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Health Products Regulatory Authority

Good Clinical Practice

Review of recent and future changes

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HPRA Information Day – GCP for IMP clinical trials

Dublin, 23 October 2018

GCP – A review of recent and future changes

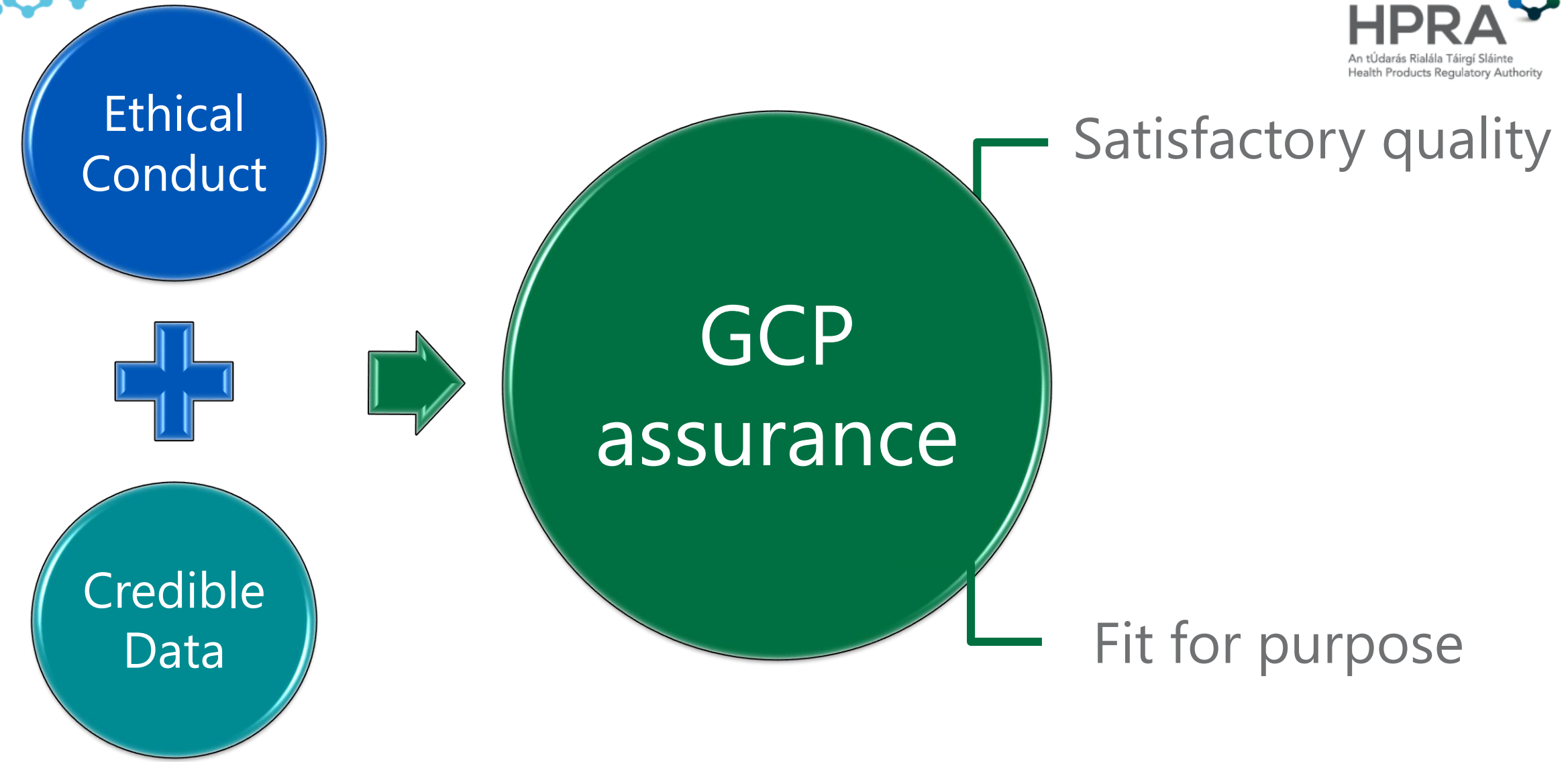
- Objective and purpose of GCP
- Background to ICH GCP E6(R2) addendum
- Key themes of the R2 addendum
- Signposting/useful resources

ICH GCP (E6) – Guideline for Good Clinical Practice

'Good Clinical Practice (GCP) is an international **ethical and scientific** quality standard for **designing, conducting, recording and reporting** trials that involve the participation of human subjects.

Compliance with this standard provides public **assurance** that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the **Declaration of Helsinki**, and that the clinical trial **data are credible**'

Ref. ICH GCP E6


Ethical Conduct
Credible Data
GCP assurance
Satisfactory quality
Fit for purpose

GCP – A review of recent and future changes

- Objective and purpose of GCP
- **Background to ICH GCP E6(R2) addendum**
- Key themes of the R2 addendum
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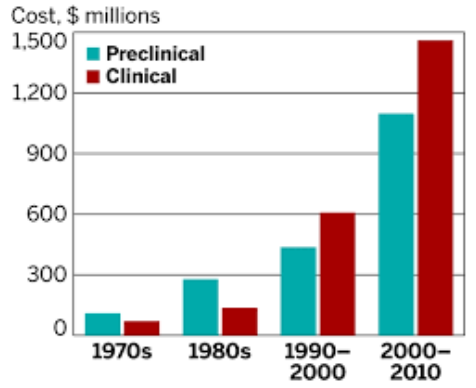
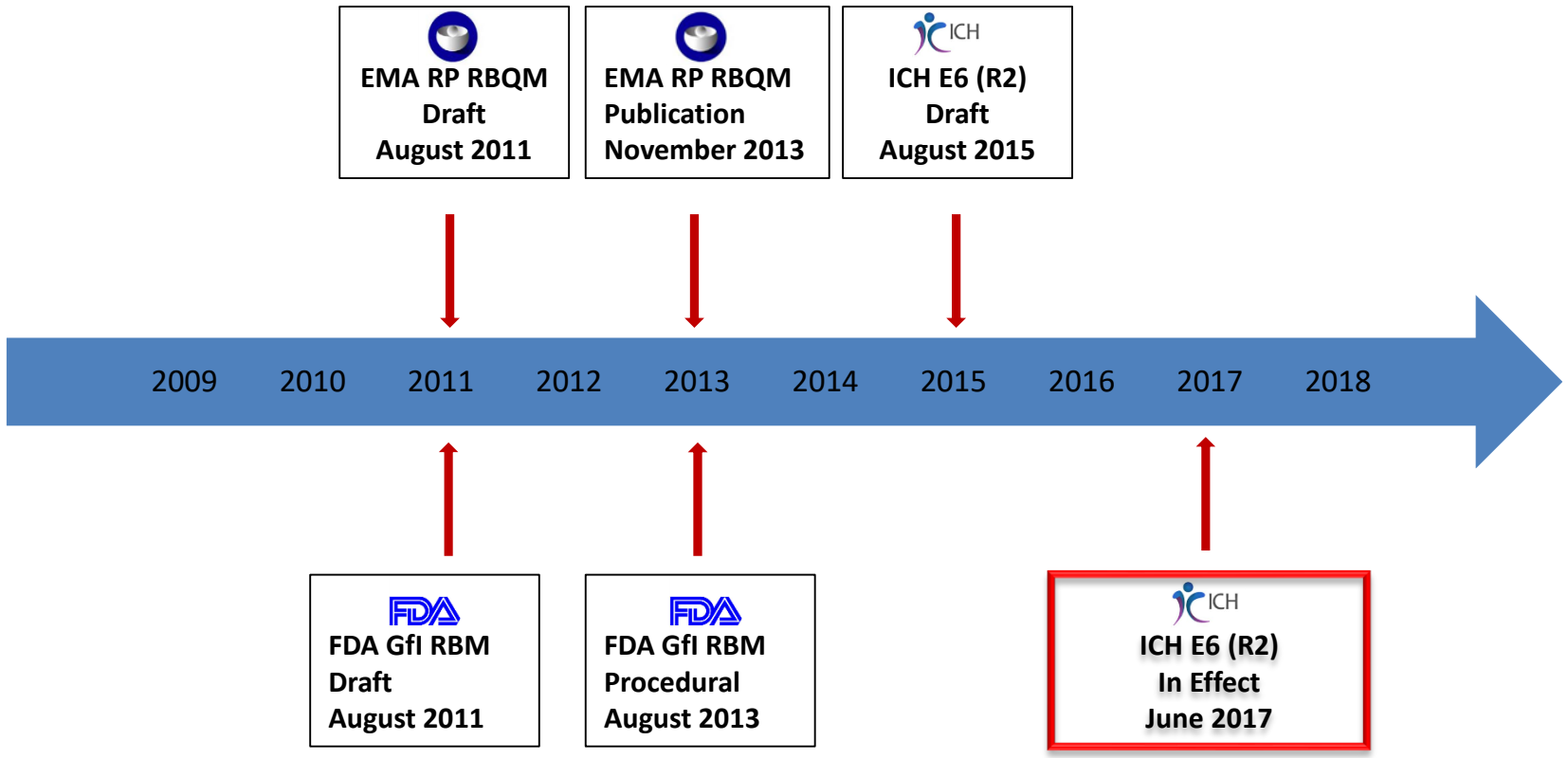
Why the need for an addendum?

'Since the development of the ICH GCP Guideline, the scale, complexity, and cost of clinical trials have increased. Evolutions in technology and risk management processes offer ***new opportunities to increase efficiency and focus on relevant activities****'*



Source: Tufts Centre for the Study of Drug Development.

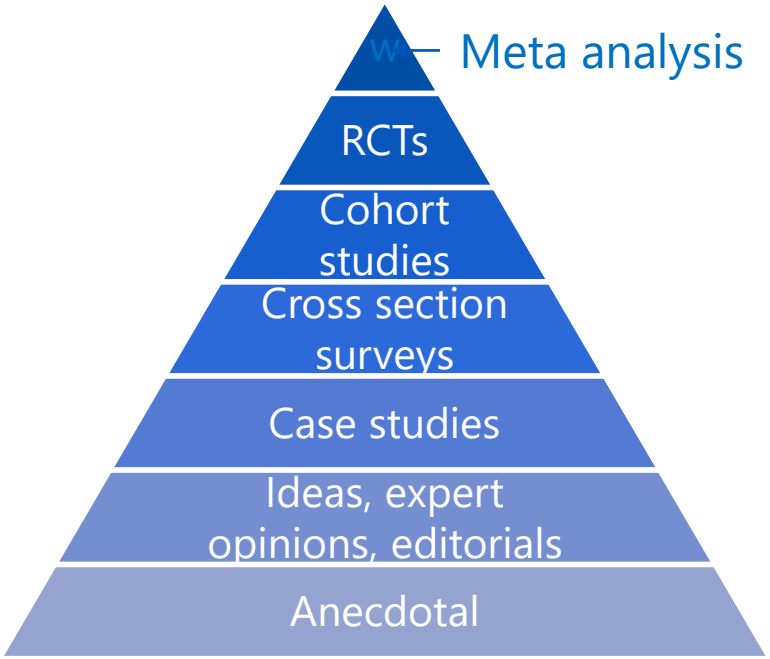
Risk based approaches
Regulatory development and implementation of ICH GCP E6(R2) addendum



Ack. Gabriele Schwarz, BfArM

GCP Renovation – Future changes

- ICH reflection on **'GCP Renovation'** January 2017
- Modernisation of ICH E8, General considerations for CTs
- Renovation of ICH E6, GCP guideline
- To continue the move towards **risk based approach**
- In recognition that the **emerging clinical trial environment** may increasingly serve as an important adjunct to traditional Randomised Controlled Trials (RCTs) to support regulatory decisions
- To provide guidance for emerging data streams and plurality of evidence



Structure: GCP E6(R1)

1. Glossary: terms and definitions
2. Set of 13 overarching principles
3. Requirements specific to ethics committee (IRB/IEC)
4. Requirements specific to investigator
5. Requirements specific to sponsor
6. Clinical trial protocol and amendments
7. Investigator brochure
8. Essential documents

Structure: GCP E6(R2) addendum*

1. **Glossary: terms and definitions** *
2. **Set of 13 overarching principles** *
3. Requirements specific to ethics committee (IRB/IEC)
4. **Requirements specific to investigator** *
5. **Requirements specific to sponsor** *
6. Clinical trial protocol and amendments
7. Investigator brochure
8. **Essential documents** *

Interpretation: in the event of conflict between R1 and R2, the R2 addendum text should take priority

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- **Key themes of the R2 addendum**
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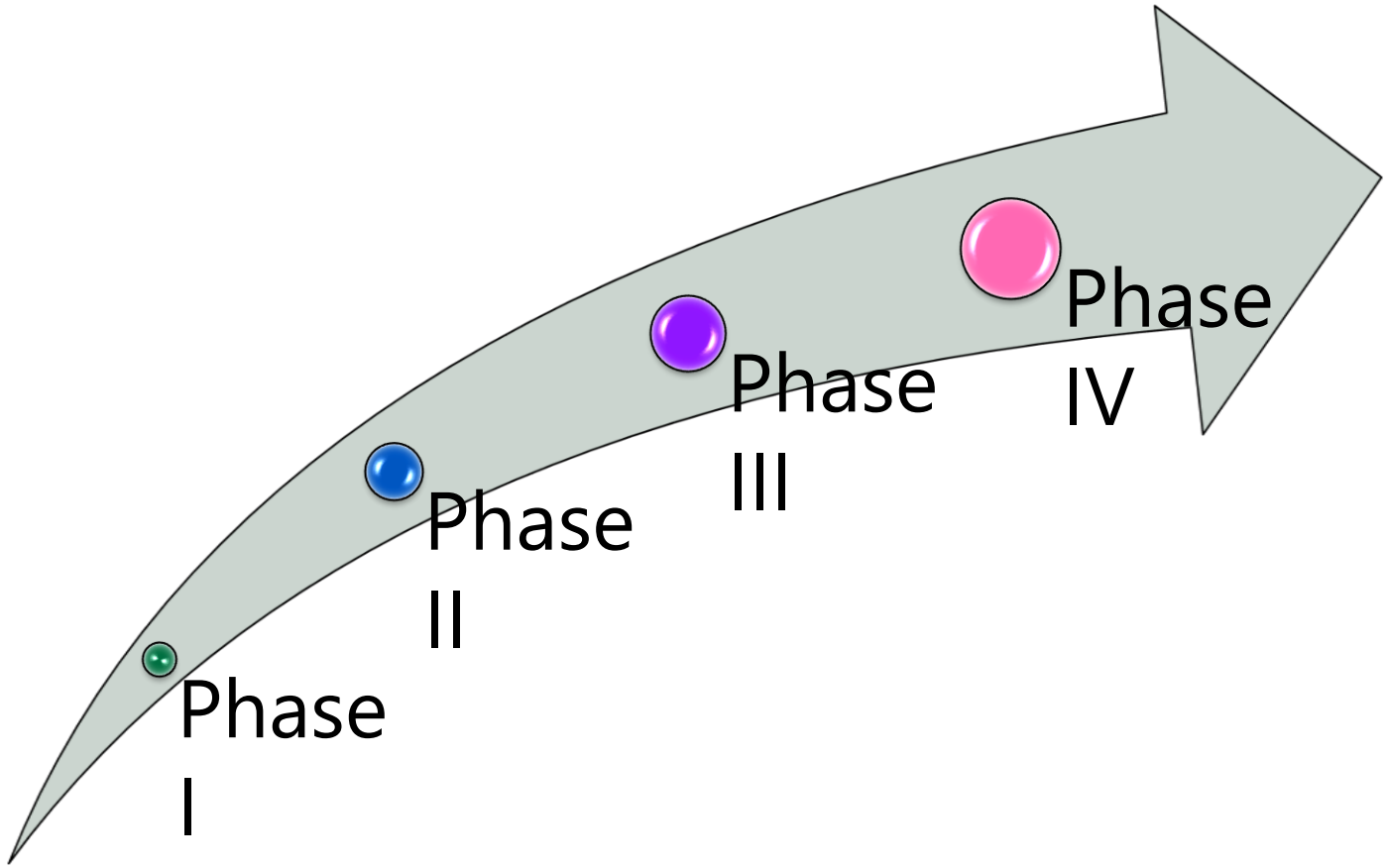
R2 addendum: Key Themes

- Quality risk management for sponsors
- Prioritized, risk-based approach to monitoring clinical trials
- Investigator oversight/ supervision
- Additional text on use of computerised systems

Quality Risk Management, Sponsors

Is management of risk a new concept in clinical trials?

Traditional phases of clinical development



Quality Risk Management (ICH Q9)

- 'some examples of use of quality risk management in the pharmaceutical industry….**limited and do not represent the full contributions that risk management has to offer**'
- '**valuable** component of an effective quality system'
- '**systematic processes** designed to coordinate, facilitate and improve science-based decision making with respect to risk'
- 'understood that risk is….combination of the **probability** of occurrence of harm and the severity of that harm'

E6(R2): Quality Risk Management - GCP

- Using the principles of quality management, identify those aspects that are critical to generating reliable data and providing appropriate protections for research participants
- Develop strategies and actions to effectively & efficiently support quality in these critical areas
- Move away from 'one size fits all', with over reliance on checklists/monitoring/auditing for quality
- **Move to** critical thinking with proactive and prospective designing of quality measures into clinical trials to manage risks

Examples of Trial Related Risk Factors

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IMP

- Nature of IMP e.g. *advanced therapy, biological, small molecule*
- Properties of active ingredient
- Authorisation status

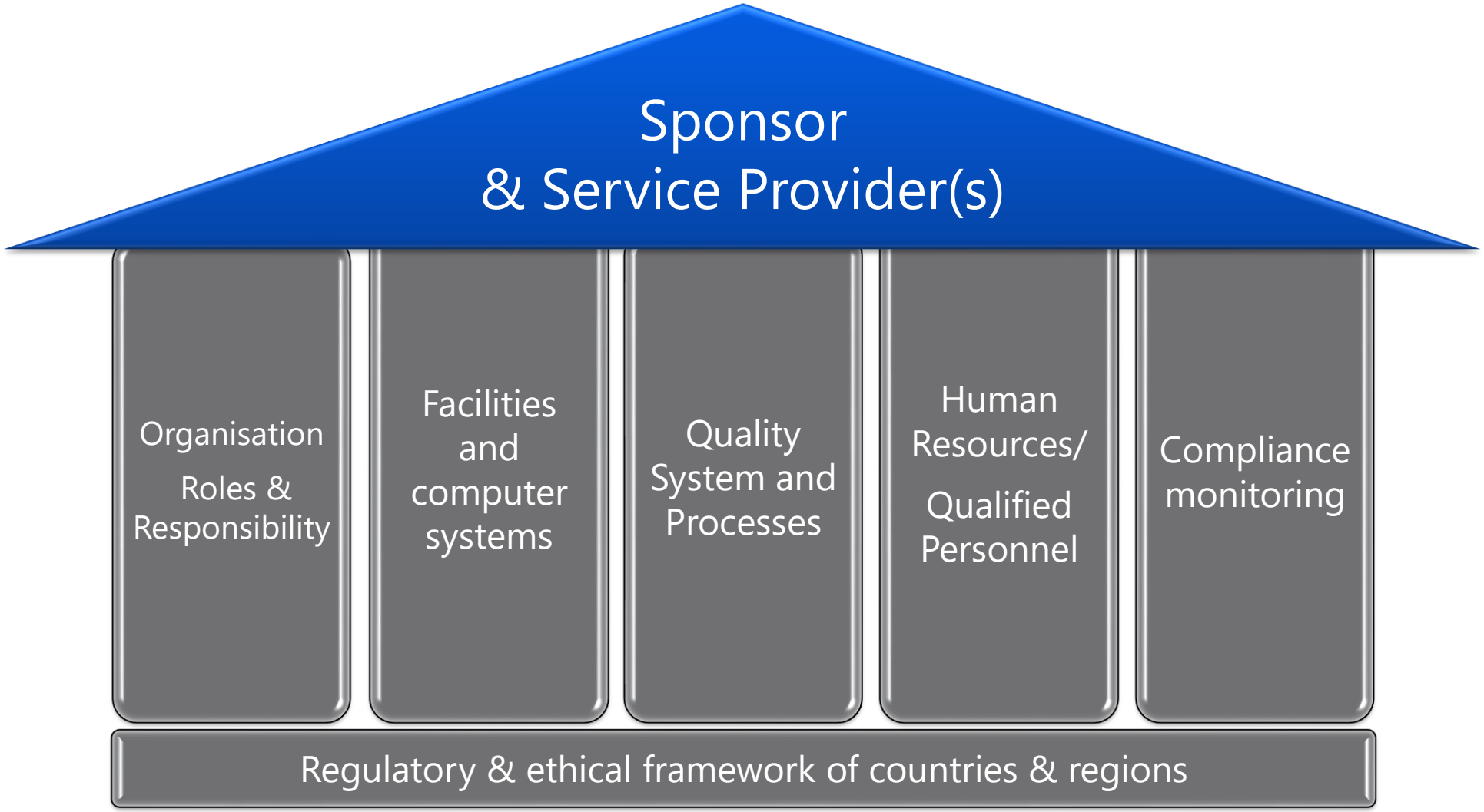
Trial Design

- Complexity of design
- Trial population
- Robustness of eligibility criteria
- Endpoint selection
- Sample size calculation
- Additional diagnostic and monitoring procedures
- Patient protection/ethics

Operations

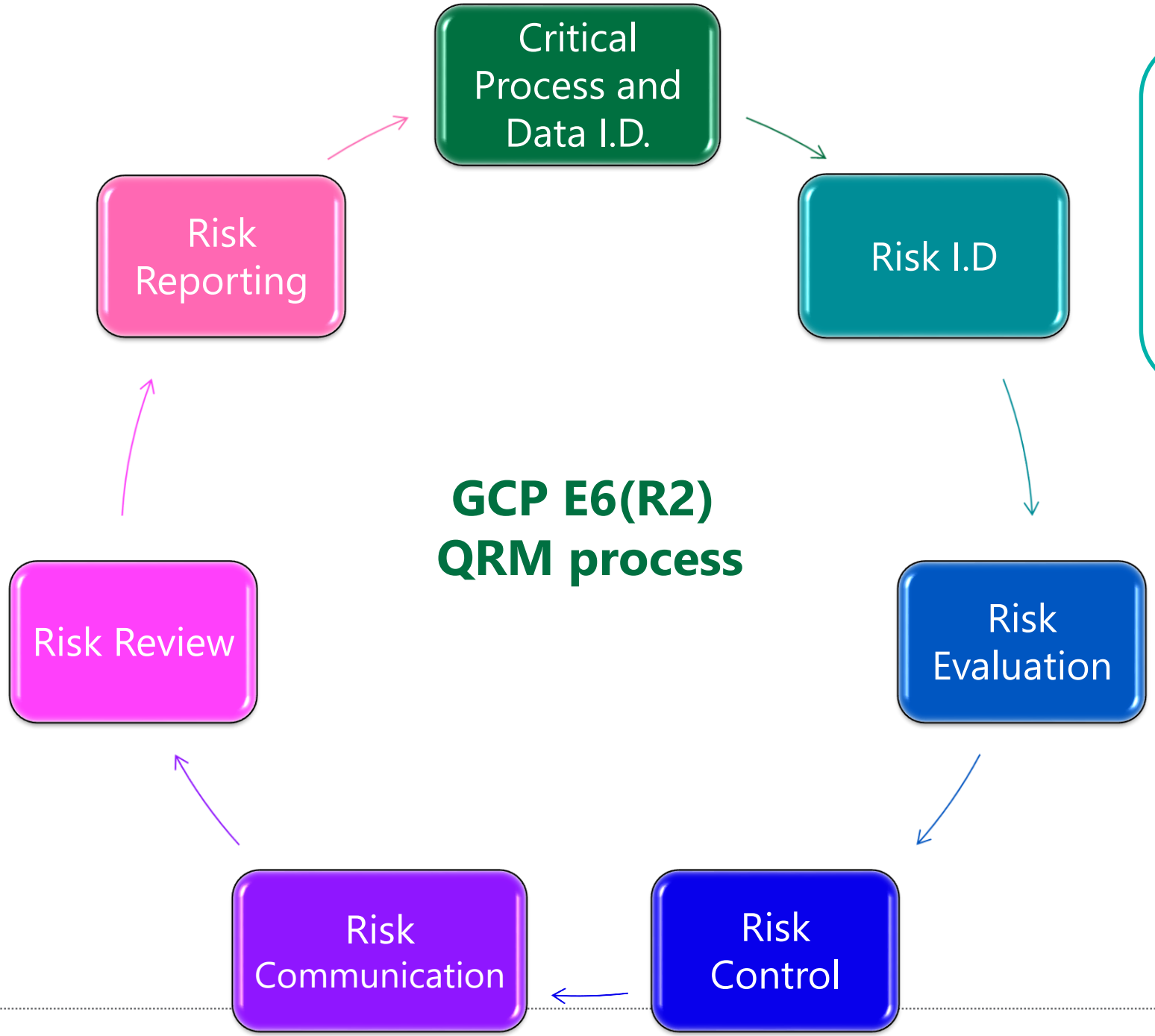
- Resources, inc. third party involvement
- Clinical site setup and infrastructure, laboratory setup
- Setup of trial databases, management of clinical data
- Clinical trial supply processes and management

System/infrastructure related risk factors (e.g.)



Applied at **<u>all stages</u>** of trial process

Focus on trial activities **<u>essential to human subject protection</u>** and reliability of trial results



GCP E6(R2) QRM process

Operationally feasible, avoid **<u>unnecessary complexity</u>**

Methods **<u>proportionate to the risks</u>** & importance of the information collected

What are the challenges?

- Converting principles into clearly defined processes, with well considered and understood criteria, for the discipline of clinical trials
- Cultural change & compliance confidence
- Misconceptions
  - QRM is not a segue to justify non-compliance, cherry pick GCP requirements or obviate obligations
  - Not mitigating the risk of non-compliance

Considerations for implementation

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Leadership

- QRM principles provided for at top of QMS hierarchy e.g. policy level
- Implementing QRM requires upfront time investment….but with a downstream value

Culture

- Truly understand the purpose of GCP
- QRM concept will benefit from information sharing across all stakeholders
- Support personnel to upskill with appropriate training, and, recognise existing experience in managing risk in clinical trials
- Careful consideration of performance metrics for trial success (e.g. first patient in)

Process attributes

- Multidisciplinary approach
- Stakeholder engagement
- Utilise knowledge from clinical development experience (e.g. 'lessons learned')
- Iterative process that reflects the state of knowledge of risk
- Provision for escalation of issues
- Good documentation practices throughout

R2 addendum: Key Themes

Quality risk management for sponsors

Prioritized, risk-based approach to monitoring clinical trials

Investigator oversight/ supervision

Additional text on use of computerised systems

Traditional approach

GCP E6(R1),5.18.3: **Extent and nature of monitoring** should be based on considerations such as the objective, purpose, design, complexity, blinding, size and endpoints of the trial.

****

Traditional monitoring:

- Reliant upon on-site monitoring, and good monitor-site relationship
- Often focused upon 100% source data verification of case report forms
- Higher risk study/problematic site; typically higher frequency of visits

Issue management:

- Largely dependent on monitoring visit report review & trending of common issues
- Periodic feedback from data monitoring committees and other trial monitoring committees

Centralized monitoring: analysis of accumulating data

Describe variability between investigator sites, regions, groups of sites managed by different organisations

Unusual patterns highlighted in real time for further investigation…

Help to understand the **underlying causes of variability** and therefore highlight priorities for additional control/monitoring

Complement on-site monitoring and **better focus resource** to activities of greater added value to trial quality

Help to implement measurements that can **describe the quality** and reliability of a trial…

On-site monitoring: important aspects

Investigator site-sponsor relationship

Verifying protocol compliance and data quality against source data

Detection of unreported events, e.g. AEs, SAEs, protocol deviations

IMP management, including storage and accountability

Investigator oversight and resources

5.18.3 Extent and nature of monitoring

- The new addendum emphasises the concept of flexibility applied to monitoring:

The sponsor should develop a systematic, prioritized, risk-based approach to monitoring clinical trials. The flexibility in the extent and nature of monitoring described in this section is intended to **permit varied approaches** that improve the effectiveness and efficiency of monitoring.

The sponsor may **choose on-site monitoring, a combination of on-site and centralized monitoring**, or, where justified, centralized monitoring. The sponsor should **document the rationale** for the chosen monitoring strategy (e.g., in the monitoring plan)..

5.18.3 Extent and nature of monitoring

- Clearly defines different approaches that can be taken:

"**On-site monitoring** is performed **at the sites** at which the clinical trial is being conducted."

"**Centralized monitoring** is a remote evaluation of **accumulating data**, performed in a timely manner, supported by appropriately qualified and trained persons (e.g., data managers, biostatisticians)."

5.18.6 Monitoring report

- Specifies the need to report on all types of monitoring activities:

"(e) Reports of **on-site and/or centralized monitoring** should be provided to the sponsor (including appropriate management and staff responsible for trial and site oversight) in a timely manner for review and follow up.
Results of monitoring activities should be documented in sufficient detail to allow verification of compliance with the monitoring plan.
Reporting of centralized monitoring activities should be regular and may be independent from site visits."

5.20.1 Noncompliance

- Necessary to have a process to manage noncompliance:

If noncompliance that significantly affects or has the potential to significantly affect human subject protection or reliability of trial results is discovered, the sponsor should perform **a root cause analysis and implement appropriate corrective and preventive actions**

R2 addendum: Key Themes

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- Additional text on use of computerised systems

Shift in clinical trial organisation…

- Increased fragmentation and distribution of tasks
- Multiple parties involved
- Investigator site e.g.
  - Specialised clinical trial facility
  - Third party pharmacy
  - Third party laboratory
  - Homecare nursing organisation
- Investigator site – sponsor e.g.
  - Site management organisation
  - Provision of archive facilities
  - IT vendors

4.2.5-6: Adequate resources

- Clarity with respect to expectations for investigator/**institution** oversight:

4.2.5 The investigator is responsible for **supervising any individual or party** to whom the investigator delegates trial-related duties and functions conducted at the trial site.

4.2.6 If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure **this individual or party is qualified to perform those trial-related duties and functions** and **should implement procedures** to ensure the integrity of the trial-related duties and functions performed and any data generated.

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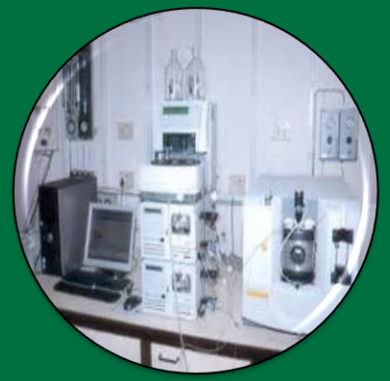
Computerised systems



Equipment and Data Processing

- Analysis instruments and data processing
- Statistical analysis and report production

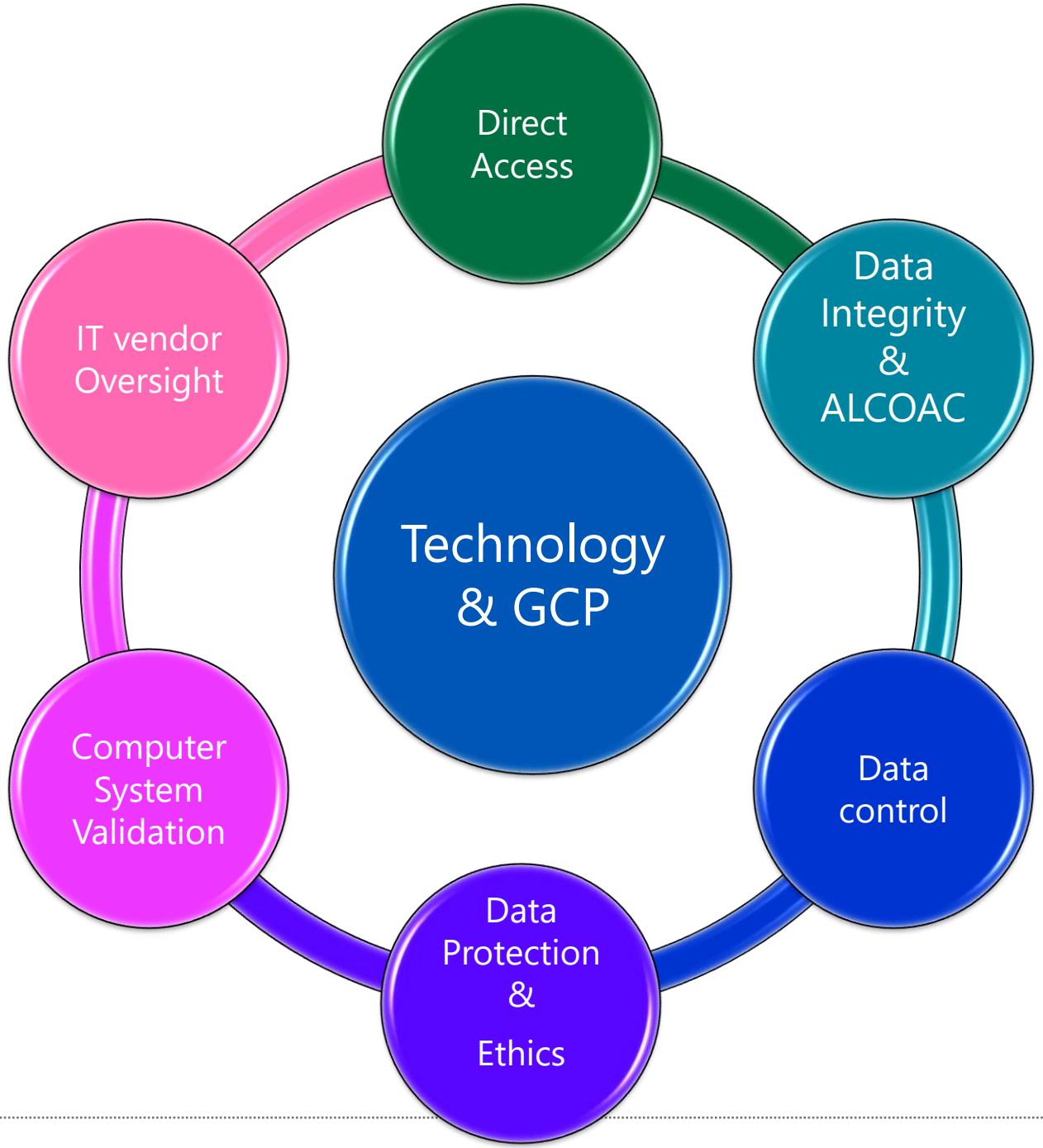
Data Capture (& Management)

- eCase Report Forms
- Patient eDiaries
- Mobile technology

Electronic Records

- eHealth Records
- eTrial Master File
- Management Systems (CTMS etc.)
- Databases (IRT, PV etc.)

Cloud Technology


Direct Access
Data Integrity & ALCOAC
Data control
Data Protection & Ethics
Computer System Validation
IT vendor Oversight
Technology & GCP

2.10: Updated principle for clinical trial data

- Concept of equivalence for all data:

2.10 All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification

R2 Addendum

This principle applies to all records referenced in this guideline, **irrespective of the type of media used**

1.63, 65: Certified copies & CSV

- New definitions

1.63 Certified Copy

A copy (irrespective of the type of media used) of the original record that has been **verified** (i.e., by a dated signature or by generation through a validated process) to **have the same information, including data that describe the context, content, and structure, as the original**

1.65 Validation of Computerized Systems

A process of establishing and documenting that the specified requirements of a computerized system can be consistently fulfilled **from design until decommissioning of the system or transition to a new system**. The approach to validation should be based on a risk assessment that takes into consideration the intended use of the system and the potential of the system to affect human subject protection and reliability of trial results.

4.9.0: Records and reports

- Investigator: data integrity rules strengthened e.g. 'ALCOAC'

4.9.0

The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be **attributable, legible, contemporaneous, original, accurate, and complete.** Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).

5.5.3: Electronic trial data handling

- Introduction of risk assessment, SOP scope and roles

The sponsor should base their approach to validation of such systems on a **risk assessment** that takes into consideration the intended use of the system and the potential of the system to affect human subject protection and reliability of trial results.

5.5.3: Electronic trial data handling

- Introduction of risk assessment, SOP scope and roles

(b) Maintains SOPs for using these systems: The SOPs should cover system **setup, installation, and use**. The SOPs should describe system validation and functionality testing, data collection and handling, system maintenance, system security measures, change control, data backup, recovery, contingency planning, and decommissioning. **The responsibilities of the sponsor, investigator, and other parties** with respect to the use of these computerized systems should be clear, and the users should be provided with training in their use.

5.5.3: Electronic trial data handling

- Concept of data integrity – including for metadata

(h) Ensure the **integrity of the data** including any data that describe the **context, content, and structure**. This is particularly important when making changes to the computerized systems, such as software upgrades or migration of data.

8.1: Essential documents

- ISF/TMF: Traceability, as well as access and control rights addressed

The sponsor and investigator/institution should **maintain a record of the location(s) of their respective essential documents including source documents…..**

…….The sponsor should ensure that the **investigator has control of and continuous access to the CRF data** reported to the sponsor. The sponsor should not have exclusive control of those data…..

The **investigator/institution should have control of all essential documents and records generated by the investigator/institution before, during, and after the trial**

R2 addendum: Key Themes

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Signposting / Useful resources

ICH GCP E6 Guideline for Good Clinical Practice

- ICH GCP E6 (R2): http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Addendum_Step2.pdf
- GCP Renovation package: http://www.ich.org/products/gcp-renovation.html

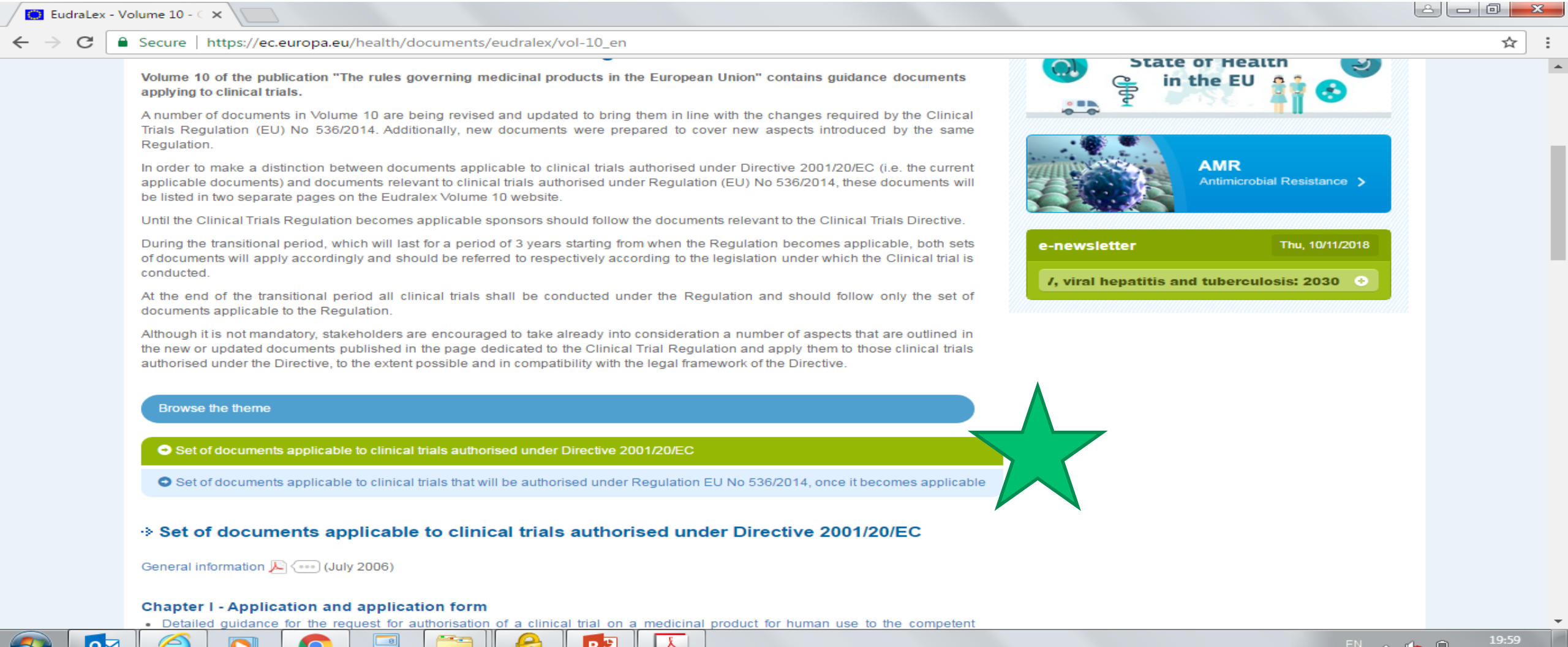
ICH E17 Multi Regional Clinical Trials: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E17/E17EWG_Step_4_Presentation_2018_0114.pdf

Clinical Trial Regulation no. 536/2014

- Implementation: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000629.jsp
- European Commission: https://ec.europa.eu/health/human-use/clinical-trials/regulation_en

Eudralex Volume 10 (Clinical trial guidelines)

- https://ec.europa.eu/health/documents/eudralex/vol-10_en



Irish Legislation

- www.irishstatutebook.ie
- http://health.gov.ie/wp-content/uploads/2014/03/Informal-Codification-Text.pdf

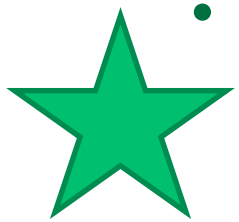
- **S.I. No. 190 of 2004 European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations, 2004, As amended by**
  - **European Communities (Clinical Trials on Medicinal Products for Human Use) (Amendment) Regulations 2004** (S.I. No. 878 of 2004)
  - **European Communities (Clinical Trials on Medicinal Products for Human Use) (Amendment No. 2) Regulations 2006** (S.I. No. 374 of 2006)
  - **Medicinal Products (Control of Manufacture) Regulations 2007** (S.I. No. 539 of 2007)
  - **Medicinal Products (Control of Placing on the Market) Regulations 2007** (S.I. No. 540 of 2007)
  - **European Communities (Clinical Trials On Medicinal Products For Human Use) (Amendment) Regulations 2009** (S.I. No. 1 of 2009)

GDPR

- Question and Answers on the interplay between the Clinical Trials Regulation and the General Data Protection Regulation – ***expected from EC***
- Data Protection Act 2018 (Section 36(2)) (Health Research) Regulations 2018
- Health Research Regulations 2018 - https://www.hrb.ie/funding/gdpr-guidance-for-researchers/gdpr-and-health-research/health-research-regulations-2018/

HPRA GCP Inspections & Topics of Interest

- General information: https://www.hpra.ie/homepage/medicines/regulatory-information/clinical-trials/good-clinical-practice-(gcp)-inspections



- Topics of special interest: https://www.hpra.ie/homepage/medicines/regulatory-information/clinical-trials/topics-of-special-interest

GCP Inspections

- Procedures: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000136.jsp

- GCP Inspectors Working Group Q&A: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000016.jsp&mid=WC0b01ac05800296c5

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Thank you