THE NEW SUBMISSION PROCESS

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Info day for SMEs – The New Clinical Trial Regulation

Introduction

- Clinical Trials Regulation and its Annexes
- Submission of Clinical Trial Application
- Submission of Substantial Modification
- Submission of Safety Reports (Annual Safety Report, SUSAR)
- Submission of Urgent Safety Measures
- Reporting of Unexpected Events which affect the Benefit-Risk Balance (Other reporting obligations relevant for subject safety)
- Reporting of Serious Breaches
- Submission of Clinical Trial Results
- Abbreviations

Clinical Trials Regulation

- Greater level of harmonisation
- Simplified submission
- Seven Annexes covering
  - CTA dossier
  - IMP labeling
  - safety reporting
- Transparency requirements

Clinical Trials Regulation

- submission of one application dossier to all the Member States concerned (MSC) through a single submission portal

Annexes to CTR

- I: Application Dossier for the Initial Application
- II: Application Dossier for Substantial Modification
- Annex III: Safety Reporting
- Annex IV: Content of the Summary of the Results of the Clinical Trial
- Annex V: Content of the Summary of the Results of the Clinical Trial for Laypersons
- *Annex VI: Labeling of IMPs and AMPs*
- *Annex VII: Correlation table (CTR vs Dir 2001/20/EC)*

Submission of the Initial Application

- CTR Article 5 + Annex I
- Submission through EU Portal only
- Selection of rMS
- rMS notifies Sponsor and other CMS that is rMS within 6 days
- Low-interventional CT: the Sponsor shall propose as rMS that MS, where the use of IMP is evidence-based

Submission of the Initial Application

- Part I:
  - Cover letter, EU application form, Protocol, IB, documentation relating to GMP compliance for the IMP, IMPD, AMP dossier, SA and PIPs, Labeling
- Part II:
  - Recruitment Arrangements, SI / ICF / ICF Procedure, Suitability of the Investigator, Suitability of the Facilities, Proof of Insurance Cover or Indemnification, financial and Other Arrangements
- Other:
  - Proof of Payment of Fee, Proof that Data will be processed in Compliance with Union Law on Data Protection

Submission of the Initial Application

- Mononational or Multinational (additional MS can be added only after the notification date of the initial authorisation decision – Article 14)
- Submission of Part I or Submission of Part I and II or Submission of Part II (<2 years after Part I)
- One contact point in each MS
- One payment per activity per Member State
- Resubmission = new application process

Validation of the Initial Application

- *Does the CT falls within the Scope of CTR?*
- *Is the CTA complete in accordance with Annex I?*
- rMS shall validate the CTA within 10 days (CMS communicate within 7 days)
  - No consideration to Validation → Evaluation process
  - There are consideration to Validation → Sponsor has 10 days to comment /complete the submission →
- rMS shall notify the Sponsor within 5 days
  - The CTA complies with the requirements → Evaluation process
  - The CTA not completed – deemed to have lapsed

Submission of the Substantial Modification

- CTR Article 15 + Annex II
- Submission through EU Portal only
- rMS = rMS for the initial procedure
- rMS (in case of Part II CMS) shall validate the CTA within 6 days
  - No consideration to Validation → Evaluation process
  - There are consideration to Validation → Sponsor has 10 days to comment /complete the submission →
- rMS shall notify the Sponsor within 5 days
  - The CTA complies with the requirements → Evaluation proces
  - The CTA not completed – deemed to have lapsed

Submission of the Substantial Modification

- Cover letter, modification application form, Description of the modification, Supporting Information, Update of EU Application Form, Proof of Payment of Fee

Submission of the Safety Reports

- Annex III
- Reporting of SUSARs
- Annual Safety Reporting

Submission of Urgent Safety Measures

- Article 54
- Where an unexpected event is likely to seriously affect the benefit-risk balance, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects
- The sponsor shall notify MSC, through the EU portal, of the event and the measures taken
- That notification shall be made without undue delay but no later than 7 days from the date the measures have been taken

Submission of Other reporting obligations relevant for subject safety

- Article 53
- The sponsor shall notify MSC through the EU portal of all unexpected events which affect the benefit-risk balance of the CT
- That notification shall be made without undue delay but no later than 15 days from the date the sponsor became aware of this event
- The sponsor shall submit to the Member States concerned, through the EU portal, all inspection reports of third country authorities concerning the CT
- When requested by a MSC, the sponsor shall submit a translation of the report or of its summary in an official language of the Union indicated in the request

Submission of Serious Breaches

- Article 52
- The sponsor shall notify MSC about a serious breach of this Regulation or of the version of the protocol applicable at the time of the breach through the EU portal without undue delay but not later than 7 days of becoming aware of that breach
- For the purposes of this Article, a ‘serious breach’ means a breach likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial

Submission of CT Results

- Annex IV: CT information, Subject disposition, Baseline characteristics, Endpoints, Adverse Events, Additional Information
- Annex V (for laypersons): CT identification, Name and contact details of the sponsor, General information about the clinical trial, Population of subjects, Investigational medicinal products used, Description of adverse reactions and their frequency, Overall results, Comments on the outcome, Indication if follow up CT are foreseen, Indication where additional information could be found
- the start, the end of the recruitment of subjects and the end should be notified
- In accordance with international standards, the results should be reported within 1 year from the end of CT

Abbreviations

AMP	Auxiliary Medicinal Product
CT	Clinical Trial
CTA	Clinical Trial Application
CTR	Clinical Trial Regulation
EU	European Union
GMP	Good Manufacturing Pracitce
IB	Investigator`s Brochure
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
MS	Member State
MSC	Member State concerned
PIP	Paediatric Investigational Plan
rMS	reporting Member State
SA	Scientific Advice
SI	Information for Subject
SUSAR	Suspected Unexpected Serious Adverse Reaction