HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

GCP inspections - changes brought about by the CTR

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Topics to discuss

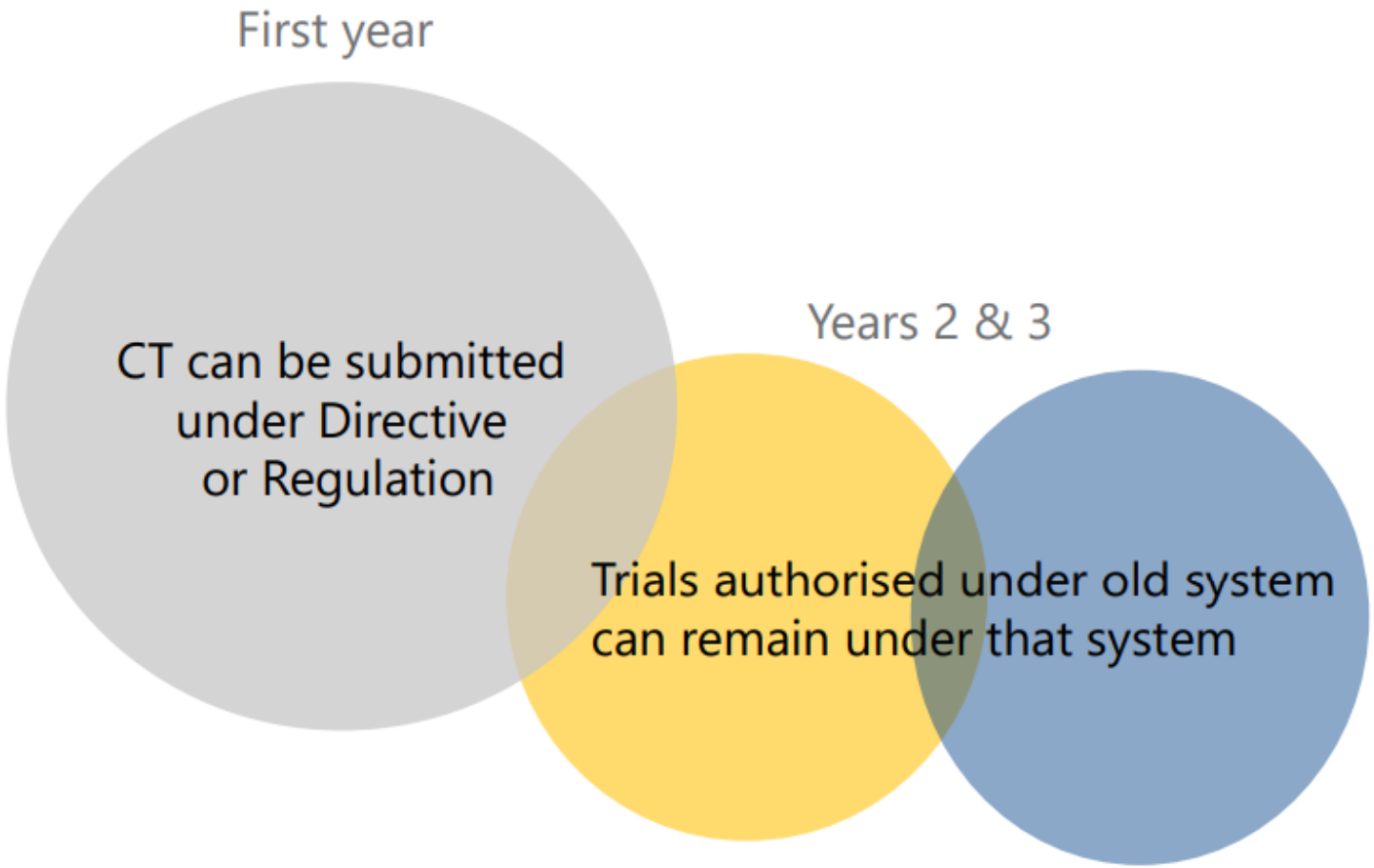
Transition period of legislation

Risk proportionate approaches

Publication of inspection reports

Inspection powers and Union Controls

Transition period



All CTs to switch to new Regulation 3 years after implementation. Voluntary earlier transition possible

CTFG Best Practice Guide for sponsors of multinational clinical trials with different protocol versions approved in different Member States under Directive 2001/20/EC that will transition to Regulation (EU) No. 536/2014

Risk proportionate approach

Increased focus on risk-proportionate approaches in clinical trials

- Recommendations (25 April 2017) published under Chapter V of Eudralex Volume 10 https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2017_04_25_risk_proportionate_approaches_in_ct.pdf
- To be read in conjunction with 2013 reflection paper published by EMA/CTFG/GCP IWG https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-risk-based-quality-management-clinical-trials_en.pdf

Introduction of low-interventional trials

- Note: Risk adaptations may be applied to any type of clinical trial, where appropriate

Inspections take these aspects into account

- Important adaptations proportionate and appropriate
- Documentation (e.g. risk assessment and mitigation plans) will be reviewed to aid in determining appropriateness

Risk proportionate approach

'Low-intervention clinical trial' means a clinical trial which fulfils all of the following conditions:

- the investigational medicinal products, excluding placebos, are authorised;
- according to the protocol of the clinical trial,
  - the investigational medicinal products are used in accordance with the terms of the marketing authorisation; **or**
  - the use of the investigational medicinal products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products in any of the Member States concerned; **and**
- the additional diagnostic or monitoring procedures **do not pose more than minimal additional risk or burden** to the safety of the subjects compared to normal clinical practice in any Member State concerned

As outlined in article 2(3) of Reg 536/2014

Risk proportionate approach

Document in risk assessment and mitigation plan

Risk proportionate approach - CTR

Investigator's Brochure

- Use of SmPC as IB (Annex I, Section E, (28) and (29))

IMPD

- Simplified IMPD by referring to other documentation (e.g. IB and SmPC) (Annex I, Section G)

Insurance

- No additional insurance for low-interventional trials if possible damage covered by compensation system already in place (Article 76(3), Annex I, Section O)

Labelling of IMP (Annex VI)

Informed consent

- Cluster trials (Article 30)

Risk proportionate approach – Recommendations of Expert Group

Safety reporting

- All adverse events should be reported to the sponsor, **unless justified in the protocol and supported by the risk assessment outcome**.
- Risk adaptations per Article 41;
  - selective recording and reporting of adverse events (e.g. use of authorised product with well established profile),
  - adaptations to immediate reporting from the investigator to the sponsor, for certain serious adverse events (e.g. high morbidity/mortality trials where endpoints meet the criteria of SAEs).
- Annual safety report should describe risk adapted approach and any SAE reported by the investigator to the sponsor

Risk proportionate approach – Recommendations of Expert Group

IMP management, traceability and accountability

- Extent of drug accountability documentation varies depending on authorisation status of IMP, use within indication, trial design (blinding, complexity), who is administering the product, toxicity of IMP and supply chain.
- For low interventional trials, routine pharmacy documentation may be sufficient.
  - Important risk considered and documented
  - Amounts prescribed and taken should be documented in the patient notes
- Article 51(2) of CTR requires information on the provisions for traceability to be contained in the application dossier.
- Temperature monitoring/protection from light may also be adapted depending on risk

Risk proportionate approach – Recommendations of Expert Group

Monitoring

- Risk-assessment required to determine extent and nature of monitoring
  - Any reduction of monitoring must be proportionate to risk
  - Monitoring plan should be developed accordingly
  - On-site, remote and centralised monitoring, as well as review of metrics and central medical review of trial data are options
  - On-site monitoring envisaged to remain a requirement in most trials
- These activities may be supported by trial oversight structures such as Data Monitoring Committees, Trial Management Groups, and Trial Steering Committee
- Escalation pathways need to be in place, and the monitoring plan amended as new risks arise

Risk proportionate approach - Recommendations of Expert Group

Trial Master File

- The TMF shall take into account all characteristics of the clinical trial including in particular whether the clinical trial is a low intervention clinical trial
- Risk adaptations include:
  - Combining documents if one document serves many purposes (e.g. signature and delegation log, screening and recruitment log)
  - Absence of documents (e.g. lack of IB as SmPC used, CSR replaced by medical journal publication, IMP supplied via routine routes (e.g. community pharmacy) may not require additional accountability)

Publication of inspection reports

Inspection reports required to be published on CTIS (public part)

- Published once inspection is completed
- In line with aims of increased transparency

Redaction guideline in draft (co-ordinated by the EMA)

- Understood staff names will be redacted with the exception of PI
- National Competent Authorities (NCAs) likely conducting redaction
- Process still in draft – not clear in relation to other particulars

Sponsors are responsible to provide in CTIS also inspection reports for inspections carried out by third countries authorities.

Inspection powers and Union controls

Inspection powers

- Power to interview subjects directly, in particular where it is suspected informed consent was not obtained
  - Anticipated this would be used very rarely
- Administrative mechanism for inspectors from other MSs to inspect trials conducted in Ireland
  - Already an informal system in place, and if needed may accompany HPRA inspectors as experts
- Other measures under discussion

Union Controls

- DG SANTE of European Commission check MSs supervise compliance with CTR, and compliance of regulatory systems relevant to trials conducted outside the EU
  - HPRA volunteered for pilot project earlier this year

Conclusion

Inspection conduct will take into account risk-adaptive approaches

Important such approaches used appropriately and rationale documented

Increased transparency per the CTR, including publication of inspection reports

Introduction of some changes to inspection powers and Union Controls