Federal Institute
for Drugs
and Medical Devices

3. D|A|CH Symposium 30. – 31.05.2022 Update on ICH E6

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isclaimer

This presentation reflects the thoughts and opinions of the presenter and are not necessarily in every aspect those of the BfArM, the EMA, the European Commission or the ICH E6 (R3) Working Group

Furthermore, this presentation reflects work in progress

- This means that for many aspects, draft text is already available and has been discussed, but may w still undergo changes
- This also means that a few points for consideration have not yet been addressed and that previousl unidentified issues may emerge in the course of editing

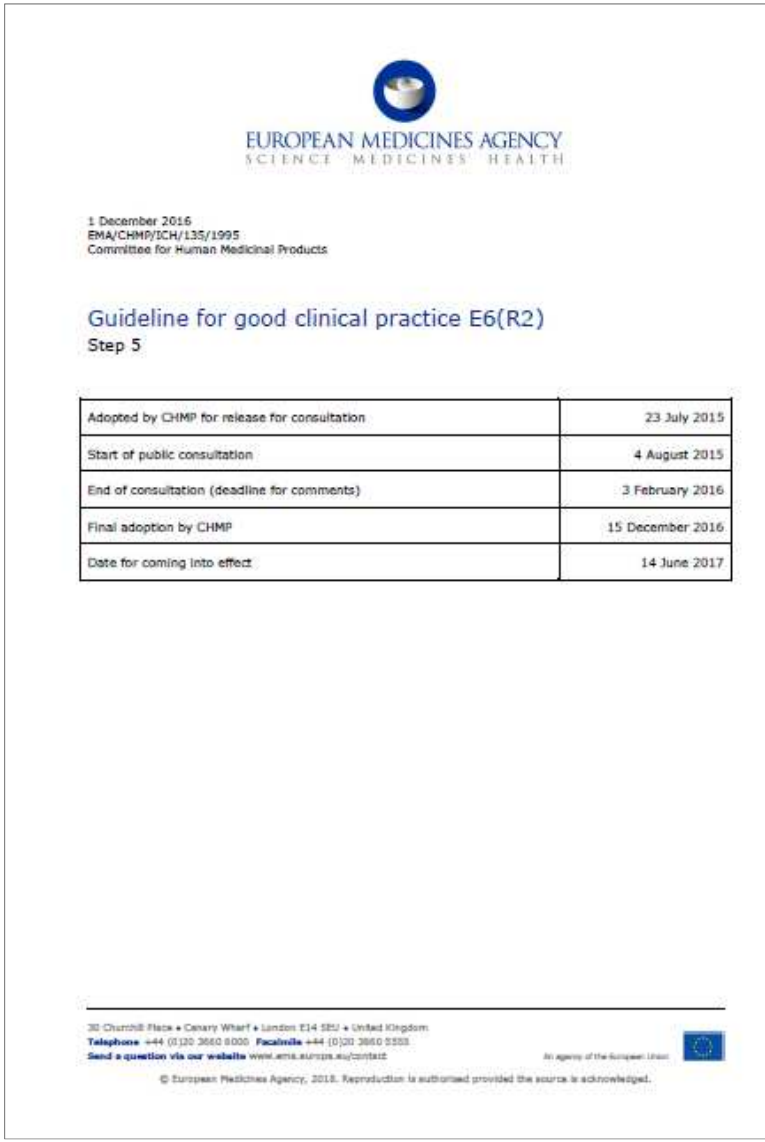
pdate on ICH E6(R3)
oncept (1)

E6(R3) EWG launched in Sep. 19

Concept paper and business plan agreed in Nov 19 at the ICH Singapore meeting

Complete revision and reorganization of the ICH E6(R2) Guideline

- Introduction to & key principles of GCP
- Annex 1: traditional interventional trials of unapproved or approved drugs, encompassing E6(R2)
- Annex 2: designs such as pragmatic clinical trials, decentralized clinical trials and trials that incorporate real world data sources (e.g. electronic health records, hospital discharge summaries, claims data, patient/disease registries)



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 December 2016
EMA/CHMP/ICH/135/1995
Committee for Human Medicinal Products

Guideline for good clinical practice E6(R2)
Step 5

Adopted by CHMP for release for consultation	23 July 2015
Start of public consultation	4 August 2015
End of consultation (deadline for comments)	3 February 2016
Final adoption by CHMP	15 December 2016
Date for coming into effect	14 June 2017

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https://database.ich.org/sites/default/files/E6-R3_FinalConceptPaper_2019_111

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oncept (2)

The principles are intended to apply across clinical trial types and settings and to remain relevant as technological and methodological advances occur.

They can be complied with using **differing approaches** and should be interpreted to fit the intended purpose of a particular clinical trial.

ICH E6 should be read in **conjunction with other ICH guidelines** relevant to the design and conduct of clinical trials, including multiregional trials.

CH E Family of Guidelines – Need to be considered together

Design and Analysis:

E 4 Dose-Response Studies
E 9 Statistical Principles for Clinical Trials
E 10 Choice of Control Group in Clinical Trials
E 17 Multi-Regional Clinical Trials

Populations:

E 5 Ethic Factors
E 7 Clinical Trials in Geriatric Population
E 11 – E 11 A Clinical Trials in Pediatric Population
E 12 Clinical Evaluation by Therapeutic Category

Conduct and Reporting:

E 3 Clinical Study Reports
E 6 Good Clinical Practice

Safety Reporting:

E 1 Clinical Safety for Drugs used in Long-Term Treatment
E 2A – E 2F Pharmacovigilance
E 14 Clinical Evaluation of QT
E 19 Safety Data Collection

Genetics/Genomics:

E 15 Definitions in Pharmacogenetics/ Pharmacogenomics
E 16 Qualification of Genomic Biomarkers
E 18 Genomic Sampling

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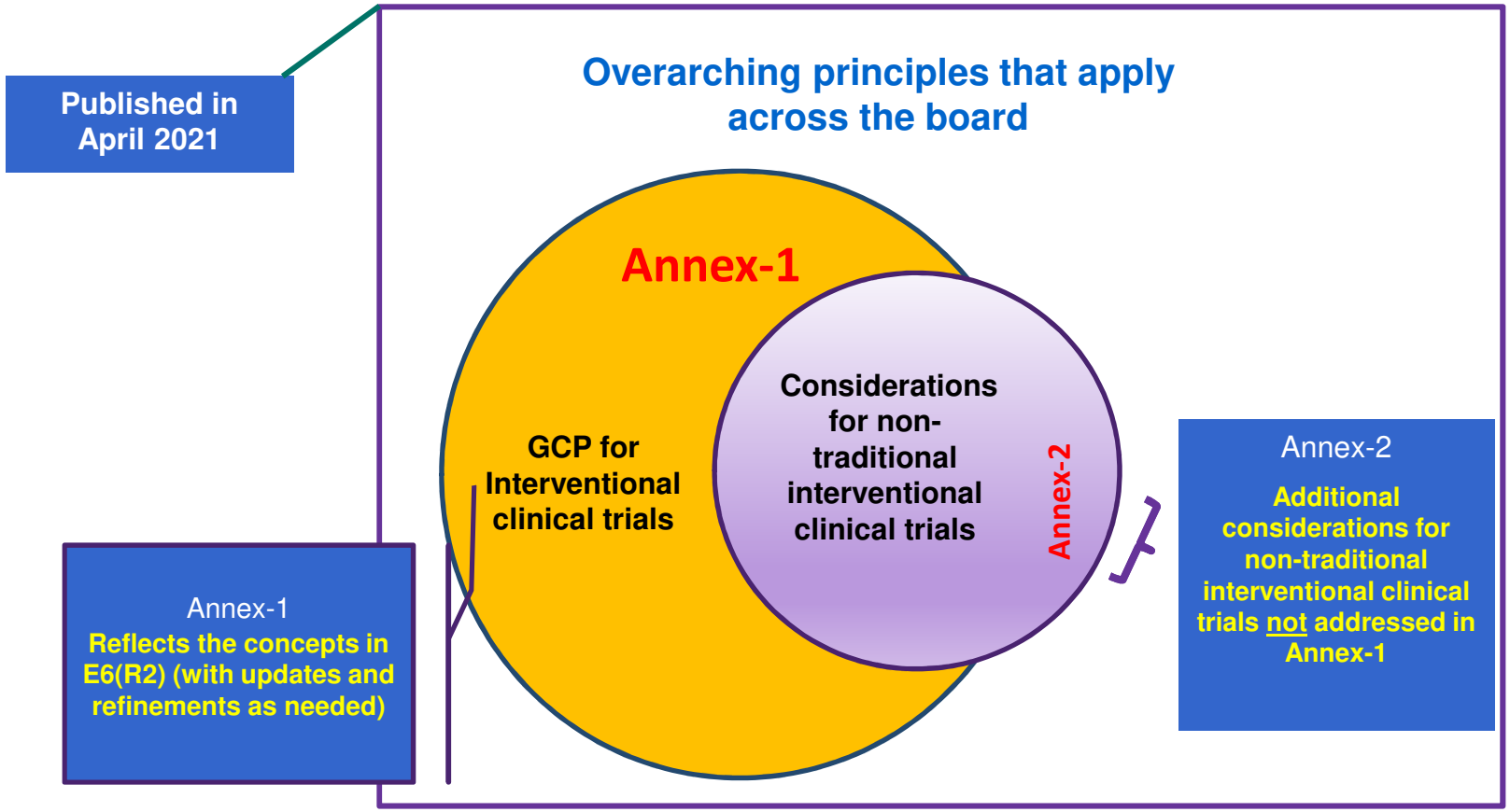
Work in Progress – Conceptual approach



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ey Considerations

Clarification that the guideline continues to apply to **interventional clinical trials on investigational products** only

Re-write of the overarching principles including key elements of human subject protection and data quality/integrity of trial results

Reiteration of the **'Quality by Design'** approach of ICH E8(R1)

Consolidation of the **'Risk-based Quality Management'** approach of ICH E6(R2)

Emphasis on **proportionality instead of unnecessary complexity** of trial-related procedures

Consideration of **current developments** in trial design, trial conduct and data sources to **future-proof** th guideline as much as possible

Stakeholder engagement

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takeholder Engagement & Transparency

Engaging representatives of academic clinical researchers and patient representatives in guideline development to ensure that stakeholders' perspectives and experiences with clinical trials and the current GCP guideline are considered in the development of ICH-E6(R3).

https://database.ich.org/sites/default/files/E6-R3_PublicEngagemenSummary_2020_0421.pdf

Direct EWG engagement with academic experts during the EWG meetings as the work on the guideline proceeds

Publication of Draft Principles on the ICH webpage in April 2021

https://database.ich.org/sites/default/files/ICH_E6-R3_GCP-Principles_Draft_2021_0419.pdf

Several public web conferences in the course of 2020/2021 (to be continued in 2022)

https://database.ich.org/sites/default/files/ICH_E6R3_WebConference_Report_Final_2021_1011.pdf

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linical Trials Transformation Initiative (CTTI) Engagement

TI conducted several efforts to help inform the International Council for rmonization of Technical Requirements for Pharmaceuticals for Human e (ICH) as it revises ICH E6 Good Clinical Practice (GCP):

- Through a global, multi-stakeholder survey with 327 research professionals from 154 countries, in-depth interviews, and a public open comment period
- CTTI issued a report outlining **the areas requiring the most focus** pertaining to sponsors, essential documents, and investigators
- CTTI co-hosted **a public event with the FDA** to help the ICH in its efforts to improve various topics within GCP
- CTTI also convened **two public web conferences** hosted by the ICH that provided an update on the progress to revise this important and impactful guideline.

https://ctti-clinicaltrials.org/our-work/quality/informing-ich-e6-renova

CH E6(R3)
raft Principles

- Published on 19 April 2021; will undergo public consultation together with Annex-1.
- The principles are applicable to clinical trials involving healthy volunteers or patients.
- They **should be considered in their totality** to assure ethical trial conduct and reliable results.
- They provide a **flexible framework** for clinical trial conduct and are structured to provide **guidance throughout the lifecycle of a clinical trial.**

ICH
harmonisation for better health

19 April 2021

ICH-E6 Good Clinical Practice (GCP)

Explanatory Note

The International Council for Harmonisation (ICH) is committed to developing timely technical requirements for pharmaceuticals for human use in a manner that is responsive to the needs of the global community. ICH is committed to stakeholder engagement and transparency in the development of its guidelines.

ICH E6 Good Clinical Practice (GCP) Guideline is widely used by clinical trial researchers beyond the membership and regional representation of ICH itself and has a significant impact on trial participants and patients. Acknowledging the wide and substantial impact of ICH E6, the ICH Management Committee is making available a draft, work-in-progress version of the updated principles that are currently under development by the ICH E6(R3) Expert Working Group (EWG). The principles are interdependent and should be considered in their totality to assure ethical trial conduct, participant safety, and reliable results of clinical trials.

The renovation of ICH E6(R2) will set out principles which will be aligned with the principles in ICH E8(R1) Revision of General Considerations for Clinical Studies. ICH E8(R1) includes a framework for designing quality into clinical trials, stakeholder engagement, trial design, proportionate trial management and focus on factors critical to the quality of trials. When complete, ICH E6(R3) will be composed of an overarching principles document (the document of which a draft is now made public), Annex 1 (addressing interventional clinical trials), and Annex 2 (providing any needed additional considerations for non-traditional interventional clinical trials). The overarching principles document and Annex 1 will replace the current ICH E6(R2).

Although the EWG's work is continuing and the group is still progressing towards *Step 2* of the ICH guidance development process (https://ich.org/page/formal-ich-procedure), the ICH Management Committee decided that sharing the draft version of the principles would facilitate transparency and common understanding. Although public comments are not requested at this time, once the updated ICH E6 Guideline achieves *Step 2* of the ICH guidance development process, public input will be invited and considered. *Step 2* will involve simultaneous publication of both the draft principles and Annex 1, along with an introduction and a glossary. Public comment will be invited at that point since the principles need to be seen and commented on alongside the details in Annex 1.

The ICH E6(R3) EWG is organizing a web conference to present the current draft of the GCP principles as a work in progress. Additionally, the general ICH process will be presented with a focus on the ICH E6(R3) development process.

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https://database.ich.org/sites/default/files/ICH_E6-R3_GCP-Principles_Draft_2021_0419.pdf

CH E6(R3)
raft Principles

Draft Principle 1: Clinical trials should be **conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki** and that are consistent with **good clinical practice (GCP) and applicable regulatory requirement(s)**

The orange italicized notes on the following slides reflect examples of current ICH E6(R3) EG discussions and considerations as work in progre

CH E6(R3)
raft Principles

Draft Principle 2: **Clinical trials should be designed and conducted in ways that ensure the rights, safety and well-being of participants**

Emphasis on

- **periodic safety reviews**
- **selection of participants** to be representative of the population to be treated
- **medical trial-related decisions** to be made by **appropriately qualified medical staff**
- compliance with **applicable privacy and data protection regulations…**

Chapter 4:

- *Although medical trial-related decisions need to be taken by the investigator, the practical interactions and the delivery of trial related medical care may, however, be carried out by appropriately qualified health care professionals in accordance with local regulations.*
- *The protocol should address the situation of early discontinuation of a clinical trial in individual trial participants and their continued treatment in this case.*

CH E6(R3)
raft Principles

Draft Principle 3: **Informed consent** is an **integral feature of the ethical conduct** of a trial. Clinical trial participation should be **voluntary** and based on a **consent process** that ensures participants are **well-informed.**

- **Freely given informed consent**, obtained and documented from every participant prior to participatio
- The informed consent process should take into consideration **relevant aspects** of the trial such as **characteristics of the participants**, the **trial design, anticipated benefit** and **risk of medical intervention(s), setting and context** in which the trial will be conducted (e.g. trials in emergency situations), and the **potential use of technology** to inform participants and obtain informed consent.

- *The length, content and comprehensibility of the patient information/consent forms for medical laypersons should be fit for its intended purpose.*
- *The withdrawal of the informed consent shall not affect the activities already carried out and the use o data obtained based on informed consent before its withdrawal.*
- *Electronic informed consent shall be possible, if permitted by regional/local legislation.*

CH E6(R3)
raft Principles

Draft Principle 4: **Clinical trials should be subject to objective review by** an **institutional review board** (IRB)/**independent ethics committee** (IEC).

- A trial should always be **conducted in compliance with the protocol** that receives prior IRB/IEC approval/favourable opinion.
- **Periodic review** of the trial **by the IRB/IEC** should also be conducted as appropriate.

Chapter 5:

- *The sponsor may consider establishing independent committees, e.g. Data Safety Monitoring Boards (DSMB), adjudication committees etc. to assess the progress of a clinical trial, including the safety dat and the critical efficacy endpoints at intervals, and to make recommendations to the sponsor (e.g. on whether to continue, modify or stop a trial).*
- *Such committees should operate on the basis of a written charter that includes well-defined, pre-specified procedures and include only members who have relevant expertise in clinical trials and no serious conflicts of interest.*

CH E6(R3)
raft Principles

Draft Principle 5: **Clinical trial processes, measures, and approaches should be proportionate to the risks to participants and to the reliability of trial results.**

- **Clinical trials should** be scientifically sound and **reflect the state of knowledge and experience with the investigational product(s); the current understanding of the underlying biological mechanism** (of both the condition and the treatment); and the **population for which the investigational product is intended**.
- There should be **periodic review of current scientific knowledge** and approaches to determine whether adjustments to the trial are needed, since new or unanticipated information may arise once the trial has begun.

➢ *Chapter 5*

➢ *In case, (an) investigator(s) deviate(s) from the protocol to eliminate (an) immediate hazard(s) to trial participants without prior IRB/IEC approval/favourable opinion, the sponsor should consider whether the protocol requires an amendment in response to the immediate hazard.*

CH E6(R3)
raft Principles

Draft Principle 6: **Clinical trials should be designed and conducted by qualified individuals**.

- Individuals with different expertise and training are needed across all phases of a clinical trial; **Individuals** involved in a trial should be **qualified by education, training, and experience to perform their respective task(s)**.

➢ *Customized training needed*

CH E6(R3)
raft Principles

Draft Principle 7: **Quality should be built into the scientific and operational design and conduct of clinical trials**

Emphasis on

- the **consideration of critical-to-quality factors** according to ICH E8(R1)
- application of a **"quality by design" approach as a multidisciplinary effort**
- implementation of strategies to prevent, detect and address serious GCP non-compliance

CH E6(R3)
raft Principles

Draft Principle 8: **Clinical trial processes, measures, and approaches should be proportionate to the risks to participants and to the reliability of trial results.**

Draft Principle 9: **Clinical trials should be described in a clear, concise, and operationally feasible protocol**

- A well-designed trial protocol is a **fundamental component for protection of participants and for the generation of reliable results.**

CH E6(R3)
ritical-to-Quality Factors According to ICH E8(R1)

A basic set of factors relevant to ensuring study quality should be identified for each study. Emphasis should be given to those factors that stand out as critical to study quality.

These quality factors are considered to be critical because, if their integrity were to be undermined by errors of design or conduct, the reliability or ethics of decision-making based on the results of the study would also be undermined.

Examples from section 7 of ICH E8(R1):

- *Competencies and training required for the study by sponsor and investigator staff, relevant to their role, should be identified.*
- *The feasibility of the study should be assessed to ensure the study is operationally viable.*
- *The protocol specifies the collection of data needed to meet the study objectives, understand the benefit/risk of the drug, and monitor participant safety.*
- *The statistical analysis plan is pre-specified and defines the analysis methods appropriate for the endpoints and the populations of interest.*

CH E6(R3)
raft Principles

Draft Principle 10: **Clinical trials should generate reliable results**

- **Quality and amount of the information** generated in a CT **should be sufficient to provide confidence in the trial's results**
- Digital systems used for clinical trial purposes should consider the factors critical to their quality in the design and be fit for purpose. To this end, **validation of systems, data protection, information technology (IT) security and user management** are important elements that should be addressed.
- **Clinical trial-related information should be retained securely by sponsors and investigators** for the required period of time and should be available to regulatory authorities upon request
- The **transparency of clinical trials** in drug development includes **registration** on publicly accessible an recognized databases, **and the public posting of clinical trial results**.
- The **principles for trial information and documentation apply irrespective of the type of media used**

CH E6(R3)
raft Principles

Draft Principle 11: **Roles, tasks and responsibilities in clinical trials should be clear and documented appropriately**

Emphasis on

- the fact that the **sponsor and** the **investigator may delegate tasks but always retain overall responsibility** for the quality and integrity of the conduct of the trial and the safety of participant
- that **agreements** should clearly define the roles, tasks and responsibilities
- that sponsors/investigators have to ensure **appropriate oversight** over delegated tasks

If sponsors acquire service providers for certain tasks of the investigator (e.g. 'home nurses'), they are responsible to determine the qualification requirements in their selection and qualification process; however, this does not release the investigators from their subsequent obligation of supervising the performance of the task.

CH E6(R3)
raft Principles

Draft Principle 12: **Investigational products** used in a clinical trial should be **manufactured in accordan** with applicable **Good Manufacturing Practice (GMP) standards** and be st**ored, shipped, and handled i accordance with the product specifications and the trial protocol**

IMP should

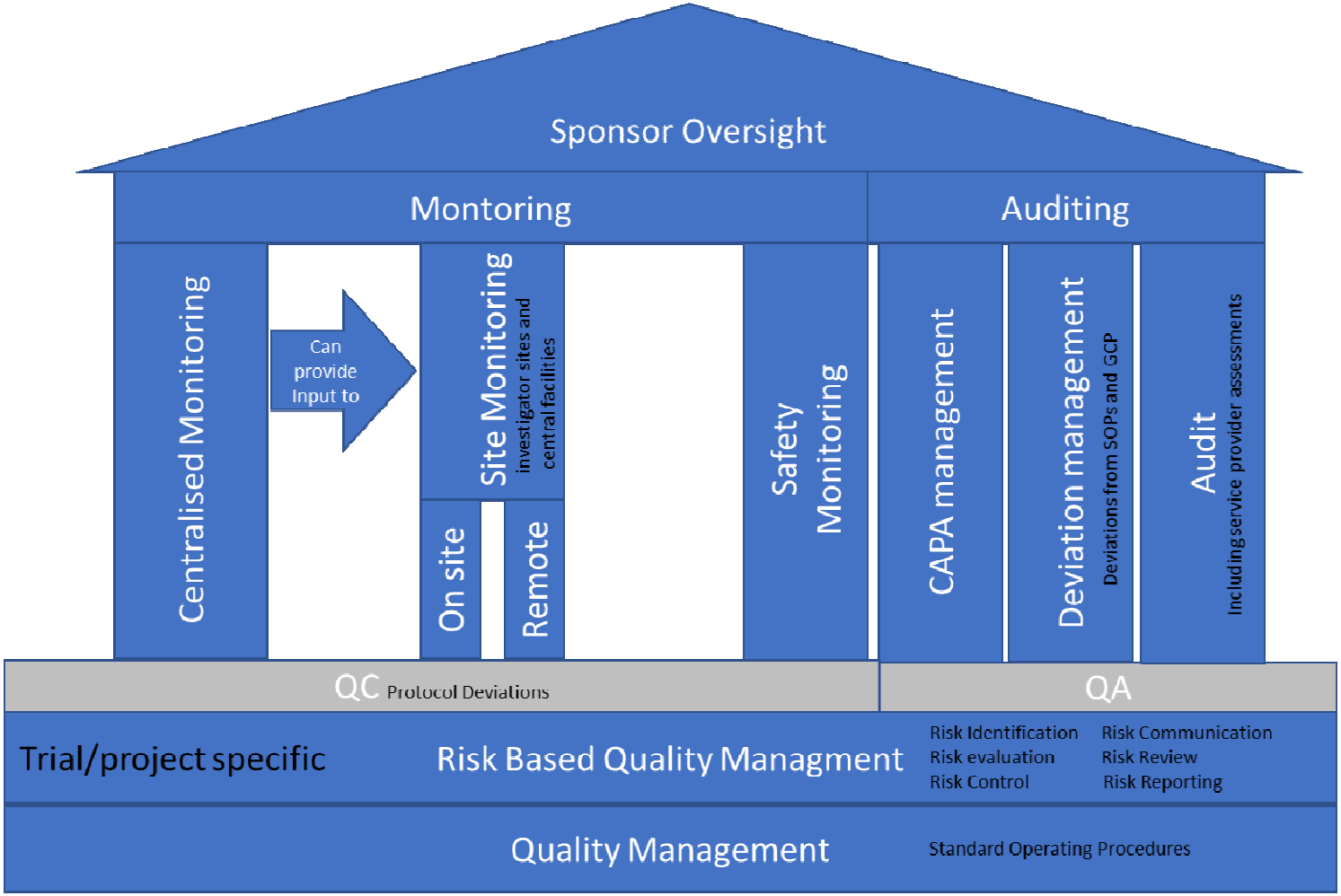
- retain its quality
- used in accordance with protocol/relevant study documents
- maintains blinding, and treatment assignment, as applicable
- be GMP-compliant manufactured and appropriately shipped and handled

CH E6(R3)
Work in Progress – Sponsor Oversight

y objectives

- Compliance with the trial protocol and related documents as well as with policies, applicable regulation and ethical standards
- Range and extent of oversight measures should be fit for purpose and tailored to the complexity of, and risks associated with the trial
- Proportionate quality assurance and quality control processes regarding trial related activities of investigators and service providers
- Adequate escalation and follow-up of issues to allow the implementation of appropriate actions in a timely manner
- Assessment of trial level decisions for their impact on participant rights, safety, and well-being and reliability of trial results

Work in Progress – Sponsor Oversight – Conceptual Approach



Source: ICH E6 Sponsor Oversight Drafting Team

CH E6(R3)
Work in Progress – Sponsor Oversight

Definition of Service Provider as overarching term in the Glossary

Restructuring of Chapter 5 to present all processes related to quality management and sponsor oversigh holistically and in relation to each other.

Revision/modernisation of the concept of monitoring

- *Distinction between centralized and site monitoring (on-site or remote)*
- *Inclusion of monitoring of key processes (e.g. those related to primary endpoints) performed outside the investigator site (e.g. central reading facilities, central laboratories)*

CH E6(R3)
Work in Progress – Data Governance

y objectives

Appropriate management of data integrity, traceability, and protection of personal information, thereby allowing the accurate reporting, interpretation, and verification of the clinical trial-related information.

Adequate fitness for purpose of digital systems and tools for data collection, management and analysis through appropriate validation, data protection, IT security and user management

Robust processes for data handling, data review, data cleaning, database lock etc. and corresponding documentation relating to those processes (closing the existing gap between E6 and E9)

Additional definitions in the Glossary as needed, e.g. 'meta data'

*New **chapter X on Data Governance** describing standards and requirement for computerized systems a data throughout the data life cycle*

CH E6(R3)

uture Anticipated Key Milestones (Status April 2022)

Expected future completion date	Milestone
l. 2022	*Update Concept Paper for Annex 2*
ug. 2022	*Plenary Working Party (PWP) Consultation Period prior to Step 1 Sign-off of Technical Document*
ep. 2022	*Step 1 Sign-off of Technical Document (Principles and Annex 1)*
ep. 2022	*Seek MC endorsement/approval of updated Concept Paper for Annex 2*
ct. 2022	*Step 2a/2b Endorsement of Technical Document (Principles and Annex 1)*
n - Feb. 2023	*Based on the approved concept paper for Annex 2, outline of the content will be developed and will seek ICH MC approval if appropriate*
lar. 2023	*Begin draft for Annex 2*
or. 2023	*Step 3 End of Public Consultation (Principles and Annex 1)*
l. 2023	*PWP Consultation Period prior to Step 3 Sign-off of Technical Document*
ug. 2023	*Step 3 Sign-off of Technical Document (Principles and Annex 1)*
ug. 2023	*Step 4 Adoption of Technical Document (Principles and Annex 1)*

hank you very much for your attention!

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