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Health Products Regulatory Authority

Sponsoring a Clinical Trial

Considerations for quality systems, risk management & monitoring

Sinead Curran, GCP/PV inspection manager

HPRA Information Day – GCP for IMP clinical trials

Dublin, 23 October 2018

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- Overview of responsibilities/obligations
- Sponsor infrastructure considerations
- Key sponsor tasks per stage of trial conduct
- Common and/or significant issues, as observed from inspections
- Regulatory supports

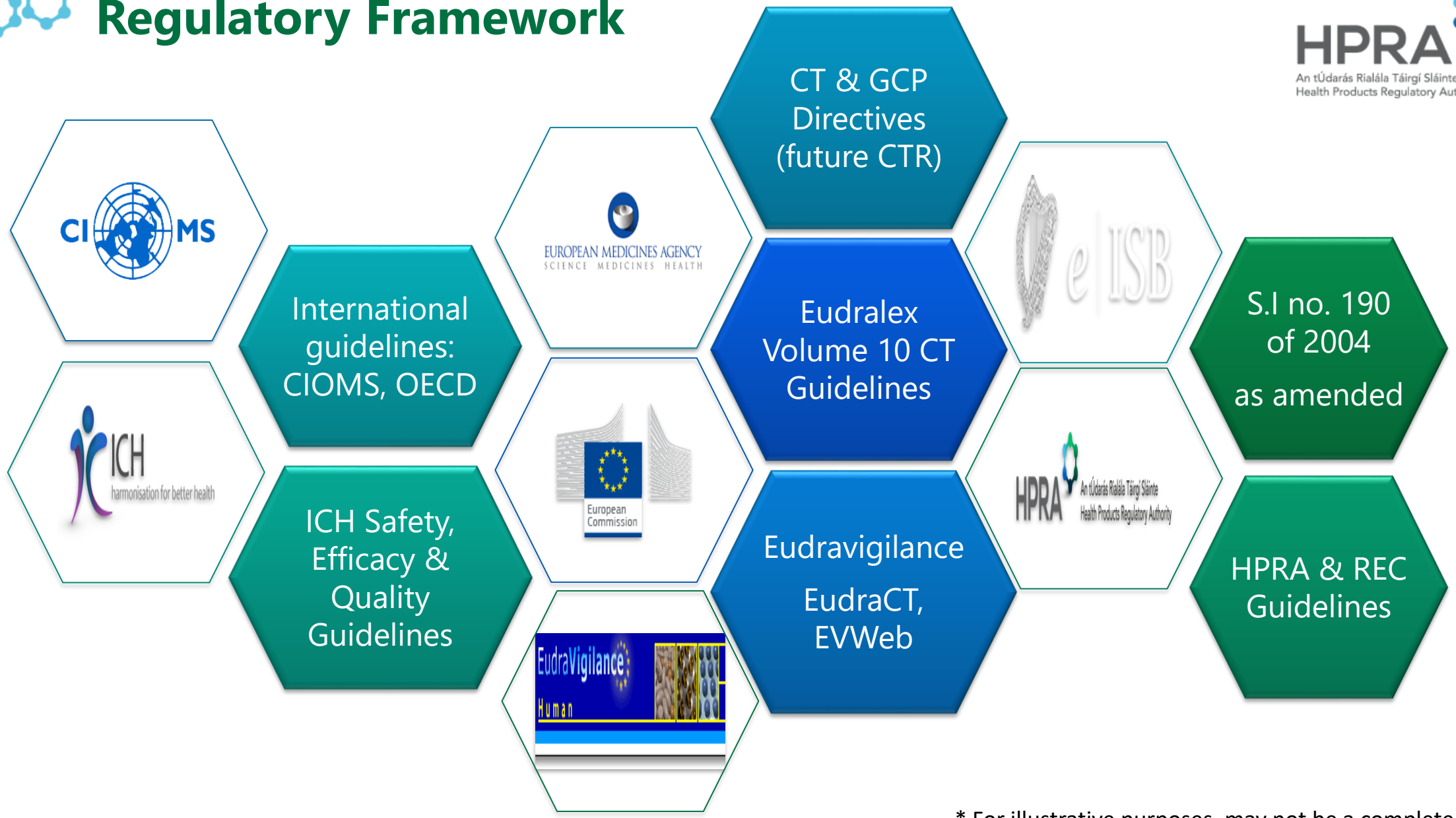
What does trial sponsorship involve?

- **Role of *'sponsor'* is defined in national legislation** as *'the person who takes on responsibility for the initiation and management (or for arranging the initiation and management) of, and the financing (or arranging the financing) for that clinical trial*
- Sponsor assumes **primary responsibility** for the conduct of a trial
- Encompasses, not only performing sponsor tasks in a compliant way, but also **governance of third parties** to whom sponsor tasks may have been transferred, and **oversight of investigator sites**
- A **robust infrastructure**, with well defined systems and processes, is essential to ensure compliance with regulations,
- Fit-for-purpose to generate **reliable information** to answer key questions and support decision making while **protecting participants**

Concept of 'non-commercial' sponsor

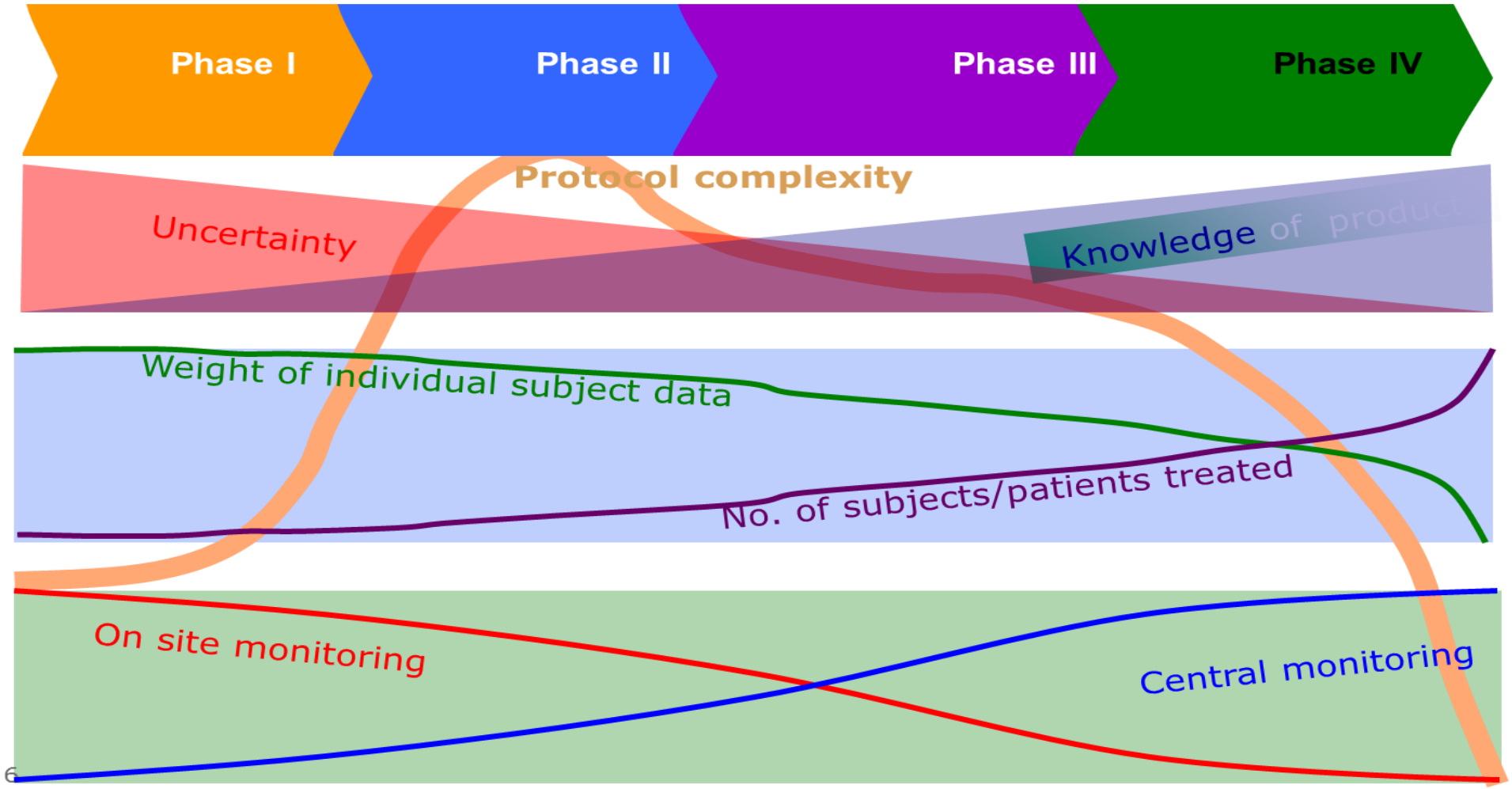
- An "*investigator-sponsor*" defined as a *'chief investigator who is also acting as the sponsor for that clinical trial'*
- Non-commercial clinical trial attributes:
  - conducted by an investigator-sponsor,
  - **without the participation** of the pharmaceutical industry,
  - in circumstances where the investigator-sponsor has **no commercial or financial interest** in the outcome of the trial
- Certain finance related obligations are waived for non-commercial trials
- Otherwise, **the same rules apply**...as the objectives are the same...credible data & participant protection

Regulatory Framework



* For illustrative purposes, may not be a complete list

Clinical trial – product lifecycle



NB: The shape of the curves, crossover, etc. are not based on specific data.
This is purely illustrative for discussion. Actual situation will vary case by case. *Acknowledgement to Fergus Sweeney for this slide*

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

01 December 2014
INS/GCP/46309/2012
Compliance and Inspections

Classification and analysis of the GCP inspection findings of GCP inspections conducted at the request of the CHMP

(Inspection reports to EMA 2000-2012)

Findings/grades

- A total of **398 GCP inspections** of products from centralised marketing authorisations or their applications (379 pre-approval and 19 post-approval) requested by the Committee for Human Medicinal Products (CHMP) have been conducted from 2000 to 2012.

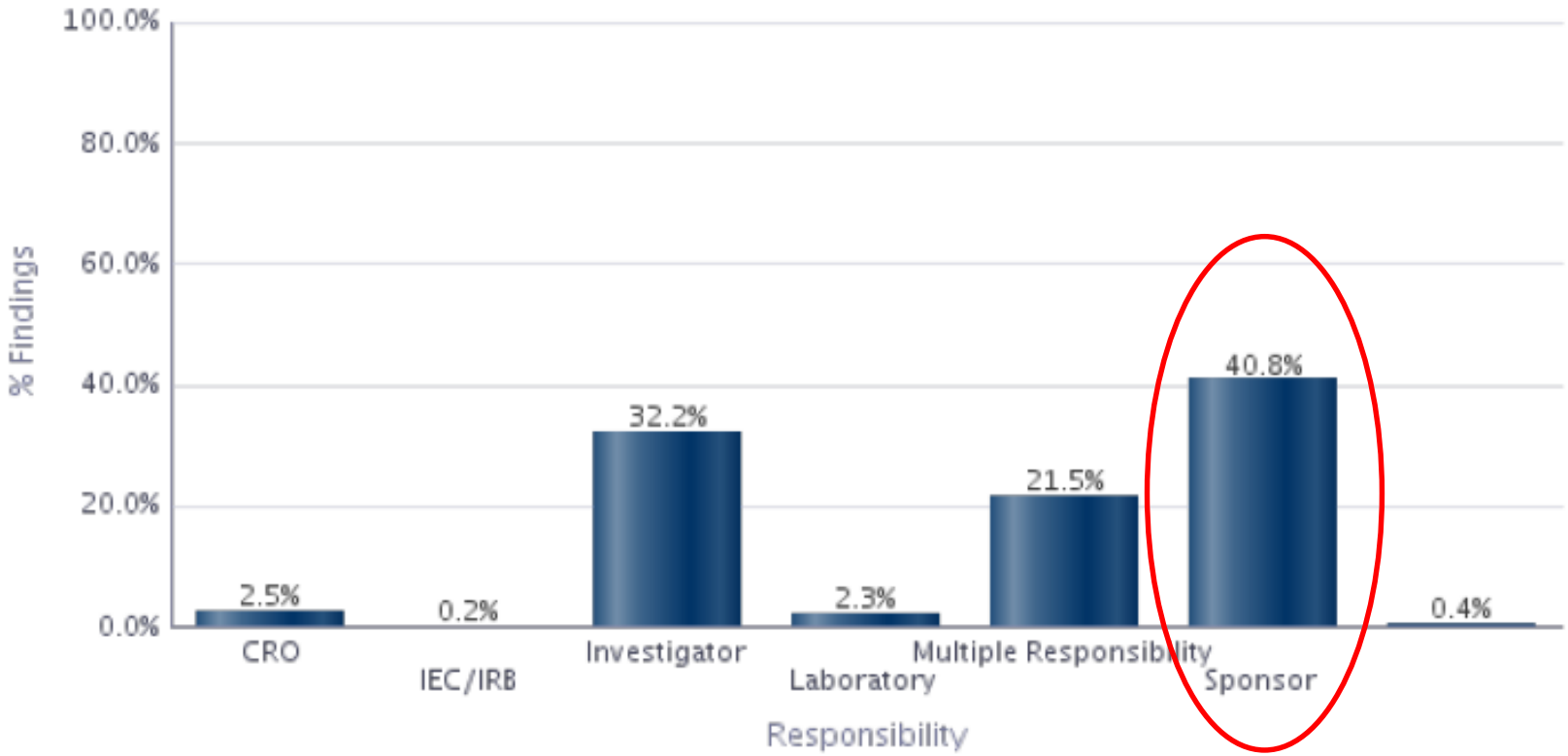
- A total of **5685 findings** were recorded during these inspections:
  - **532 critical (9.4%),**
  - **2583 major (45.4%)**
  - and 2570 minor (45.2%)

- Link to full report http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/12/WC500178525.pdf

5.2.3. Responsibility for the findings

The sponsor and CRO are responsible for 43.3% of the total findings (figure 6) although only 15.6% of the inspections were carried out at the sponsor site and 5.5% at the CRO site.

Figure 6. Responsibility of the findings from all sites



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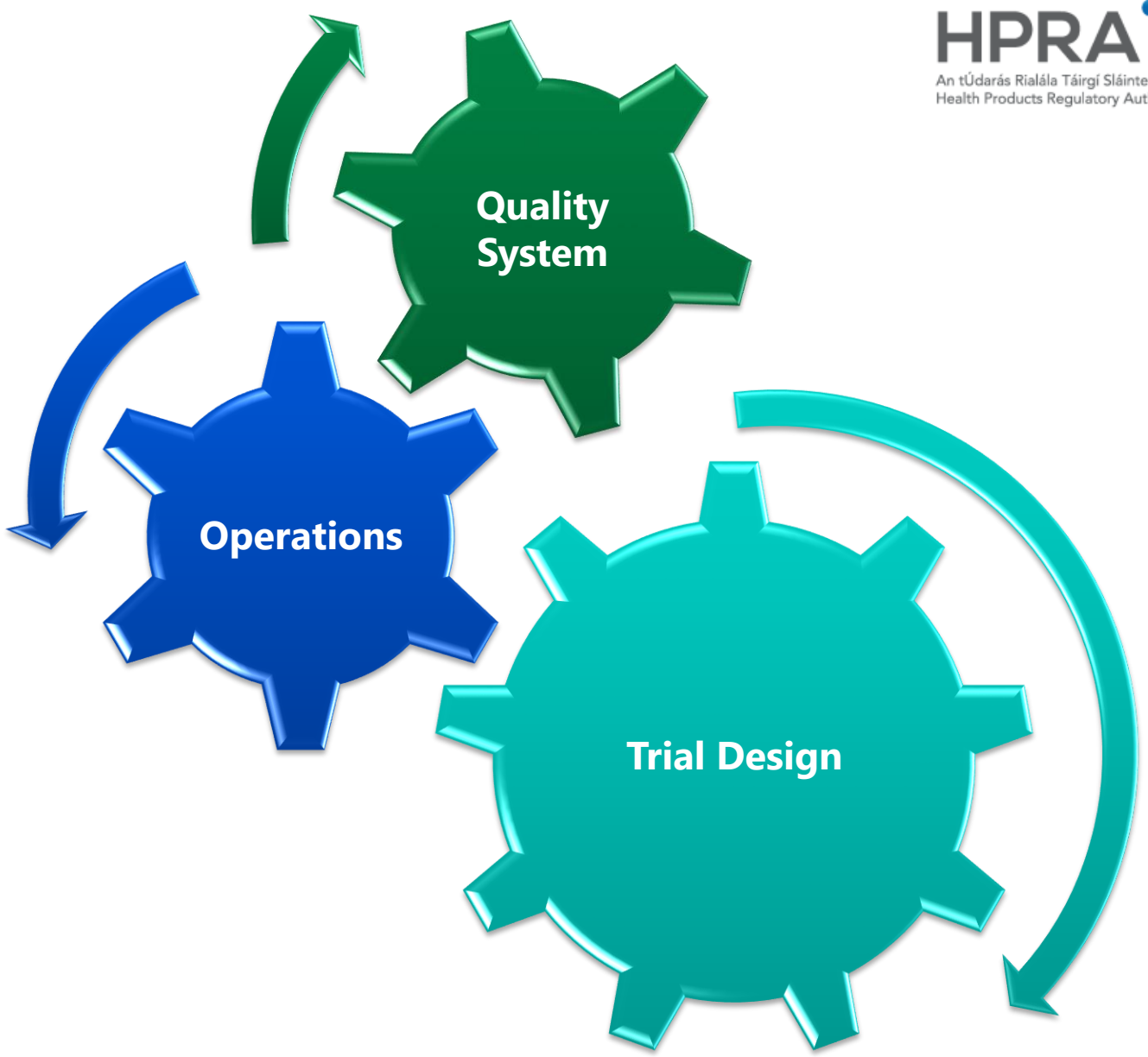
Focus on new sponsors

Translate legal obligations into tangible systems & processes

- Assure compliance
- Credible data
- Protect participants



Trial Design

- Clearly written protocol
- Scientifically robust & ethically sound

Operations

- Regulatory/ethics
- Trial mgt./governance
- Site monitoring
- Pharmacovigilance
- IMP management
- Clinical data mgt.
- Trial Master File

Quality System

- Roles & responsibilities
- Document control
- Written procedures
- Training
- Deviation/CAPA
- Compliance monitoring
- Quality risk management

* For illustrative purposes, may not be a complete list

Lifecycle of a trial: key stages

Planning → Conduct → Close-out

- Designing the trial
- Writing the protocol
- Critical to quality factors
- Establishing critical systems and processes
- Assigning tasks/roles
- Identifying & qualifying investigator sites
- Enter into written agreements
- Obtain regulatory & ethical approvals
- Trial Master File (TMF) setup
- Indemnity/insurance arrangements

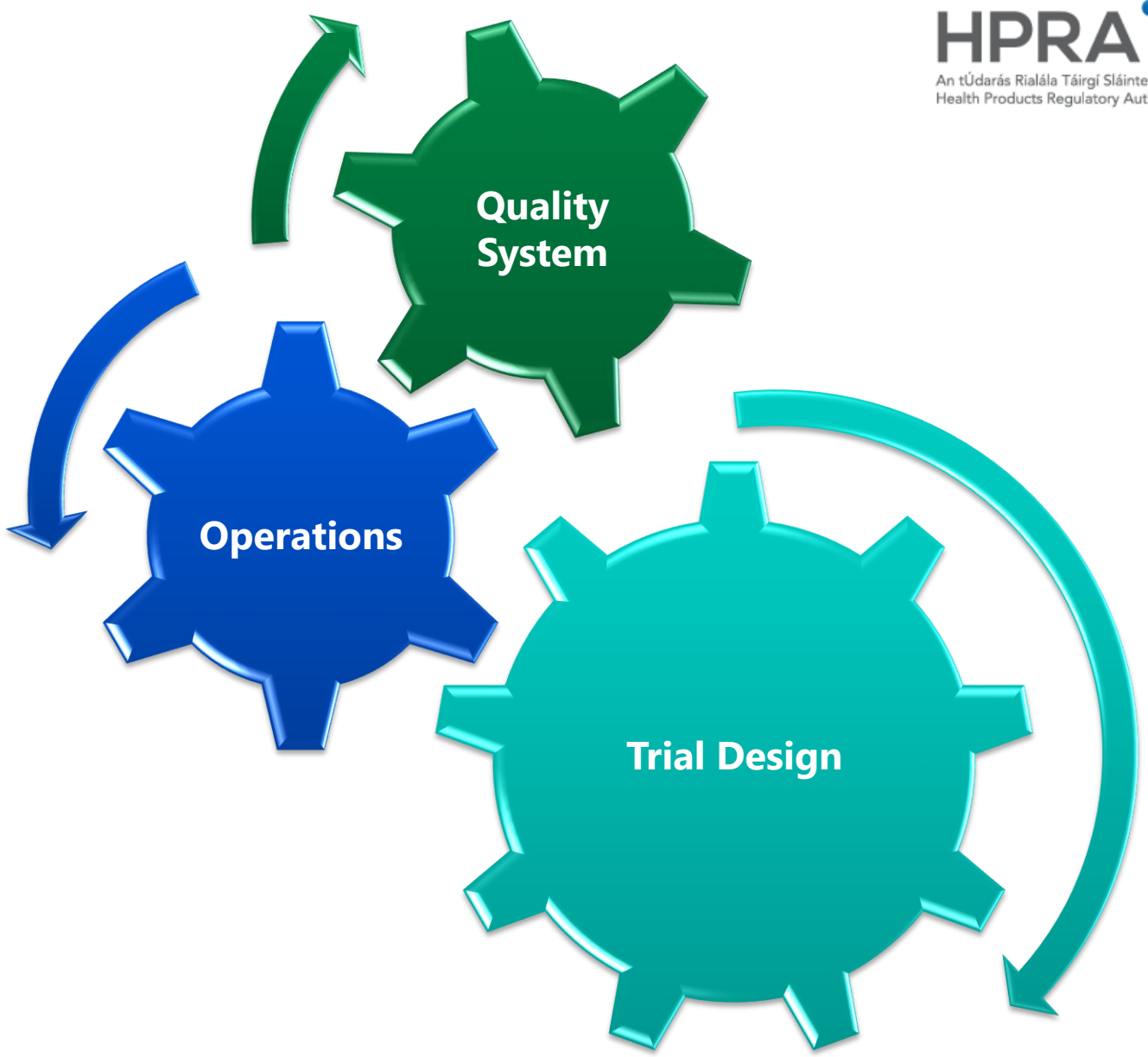
Planning → Conduct → Close-out

- Monitoring trial quality
- Monitoring participant safety
- Periodic review of factors critical to trial quality
- Update systems and processes, as needed
- Addressing any issues that arise, e.g. protocol deviations, legislative changes
- Collecting and cleaning data on ongoing basis
- Maintaining regulatory & ethical approvals
- Submission of safety reports etc.
- Keeping TMF up-to-date

Planning → Conduct → Close-out

- Close out of investigator sites
- Fulfilling any outstanding/follow up obligations for participants
- Final clean of data and ‘database lock’
- Analysing data & interpreting results
- Fulfil transparency obligations
- Reg/ethics submissions
- Archive of TMF
- Reporting – either Regulatory Authorities (licence) and/or via publications

So…there is a lot to consider before undertaking clinical trial sponsorship for the first time…



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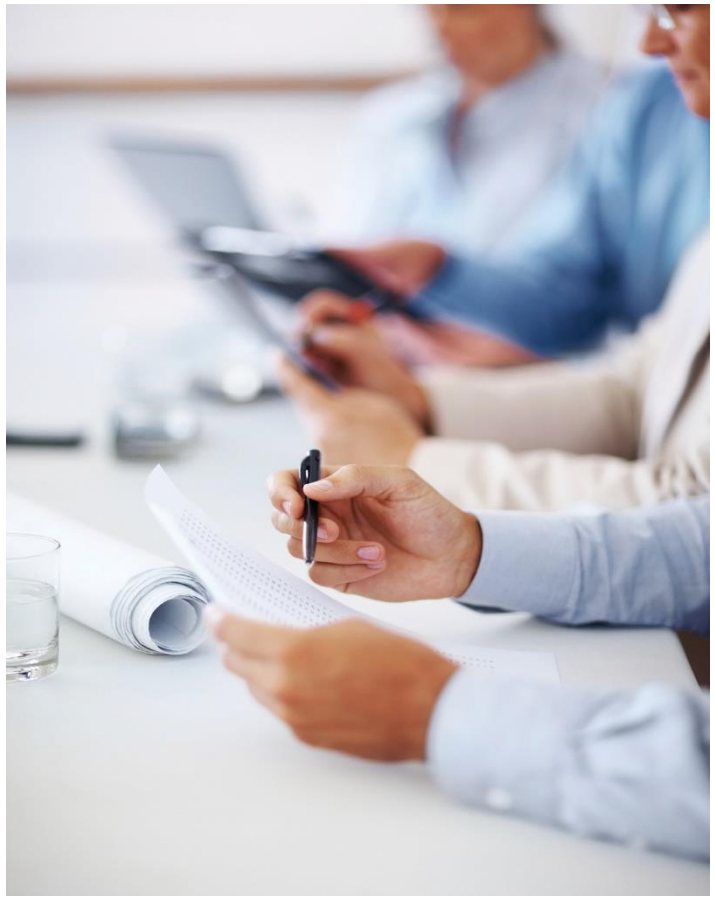
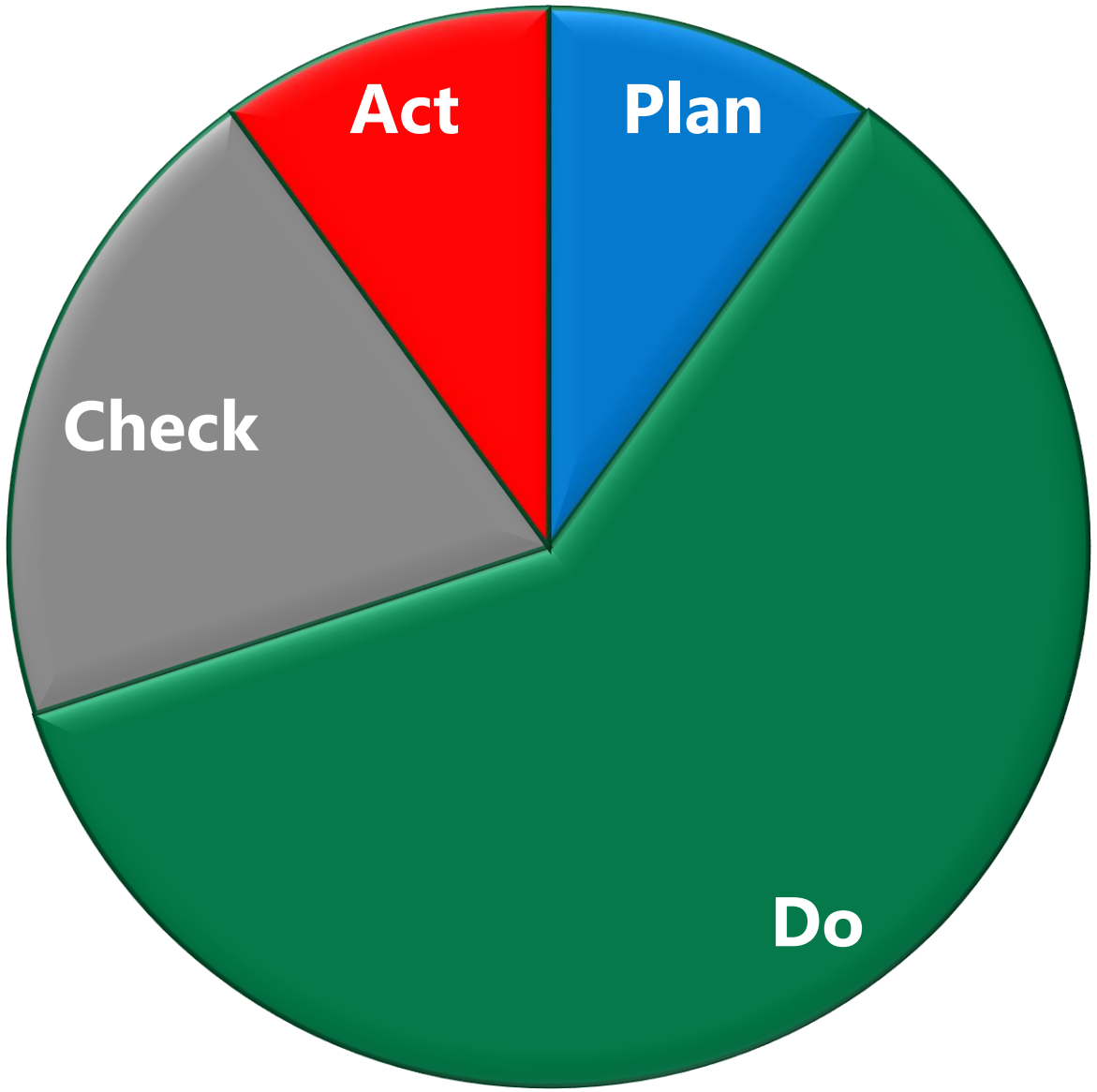
  - **Planning**
  - **Conduct**
  - **Close out**
- Regulatory supports

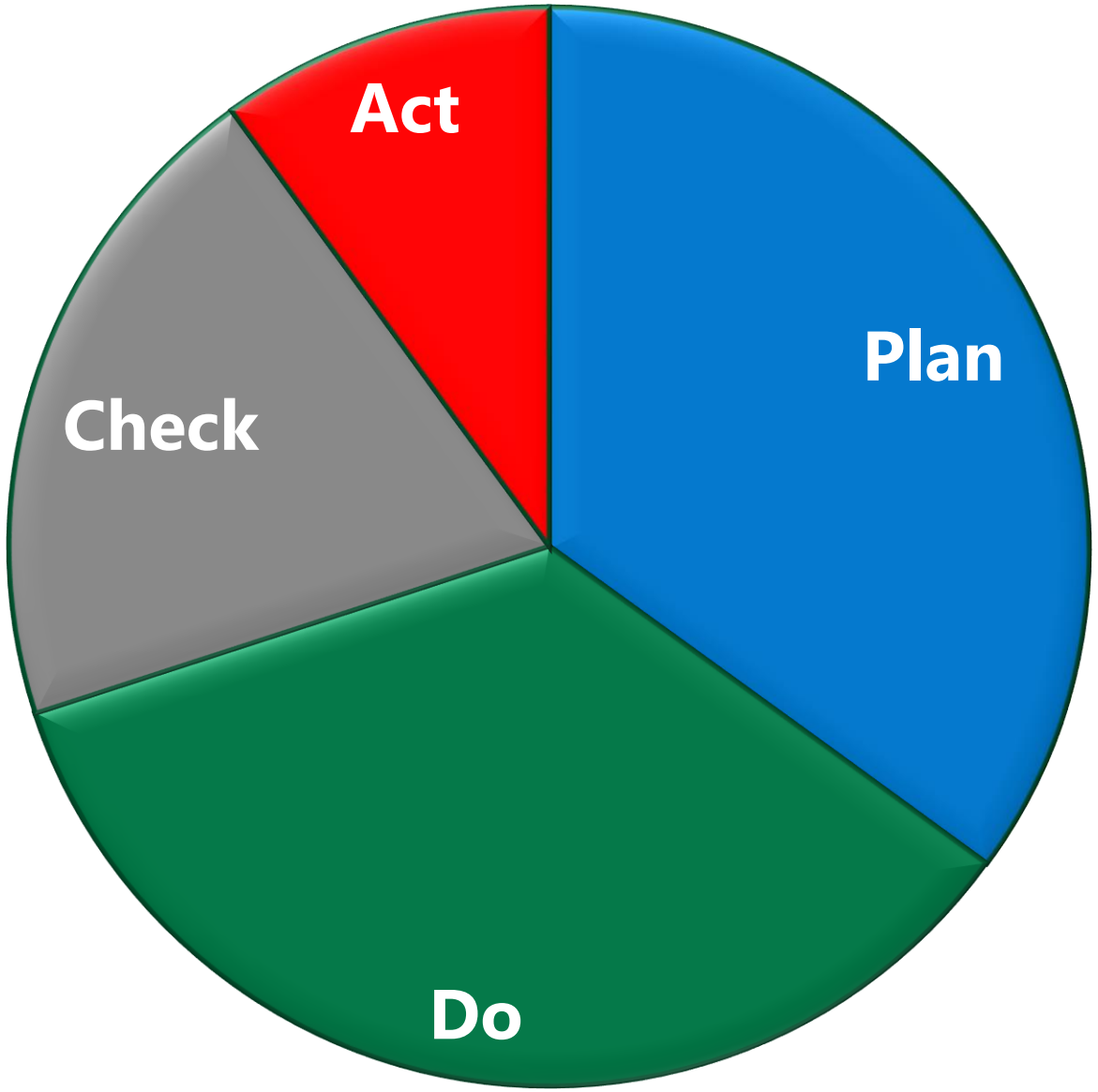
General planning: common/significant deficiencies



Trial initiated, without resources, systems and processes established in a manner that is fit for purpose, and, ensures satisfactory compliance with legal obligations



For illustrative purposes only



For illustrative purposes only

General planning: expectations/considerations

See earlier GCP presentation also!

- ✓ Satisfied understand legal obligations & liabilities
- ✓ Systems and procedures available to ensure compliance
- ✓ Clearly defined plan for trial governance/management
- ✓ Adequate resources and expertise available
- ✓ Roles & responsibilities assigned
- ✓ 'Critical to quality' factors determined in advance and reflected in protocol or relevant study documents
- ✓ Proactive supports to ensure correct implementation (e.g. broad training to all relevant site staff and reminders, description in the protocol, monitoring focus)

Planning stage: Example of Quality Risk Management Process

'Top level' risk assessment

- Identify trial governance structures for ongoing monitoring of trial quality and risk/benefit *e.g. IDMC, dose escalation committee, internal safety review committee, medic line listing review, trial steering committee*

'Protocol/study level' risk assessment

- Identify critical to quality data and processes & non-routine matters, evaluate and minimise the risks

'Systems, processes' risk assessment

- Consider if current systems and process are appropriate for trial, and adapt if needed

- Multidisciplinary team involvement
- Records of meetings & justification for decisions
- Plans documented
- Approval evidenced in writing

Planning stage deficiencies: trial design

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Protocol unnecessarily complicated

- ✓ Critical analysis of protocol
- ✓ Feasibility with multi-stakeholder involvement
- ✓ Are all aspects operationally feasible?
- ✓ Is this protocol prone to amendment?
- ✓ Are there superfluous objectives & endpoints?

'Critical to qualify' factors identified but proactive supports are deficient

Consider need for…

- ✓ Training/initiation
- ✓ Instructions in protocol
- ✓ Additional guidance/manuals
- ✓ Monitoring plan
- ✓ Other QA measures e.g. use of central/blind reader

Protocol not consistent with other study documents

- ✓ Robust QC process
- ✓ Internal consistency
- ✓ Consistency with other study documents e.g. CRF, manuals, data mgt. plans, study schedules
- ✓ QC should be independent, insofar as possible, and always recorded

Planning stage deficiencies: operational aspects

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Late implementation of critical documents/systems

e.g. 'site initiated with no access to CRF for x months'

- ✓ Identify timelines by when critical documents are needed
- ✓ The impact of delays need to be considered prior to initiating a site
- ✓ Data collection/cleaning should be ongoing over duration of a trial

Written agreements with CROs not detailed and/or implemented after tasks started

- ✓ Ref. GCP 5.7 (task allocation), 5.5.2 (CRO, specified in writing)
- ✓ Qualification process
- ✓ Oversight plan
- ✓ Written agreement: roles & responsibilities, standards, quality system expectations, escalation process

Inaccurate information submitted in Reg/Ethics documentation

- ✓ EudraCT form; QC check on important data e.g. sponsor details, CRO details, IMP identification
- ✓ Ethics application forms; QC check for accuracy/completeness e.g. informed consent, site description including any third party sites

Planning stage deficiencies: operational aspects

See earlier GCP presentation

Site monitoring plan deficiencies

- *Confusion between centralised monitoring, remote monitoring & routine data cleaning*
- *Remote monitoring planned for routine SDV*
- *Lack of consideration of all relevant factors for risk adaptation e.g. investigator site experience*
- *Process for handling protocol deviations not defined*

- ✓ Site monitoring plan decided based on assessment of risk, using well considered and relevant criteria
- ✓ Considered in context of other trial monitoring activities (e.g. DSMB, interim analysis, dose escalation committee, central reader, medical review, data cleaning)
- ✓ Centralised : based on well defined and documented statistical assumptions
- ✓ On site: Criteria leading to reduction or increase in activities (e.g. % SDV, frequency of visits) should be clear
- ✓ Remote: used for appropriate tasks (e.g. delegation log, IMP accountability records)
- ✓ Plan for handling protocol deviations and escalation of significant matters
- ✓ The monitoring plan, and rationale, should be documented

Planning stage deficiencies: quality system

Quality system not (fully) established

e.g. doc control, training, compliance monitoring

Existing quality system not considered in context of a new trial or other substantial change

e.g. large increase in activity, or different phase of trial

Written procedures not in place/not well described for critical processes/steps

- ✓ Functioning quality system is a fundamental GCP requirement
- ✓ QRM process should identify when the existing quality system needs to be adapted/strengthened, in line with concept of risk proportionality
- ✓ Quality planning and document control should ensure written procedures for critical steps are implemented

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Conduct stage deficiencies: trial design

Noncompliance with provisions of protocol, relating to sponsor ***monitoring of trial benefit/risk***

e.g. IDMC not established, interim analysis not performed, safety monitoring not performed as expected

Lack of a defined process for assessing & acting on trends critical to trial quality

e.g. frequent protocol deviations – no action taken

Submission/implementation of protocol amendments not timely

- ✓ **Full adherence to provisions in protocol for trial/safety monitoring**
- ✓ Trial governance/oversight processes need to be considered during the planning stage as part of QRM process.
- ✓ During trial conduct, risk review should be performed on a periodic basis, and where necessary additional risk mitigation taken
- ✓ When the need for a protocol amendment is identified, the change control process (from writing, submission, receipt of approval, distribution and confirmation of implementation across sites) should be managed

Conduct stage deficiencies: operational aspects

Deviation from monitoring plan

e.g. frequency or number of visits

SDV and/or data cleaning activities not timely relevant to trial objectives

e.g. Phase I dose escalation, interim analysis

Monitoring objectives not achieved, as evidenced by persistent and/or significant noncompliance at investigator site(s)

- ✓ Monitoring plan should be complied with, and where a change is necessary, this should be implemented via a controlled process
- ✓ Study level QRM process should identify the need to coordinate dependent activities (e.g. data cleaned prior to interpretation)
- ✓ Do audit/inspection findings that identify persistent and/or significant noncompliance at investigator site(s) call into question the underlying assumptions of a monitoring plan?
- ✓ Does a risk based monitoring approach require an increased focus on investigator site systems/processes?

Conduct stage deficiencies: operational aspects

SUSARs & DSURs late submission

TMF not kept up-to-date on ongoing basis

Care not taken to protect against potential bias resulting from sharing of comparative/unblinded data

- ✓ PV system and processes critical to quality and compliance (see later presentation)
- ✓ TMF should be kept up-to-date at all times, and not just at time of audit/inspection
- ✓ Risk of bias should be considered as part of QRM, and appropriate 'firewalls' implemented
- ✓ Watch out for conferences or abstracts!

Conduct stage deficiencies: quality system

Lack of basic version control, possibly impacting traceable change control for trial conduct (what was implemented and when)

Failure to keep written procedures up-to-date

e.g. periodic SOP reviews

- ✓ Implement rules for version control from the start, in particular for critical documents
- ✓ Establish quality system, including QRM processes as part of planning, review on periodic basis and update as needed

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Close-out stage: operations (data management)

See earlier GCP presentation

Data cleaning not performed throughout conduct of trial, leading to a high volume of queries at end stage of trial

Data management tasks not complete

e.g. no or incomplete reconciliation with safety database, no oversight of query status to sites

Data mgt/statistics: lack of formalised procedures and records to ensure a clear audit trial of activities

i.e. sequence of stats plan approval, to data cleaning, to protocol deviation review, to analysis populations determination, database lock, disclosing treatment allocation, and analysis

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- **Reflection & Regulatory supports**

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Reflection..

- Taking on the role of sponsor is a significant decision
- Good quality research needs to be supported by a well resourced and robust infrastructure, with systems and procedures established to assure satisfactory compliance, throughout the lifecycle of the trial
- Both the GCP(R2) addendum and CTR introduce a quality risk management approach, which if implemented correctly, will enable a more efficient and effective approach for running trials
- Concepts require open discussion and exchange of experiences in order to mature and develop as intended

HPRA supports Compliance/Inspections

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Special topics – GCP @ www.hpra.ie

Query service mailbox: compliance@hpra.ie

Non commercial:

Assistance with electronic report submission to Eudravigilance Clinical Trials Module

Newly agreed annual engagement with HRB CRCI

No fees for inspections or advice for non-commercial sponsors

HPRA supports:
Authorisation/Assessment

Guide to Clinical Trial Applications (AUT-G0001)

Classification support clinicaltrials@hpra.ie

Pre-submission meetings

Scientific advice

Protocol template

No fees for non commercial applications

Innovation office

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Thank you