Transition: to switch or not to switch?

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Content

Transition period

- Clinical Trial Regulation (CTR) to become applicable on January 31, 2022
  → start and conduct of a clinical trial under Clinical Trial Directive (CTD) allowed during transitional period in order to facilitate the transition

- All new trials need to be submitted under CTR 1 year after the date of application of CTR (January 31, 2023)
  → within the first year choice to submit new trials under CTD or CTR

Transition period

- Transition period for trials submitted under CTD to last 3 years after the date of application of CTR (January 31, 2025)
  - → trials can continue under CTD until end of 3-year transitional period, trials under CTD still ongoing on January 31, 2025 have to transition to CTR
  - → transition possible from day of entry into application of CTR until end of transition period

- Application to transition ongoing trials from CTD to CTR needs to be submitted in CTIS in time for full assessment to be completed before end of transitional period

- Only active clinical trials without any pending/ongoing assessment in any of the EU/EEA countries eligible for a switch from CTD to CTR (temporary halted trials or trials for which a substantial amendment was submitted not eligible until procedure is completed)

Transition period

- Only trials that comply with CTR as regards their substantial requirements eligible for a switch from CTD to CTR
  - → sponsor's responsibility to assess this compliance
  - → substantial amendments under CTD used to make trial compliant with CTR, sponsor to specify the intention to align the trial with CTR
  - → Member states able to take corrective measures as foreseen in article 77 of CTR if a trial which has switched from CTD to CTR does not comply with CTR

Transition period

- Trials started prior to application date of CTD and not in line with CTD cannot continue after entry into application of CTR
  - → sponsor to assess whether those trials are interventional or merely observational → if interventioal and impossible to terminate due to patient safety or scientific soundness, sponsor to apply for a new authorisation of that trial under CTR
  - → trials in line with CTD but started before application date of CTD can be transitioned

Submission of an application for transition

- Initial application (art. 5 CTR) to CTIS
- Based on latest authorized version of dossier under CTD
- New documents: cover letter, CTR application form (Part I and II) in CTIS, harmonised or consolidated protocol for multi-country trials
  - → harmonised protocol: identical protocol including identical trial procedures in all countries approved across all EU member states
  - → consolidated protocol: differences in procedures in different member states, but protocol itself identical (member state-specific issues outlined in protocol or in annex to protocol)
- Additional mandatory documents: all part I and II documents need to be submitted in their latest approved version (not necessary to prepare new versions for CTIS submission)

Cover letter requirements application for transition

- Declaration protocol does not include substantial differences to version(s) approved in each MSC as well as listing of dates of authorisation in each MSC (CTFG template declaration)

- Declaration all other part I documents identical to the ones authorised under CTD, including a listing of the versions of IB and IMPD (or SmPC) approved under CTD in all MSCs when transitioning

- Possibility to confirm the same for part II documents: declare which version of which documents approved per MSC

Protocol requirements application for transition

- Sponsor responsible for ensuring transitioned protocol of multinational clinical trial won't contain any substantial differences across Member states concerned to authorised protocol in all Member States where ongoing

  → transitioned protocol not subject to assessment by RMS or any MSC

- If significant differences across Member States, authorisation of harmonised or consolidated protocol under CTD required prior to transition

- Aspects of the protocol to be the same across all MSCs for transition of multinational clinical trial protocol: EudraCT number, trial title, protocol version number, primary objective, primary endpoint, definition of end of trial as well as main inclusion and exclusion criteria

Scenarios

- Harmonised protocol already approved in all MSC
  → Transition to CTR can proceed by submitting initial application to CTIS without prior substantial amendment under CTD + sponsor to declare in cover letter this protocol is version approved in al MSCs under CTD

- Non-substantial differences (e.g. administrative differences) across MSC in authorised protocol versions
  → Consolidated or harmonised version may be submitted / transitioned as new single version + sponsor to declare in cover letter there are no substantial differences in content to latest versions approved in respective MSCs under CTD

Scenarios

- Substantial differences among MSCs in aspects of protocol that should be the same for transition (EudraCT number, trial title, protocol version number, primary objective, primary endpoint, definition of end of trial, main inclusion and exclusion criteria)
  → Substantial amendment to be submitted under CTD to NCAs and ethics committees in Member states where ongoing in order to harmonise those protocol aspects across MSCs, prior to transition to CTR

- Sponsor wishes to harmonise protocol so all trial procedures are the same across all MSCs and this would result in substantial change with respect to authorised protocol version in a MSC
  → Substantial amendment under CTD required in that Member state

- Trials in Voluntary Harmonisation Procedure (VHP)
  → VHP's Ref-NCA to be indicated as Reporting Member State, also for trials partly in VHP

Transparency requirements

- Transparency requirements and publication rules applicable to all documents submitted in CTIS
- Documents under CTD outside of CTIS not destined to be made public initially not to fall retroactively under transparency requirements (inspection reports, notifications)
- Any new document produced as of moment of transition of a trial to fully fall under transparency rules of CTR
- Trials initially started under CTD and switched to CTR to comply with all obligations of CTR (e.g. publication of summary of results, notifications and, if applicable, Clinical Study Report)

Useful links

- Transition of Clinical Trials to Regulation (EU) No. 536/2014: 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 https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2018_05_CTFG_Best_Practice_Guide_for_sponsors_of_transition_multinational_clinical_trials.pdf

- Draft - Questions and Answers Document - Regulation (EU) 536/2014 – Version 4 (July 2021) https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf

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