EFSPI Regulatory workshop

Session 5: Openstatsware

General GCP principles with focus on software

Sarianne Päivike, FIMEA

12.9.2024

Disclaimer

This presentation reflects the views of an individual GCP-inspector of an EU member state inspectorate

- GCP scope in statistics
- ICH E6 (GCP) evolution
- Sample of GCP requirements
- Summary

GCP scope - Does GCP apply to study statisticians?

YES!

- The computerised systems they use
  - Can you trust the system is fit for purpose
- The work they do
  - Processes followed
  - Records generated →
  - Traceability: who did when and what and **why** → apply critical thinking
  - Proof that data itself and analysis of the data is trustworthy
- → Statisticians need (documented) training on GCP- and other relevant principles as regards the activities they are undertaking

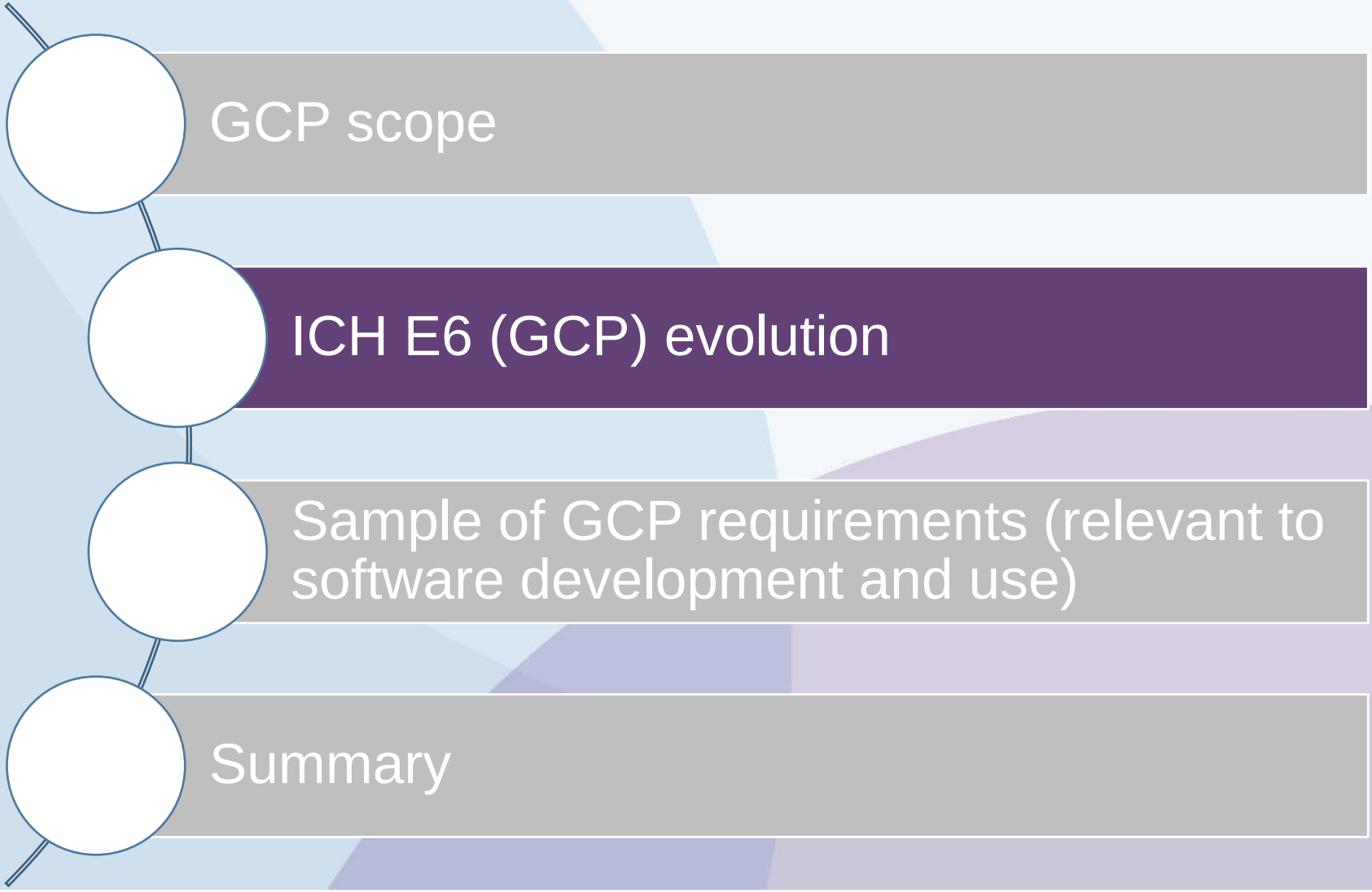
- ICH GCP E6 applies to CTs to support registration of medicinal products but widely applied for other type of trials.
  - EU clinical trial regulation 536/2014 recital (43) and Article 47: GCP should be taken into account/ clinical trial conducted in accordance with the protocol and with the principles of GCP

GCP scope – statistical activities are inspected

GCP inspection coming – what can you expect?

The pre-inspection material requested will include e.g.

- SAP and any updates, master randomization list, data flow description etc
- Organisational chart/list of **personnel involved**, list of **third parties** contracted (service providers/vendors)
- List of **standard operation procedures (SOPs)/written procedures,** study specific plans/ manuals
- List of all **electronic/computerised systems applied** (use/functionality, version)**, system owner** (host)**, validation status**, system interfaces, quality control steps, audit trails available


GCP scope
ICH E6 (GCP) evolution
Sample of GCP requirements (relevant to software development and use)
Summary

ICH E6 (GCP) evolution

- E6: Good Clinical Practice (GCP) – 1996
  - Principles (section 2), Ethics Committee (3), Investigator (4), **Sponsor (5),** Protocol (6), Investigator's Brochure (7), Essential documents (8)
- E6 (R2) – Nov 2016 (in force in Europe in June 2017)
  - Integrated addendums in sponsor section 5 e.g.:
    Quality management new 5.0 – identification of critical processes and data, risk management
    Sponsor oversight 5.2.2 Addendum (work can be delegated but not responsibility)
    Electronic data handling 5.5.3 Addendums: approach to validation based on a risk assessment, the SOPs should cover system setup, installation, and use

ICH E6 (GCP) evolution cont.

- Diverse & complex study types/ data sources →
- ICH E6 (R3) in development
  - Modernization, adaptability, flexibility
  - More focus on risk proportionate/ risk-based approaches

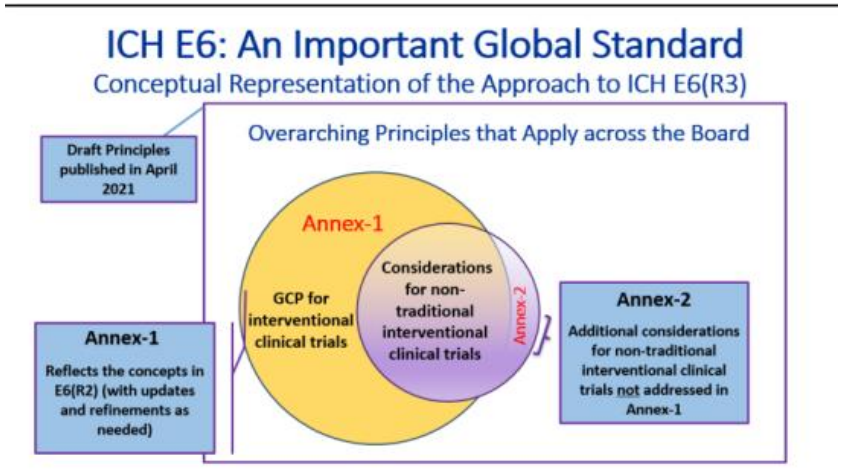
https://www.ich.org/news/ich-reflection-gcp-renovation-modernization-ich-e8-and-subsequent-renovation-ich-e6

- Encourage **fit-for-purpose** approaches.
  - **Proportionality and risk-based** approaches with a focus on the clinical trial's critical-to-quality factors whose integrity is fundamental to safety of participants and the **reliability of trial results;**

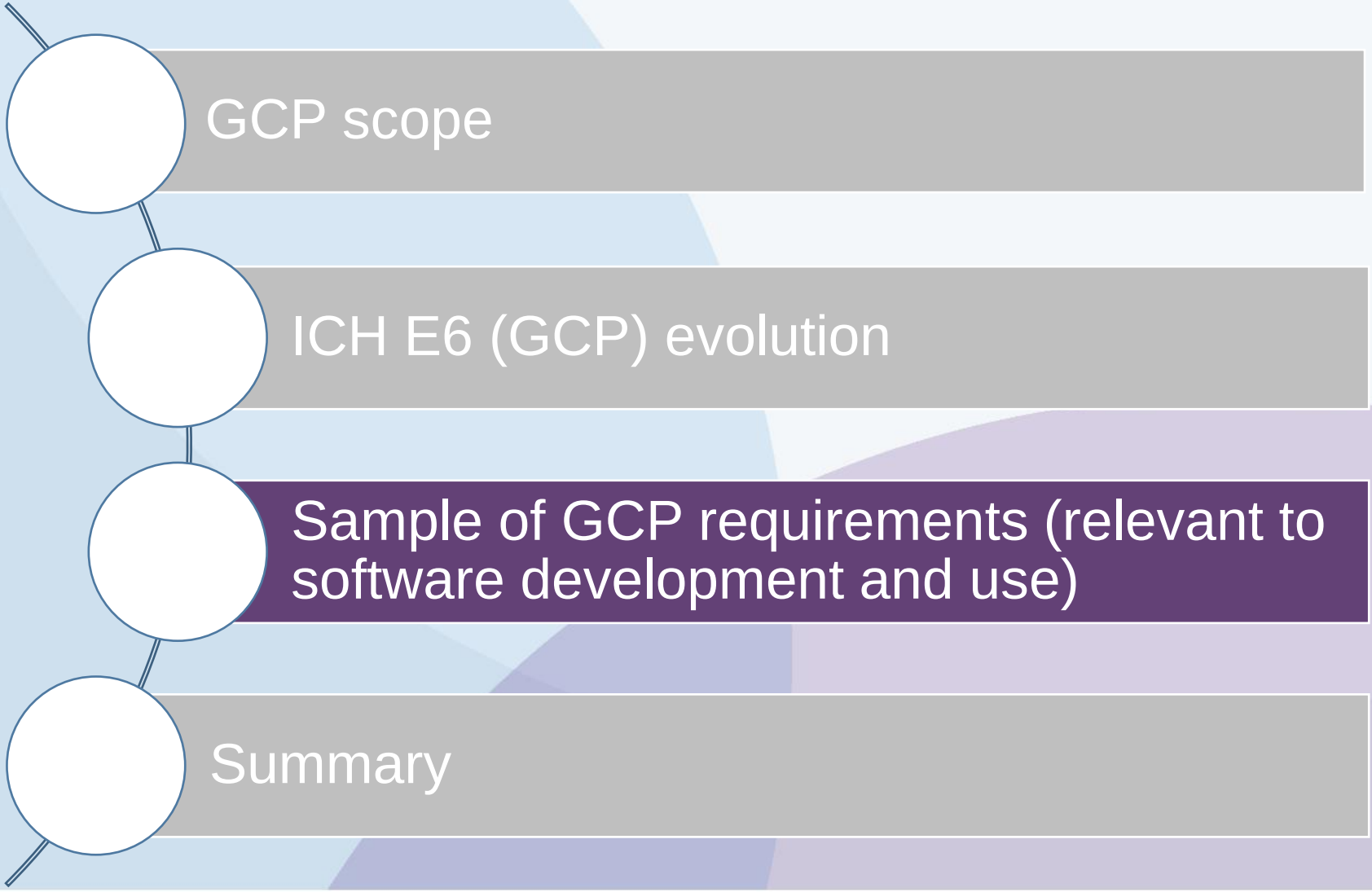
ICH E6 (GCP) evolution cont.

New structure – much of the old, but also new:

- I - Intro
- II – Principles of ICH GCP (public consultation ended and draft updated)
- III Annex 1 – interventional trial considerations (public consultation ended, finalization expected within 2024)
    - 1. IRB/IEC
    - 2. Investigator
    - 3. Sponsor
    - 4. Data governance (inv and sponsor relevant)
- Annex 2 – under development: additional considerations for alternative trial types (decentralised clinical trials, pragmatic elements, real-world data, digital health technologies)
- Glossary
- Appendices
    - A. Investigator's Brochure
    - B. Clinical trial protocol
    - C. Essential records



ICH E6 GUIDELINE FOR GOOD CLINICAL PRACTICE (GCP) – UPDATE ON PROGRESS PUBLIC WEB CONFERENCE REPORT MAY 18 & 19, 2021


GCP scope
ICH E6 (GCP) evolution
Sample of GCP requirements (relevant to software development and use)
Summary

Sample of GCP requirements

Draft E6(R3) II **Principles** apply for all trials/ processes: re-arranged/ more details

9. Clinical trials should generate reliable results [E6(R2) 2.10, 2.13]

- Computerised systems used in clinical trials should be fit for purpose, and factors critical to their quality should be addressed in their design or adaptation for clinical trial purposes

- Essential records should be retained securely by sponsors [and investigators] for the required period, available to regulatory authorities (monitors, auditors, IEC/IRB) upon request to enable evaluation of the trial conduct in order to ensure the reliability of trial results

10 New in principles: Roles and responsibilities should be clear and appropriately documented

- Where activities have been transferred or delegated to service providers, the responsibility for the conduct of the trial, including quality and integrity of the trial data, resides with the sponsor [or investigator, respectively]

  → even if not developed a statware itself, the sponsor is responsible for ensuring it is appropriate for the trial

Sample of GCP requirements

Draft E6(R3) Annex, **3 Sponsor** – applicable to any stat software

3.16 Data and records/ 3.16.2 Statistical Programming and Data Analysis

- New - read in conjunction with ICH E9 Statistical Principles
- More specific:
  - The sponsor should ensure that appropriate and documented quality control of statistical programming and data analysis is implemented
  - The sponsor should retain the statistical programming records that relate to the output contained or used in reports of the trial results, including quality control/validation activities performed. Outputs should be traceable to the statistical software programs, and they should be dated and time stamped and protected against any changes

Sample of GCP requirements

Draft E6(R3) Annex, **3 Sponsor –** how applied if “service provider” is an openstatware developer?

3.6.7 The sponsor is responsible for assessing the suitability of and selecting the service provider to ensure that they can adequately undertake the activities
→ justification for choosing an openstatware?

3.6.8 The sponsor should have access to relevant information (e.g., SOPs and performance metrics) for selection and oversight of service providers
→ transparency of software development records?

3.10 Quality management → risks with using an openstatware are manageable?

3.11 Quality Assurance and Quality Control (including auditing strategy)
→ if not audited, the statware developer’s records are assessed?

Sample of GCP requirements

Draft E6(R3) Annex, **3 Sponsor –** applied if “service provider” is an openstatware developer?

Draft 3.6.3 The sponsor should obtain … where applicable, service provider’s **agreement**

- to **retain the essential records** [e.g. of validation] for the required retention period in accordance with applicable regulatory requirements
- to permit monitoring, auditing and inspections by sponsors/ regulatory authorities (domestic and foreign) including **providing direct access to source records and facilities**, including to those of service providers.

→ EU CTR 536/2014: archiving period 25 years

Draft 3.6.6 Any service provider used to perform clinical trial activities should implement appropriate quality management and **report to the sponsor any incidents** that might have an impact on trial results.

→ Openstatware developer doesn’t alert sponsor? Sponsor has to track (critical) updates?

Sample of GCP requirements

Draft E6(R3) Annex, **4 Data governance**

4.3 Computerised Systems – applicable to any stat software

The responsible party should ensure that those developing computerised systems for clinical trials are aware of the intended purpose and the regulatory requirements that apply to them

- Training (of users) [multilingual in programming languages?]
- Security (user mgmt., security patching, system monitoring etc)
- Validation
  - Approach = based on a risk assessment that considers the intended use of the system
  - Systems should be appropriately validated prior to use, adequate change control procedures
  - Where relevant, procedures should cover the following: system design, system requirement, functionality testing; configuration, release; setup; installation and change control (until decommissioning)
- System failure (contingency procedures)
- Technical support
  - .., document, evaluate and manage issues with the computerised systems (e.g., raised by users), there should be periodic review of these cumulative issues to identify those that are repeated and/or systemic
  - Defects and issues should be resolved according to their criticality. Issues with high criticality should be resolved in a timely manner.

Sample of GCP requirements – see also

EMA/226170/2021 Guideline on computerised systems and electronic data in clinical trials (9 March 2023)

https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-computerised-systems-and-electronic-data-clinical-trials_en.pdf

- Section 4.10 Validation of systems,
- Annex 2 Computer system validation

EMA GCP Q&A B. GCP-matters (with refs to ICH E6(R2))

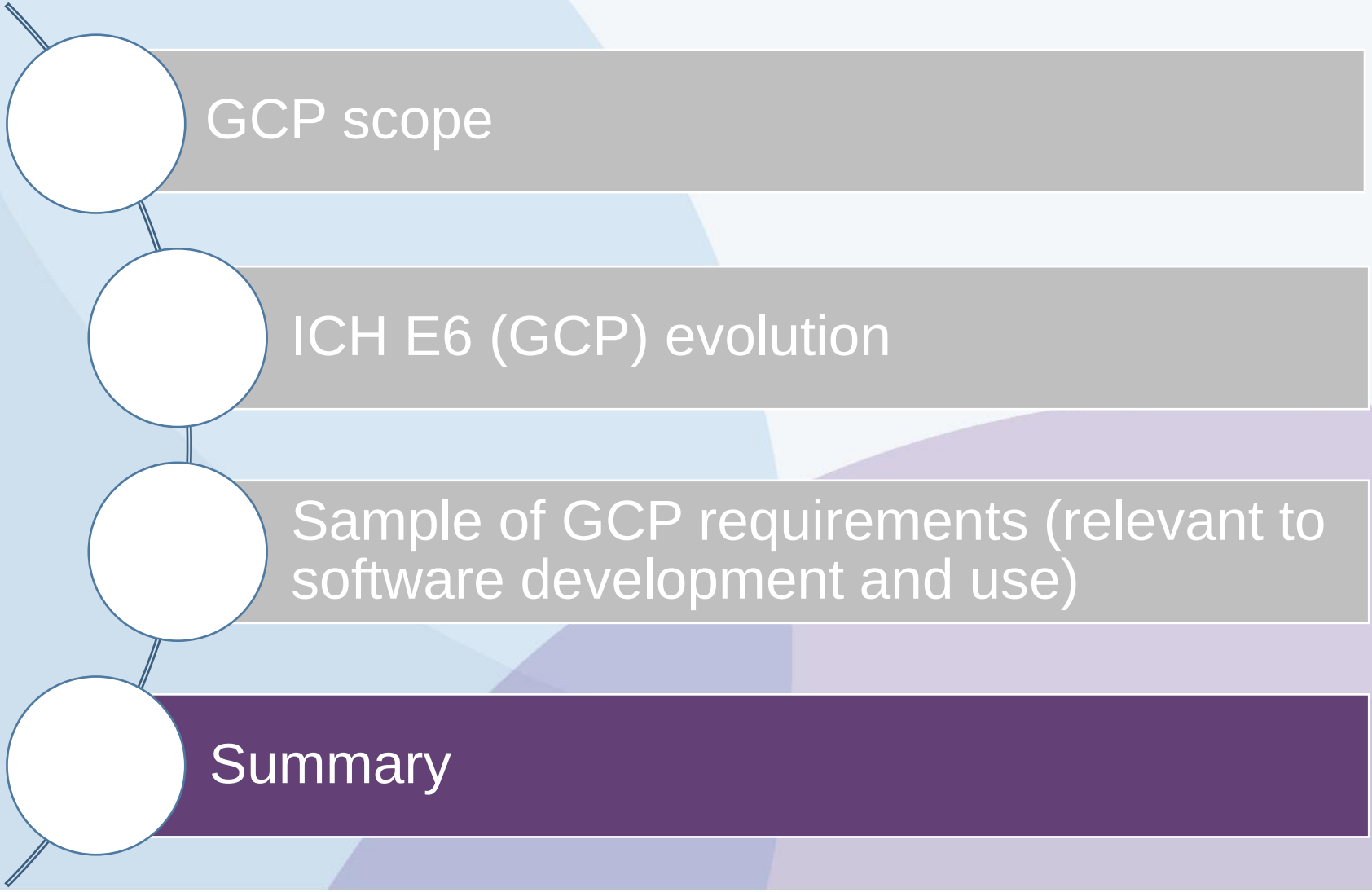
https://www.ema.europa.eu/en/human-regulatory-overview/research-development/compliance-research-development/good-clinical-practice/qa-good-clinical-practice-gcp

8. What are the pitfalls to be aware of regarding contractual arrangements with vendors for electronic systems in connection with clinical trials? Rev. March 2022

9. What is the level of validation/qualification needed to be performed by a sponsor when using an electronic system previously qualified by a provider? What documentation is required to be available for inspections? Rev. April 2020

Amendment - April 2020

What should a sponsor do if the sponsor intends to submit an MAA without being able to provide documentation of qualification activities for clinical trial computerised data collection tools/software and access for inspectors is not ensured contractually?


GCP scope
ICH E6 (GCP) evolution
Sample of GCP requirements (relevant to software development and use)
Summary

Summary

For any statware:

- Define system, assess/control/mitigate risks, test system upon predetermied specifications, confirm it is fit for purpose
- Remember to re-review risks regularly; new system defects identified, new versions validated
- Validation records are requested in audits/inspections = show and tell. How did you do it yourself or assess the performance of a provider (did you go sufficiently deep)?
- Maintain a quality system to manage computerised systems (define standards to support the process)
- Document (justified) decision making!

(w) When using computerised systems in a clinical trial, the sponsor should:

(i) have a record of the computerised systems used in a clinical trial. This should include the use, functionality, interfaces and validation status of each computerised system, and who is responsible for its management should be described. The record should also include a description of implemented access controls and internal and external security measures;

(ii) ensure that the requirements for computerised systems deployed by the sponsor (e.g., requirements for validation, audit trails, user management, backup, disaster recovery and IT security) are addressed and implemented and that documented procedures and adequate training are in place to ensure the correct development, maintenance and use of computerised systems in clinical trials (see section 4). These requirements should be proportionate to the importance of the computerised system and the data or activities they are expected to process;

(iii) maintain a record of the individual users who are authorised to access the system, their roles and their access privileges:

Thank you! Kiitos!

Support process when something goes wrong?

Qualifications of the software developers?

Sigma (original) or delta (change) validation records available?

Test and production configurations separate?

CAPA procedures?

Are the testing records sufficiently granular?

Were all user/functional requirements tested and recorded according to plan/ test scripts?

Unequivocal acceptance criteria?

Are records in human readable/evaluable format?

Installation/admin manuals/ user guides available?

Quality and details of validation reports produced?

High pace of changes in the software?

Traceability when there are thousands of testers?

Tester is not the author of the test case?

Validation of the system installation/ performance in sponsor ICT-environment?

Testers with pure intentions?

Who has admin/ edit rights?

Were the critical functionalities identified and passed testing before release, nice-to-have functionalities tested - passed or failed?

Software version change – do the analysis results change (reproducibility)?

Is there a formal change control process?

Accurate and unambiguous time stamps?

fimea