EU Clinical Trial Regulation (536/2014)
CTR and CTIS

what you need to know

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CTR applicable 31 January 2022

Two months and 21 days to go .....

Content

1. Transition period
2. CT application (documents part I and part II)
3. Clinical Trial Information System (CTIS)
4. Transparancy rules
5. CCMO guidance Review Site Suitability

What does this mean for ongoing clinical trials on January 31, 2022?

→Clinical trials authorized before Directive 2001/20/EC (application submitted before March 2006)

- The sponsor should determine whether the clinical trial still fulfills the definition of a clinical trial or is a non-interventional study.
- Non-interventional study can continue.
- Interventional clinical trial:
  - ✓ Terminate clinical trial; OR
  - ✓ Submit substantial modification and register clinical trial in EudraCT/ToetsingOnline before 31 January 2022; OR
  - ✓ Submit full application through CTIS as from 31 January 2022

→ Clinical trials authorized under Directive 2001/20/EC

- Clinical trial can continue under current legislation during transition period

→VHP dossiers

- VHP has ended. These multinational clinical trials can be switched to CTR regime following the transition arrangements (Q11 of Q&A CTR, Eudralex volume 10)

What does this mean for new clinical trials on January 31, 2022?

Sponsor can choose during the 1st year of transition period:

→Going for current legislation (EudraCT/ToetsingOnline)

→Going for new legislation CTR (CTIS)

Transition period – up to 31 January 2024

- 1st year: initial applications according to old and new legislation
- 2nd year: all initial applications according to Clinical Trial Regulation
- 3rd year: all applications (initial and substantial modifications) according to Clinical Trial Regulation
- 4th year and later: all ongoing clinical trials approved under legislation 2001/20/EC should be governed by Clinical Trial Regulation

POLL

Welk percentage van verwachte nieuwe indieningen van geneesmiddelenonderzoek in 2022 denk jij dat jouw organisatie indient via CTIS?

- ❑ 0%
- ❑ 25%
- ❑ 50%
- ❑ 75%
- ❑ 100%

Part I – central

Part II - national

One application dossier EU-portal (CTIS)

- ❑ Cover letter **(T)**
- ❑ Protocol (incl. synopsis lay person in Dutch **(T)**)
- ❑ Statement GDPR compliance
- ❑ Investigator's Brochure
- ❑ IMPD/SmPC – IMPs and auxilliairy medicinal products
- ❑ GMP compliance/certificates
- ❑ Scientific advice and PIP (if applicable)
- ❑ Labels

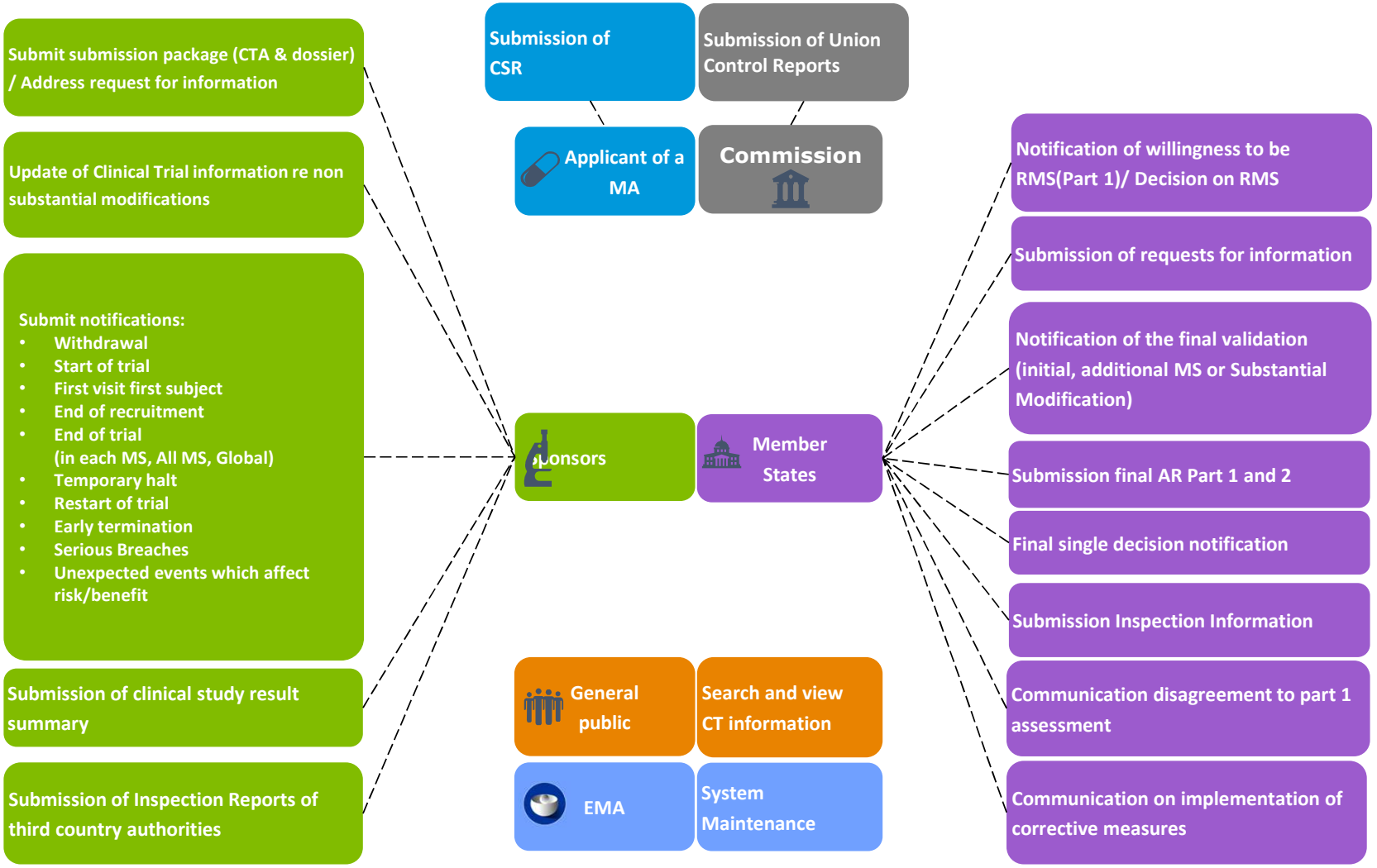
- ❑ Subject information and ICF **(T)**
- ❑ Recruitment procedure (incl recruitment material) **(T)**
- ❑ Compensation subject/ investigator/ finance/agreements **(T)**
- ❑ Suitability investigator (CV and DoI) **(T)**
- ❑ Suitability trial site (VGO) **(T)**
- ❑ Damage compensation (WMO insurance and liability insurance)
- ❑ Compliance data protection rules **(T)**
- ❑ Compliance collection, storage, and future use biological samples **(T)**

~~EudraCT form~~ – data direct in CTIS

~~ABR-form~~

(T)= template available

EU single portal - CTIS



CTIS – some points of attention

- Simple user registration via IAM (EMA account page): https://register.ema.europa.eu/identityiq/home.html
- Organisations (sponsor organisations, clinical trial sites) have to be registered in Organisation Management System (OMS): https://spor.ema.europa.eu/sporwi/
- The registration process of a new organisation in OMS takes from five to ten working days!
- Ensure that details of medicinal products used in clinical trial are already registered in eXtended EudraVigilance Medicinal Product Dictionary (XEVMPD)
- Placebo's can be added manually (without use of XEVMPD)
- Sponsor-centric approach or CT-centric approach?
- Sponsor-admin appointed → no CT-centric approach
- Sandbox for all end users → end 2021

CTIS – public portal

- Uitgangspunt van Verordening is dat de **CTIS openbaar** toegankelijk is (artikel 81, lid 4), **tenzij** geheimhouding gerechtvaardigd is op grond van **bescherming persoonsgegevens,** de **bescherming van commercieel vertrouwelijke informatie, vertrouwelijke communicatie tussen lidstaten** en **waarborgen doeltreffend toezicht**

- 3 categoriën onderzoek

  1. fase 0/I (incl. bioequivalence, bioavailability, biosimilarity trials)
  2. fase II/III
  3. fase IV en *low-intervention trials*

- Openbaarmaking na besluit van de belangrijkste kenmerken (titel, studie opzet, wetenschappelijk en therapeutisch doel, IMP, behandelarmen, populatie, inclusie en exclusiecriteria, doel van het onderzoek en eindpunten), het onderzoeksdossier met uitzondering IMPD-Q, beoordelingsrapport, vragen, antwoorden indiener.

- Openbaarmaking inspectierapporten, veiligheidsinformatie, corrigerende maatregelen, samenvatting resultaten, eindrapport (CSR) .

CTIS – public portal (deferral rules)

- Uitstel voor openbaarmaking categorie 1 onderzoek :
  - aantal kerngegevens tot 1 jaar na einde studie in EU
  - protocol, PIF, IMPD (muv Q-section), IB, RFIs (muv Q gerelateerde vragen/ antwoorden): tot registratie of max 7 jaar na einde studie
  - resultaten studie: max 18 maanden na datum upload samenvatting resultaten (12 maanden na einde studie of later om wetenschappelijke redenen)

- Uitstel voor openbaarmaking categorie 2 onderzoek
  - protocol, PIF, IMPD (not Q-section), IB, RFIs (muv Q gerelateerde vragen/antwoorden): tot registratie of max 5 jaar na einde studie

- Uitstel voor openbaarmaking categorie 3 onderzoek
  - protocol, PIF, IMPD (not Q-section), IB, RFIs (muv Q gerelateerde vragen/antwoorden): tot max 1 jaar na einde studie

- Uitstel overige documenten (bijv beoordelingsrapport): met rechtvaardiging op basis van de gronden genoemd in artikel 81 lid 4 CTR.

https://www.ema.europa.eu/en/documents/other/appendix-disclosure-rules-functional-specifications-eu-portal-eu-database-be-audited_en.pdf

CTIS – public portal

- Redacted and unredacted documents
- Example: CV investigator (with and without signature) (*NL: recent CV by version and date; signed CV not mandatory for upload CTIS, mandatory to include in Trial Master File*)
- Upload two versions in CTIS:
  - First upload version “for publication” (= redacted CV without signature)
  - Next step: upload version “not for publication” (= unredacted CV with signature)
- Only “for publication” versions will be made public in line with rules of disclosure.

Adaptive pathways
Advanced therapies
Clinical trials
Clinical Trials Regulation
Training and support
Modular training programme
Compassionate use
Compliance
Data on medicines (ISO IDMP standards)
Ethical use of animals
Innovation in medicines
Medicines for older people

Clinical Trials Information System (CTIS): online modular training programme

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EMA is delivering an online modular training programme to help clinical trial sponsors, national competent authorities, ethics committees, European Commission and EMA staff prepare for using the Clinical Trials Information System (CTIS). The training programme consists of several modules, covering the full lifecycle of clinical trial submission, authorisation and supervision.

EMA's online training modules are available on this page. EMA is adding new modules and materials throughout 2021, as they become available.

An overview of available and planned training modules is available in the guide below. The guide outlines the various life-cycle stages of a clinical trial and the relevant training modules in each stage. It also covers the preparatory steps needed to use CTIS, such as user registration.

Guide to CTIS training material catalogue (PDF/363.2 KB)

https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trials-information-system-ctis-online-modular-training-programme#sponsor-workspace-section

CCMO guideline – review site suitability

CCMO richtlijn – Toetsing Geschiktheid Onderzoeksinstelling (TGO)

- Research declaration (*Onderzoeksverklaring*) replaced by Declaration Site Suitability (*Verklaring Geschiktheid Onderzoeksinstelling*, VGO)
- VGO part A: signed by board of directors (suitability facilities, personnel, liability insurance)
- VGO part B: form (general info and overview involved departments/ officers), basis for signing part A
- VGO part A, signed → to be reviewed by MREC. VGO part B (or equivalent) stays at clinical trial site
- Applicable 1 november 2021 for clinical trials with investigational medicinal products

CCMO guideline – review site suitability

CCMO richtlijn – Toetsing Geschiktheid Onderzoeksinstelling (TGO)

- All new initial applications and subsequent substantial modifications
- Substantial modifications do not need new VGO unless:
  - it concerns an addition of new clinical trial site
  - the MREC request one
- Change of principal investigator in authorised CT site: no new VGO needed, CV investigator to be assessed by MREC
- Addition of new clinical trial site for studies submitted before 1 November 2021 can still use *Onderzoeksverklaring.*

Thank you for your attention!

Questions?

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Going for new legislation – what's new?

Mainly operating procedures:

- Central (single) EU portal for submissions and notifications (Clinical Trials Information System – CTIS)
- One application dossier (central part I and national part II)
- Maximum (mostly fatal) timelines for member states (MS) and sponsors
- Multinational clinical trials: a coordinated consolidated assessment with all MS concerned (MSC) and one reporting MS (RMS)
- MS assessment report for every clinical trial: structured report - not limited to questions/comments for sponsor
- Public disclosure clinical trial information in CTIS (all, except personal data and confidential information like Q-IMPD and related documents/data)
- Low-intervention clinical trials (less stringent rules for traceablity IMP, insurance, monitoring, content trial master file)
- Strict procedures for submission substantial modifications, article 81.9 non-substantial modifications, addition of MS and notifications