third party processes as applied to projects.

Level 3 Consistent Oversight
- Clear oversight policies, guidelines, standards, and tools developed.
- Processes documented and trained.
- Formal and consistent oversight plans implemented.
- Oversight documentation requirements understood, with audit trails deployed for regulated projects.
- Introduction of structured management monitoring to drive consistency of practice.
- Documentation of third party SOPs used.

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What now? - Development of the oversight process

Level 4 Predictable Oversight
- Oversight tools/ tool kits err effectively implemented.
- Process improvement and simplification drives efficiency and lowers resource requirements.
- Oversight practices and documentation are capable of withstanding auditor reviews.
- Integrated process leadership teams oversee process performance.
- Synergistic joint process development with service providers.

Level 5 Innovative Oversight
- Process is oversight streamlined and efficient.
- Advanced process approaches (e.g. QbD) jointly implemented with service providers and providing strategic value.
- Reduced regulatory or other audit findings around the oversight process and tools.
- Documentation and tracking of third party SOPs used.

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Final thoughts

Service Provide Oversight does not stop with the initial qualification

Sponsor Oversight is for the long-term!

- The Sponsor **maintains overall responsibility** for the conduct and reporting of the trial and so there should be mechanisms in place to demonstrate oversight of activities contracted/ delegated to ensure patient safety and data integrity
- **This responsibility can not be delegated**

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References

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https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice/qa-good-clinical-practice-gcp
Refer to Section 17 (publication DEC2022)

MHRA

https://www.gov.uk/government/publications/oversight-and-monitoring-of-investigational-medical-product-trials/oversight-and-monitoring-activities

Oversight and monitoring activities - GOV.UK (www.gov.uk)

Sponsor Oversight- Part 1 – MHRA Inspectorate (blog.gov.uk)

Sponsor Oversight- Part 2 – MHRA Inspectorate (blog.gov.uk)

Interesting publications

- Current practice and perspectives in CRO oversight based on a survey performed among members of the German Association of Research-Based Pharmaceutical Companies (vfa) - PMC (nih.gov)
- Recognizing and Addressing Inefficiencies in Vendor Qualification – One Step at a Time - Avoca, a WCG company (theavocagroup.com)
- 2019-Avoca-Industry-Report_Quality-Oversight.pdf (theavocagroup.com)
- https://www.theavocagroup.com/?s=Sponsor+Oversight

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