Lessons-learned workshop on Clinical Trials in Public Health Emergencies

CTCG

Amsterdam

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Summary

1. The Clinical Trial Regulation - Roles and responsabilities of Member States: general introduction

2 . Joint Action CT Cure
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   - Scope
   - Best Practice Guide (BPG) on expedited assessment
   - State of Play
   - Feedback of BPG used for CT Cure applications and M-pox applications from NCA's perspective
   - Feedback from Ethics Committees perspective

3. Optimisations on the workprocess already implemented
   - In general
   - Focus on harmonisation of the workprocesses
   - Pre-CTA advice via ETF

4. Interplay with ACT-EU program

1. CTR - Roles and responsabilities of Member States: general introduction

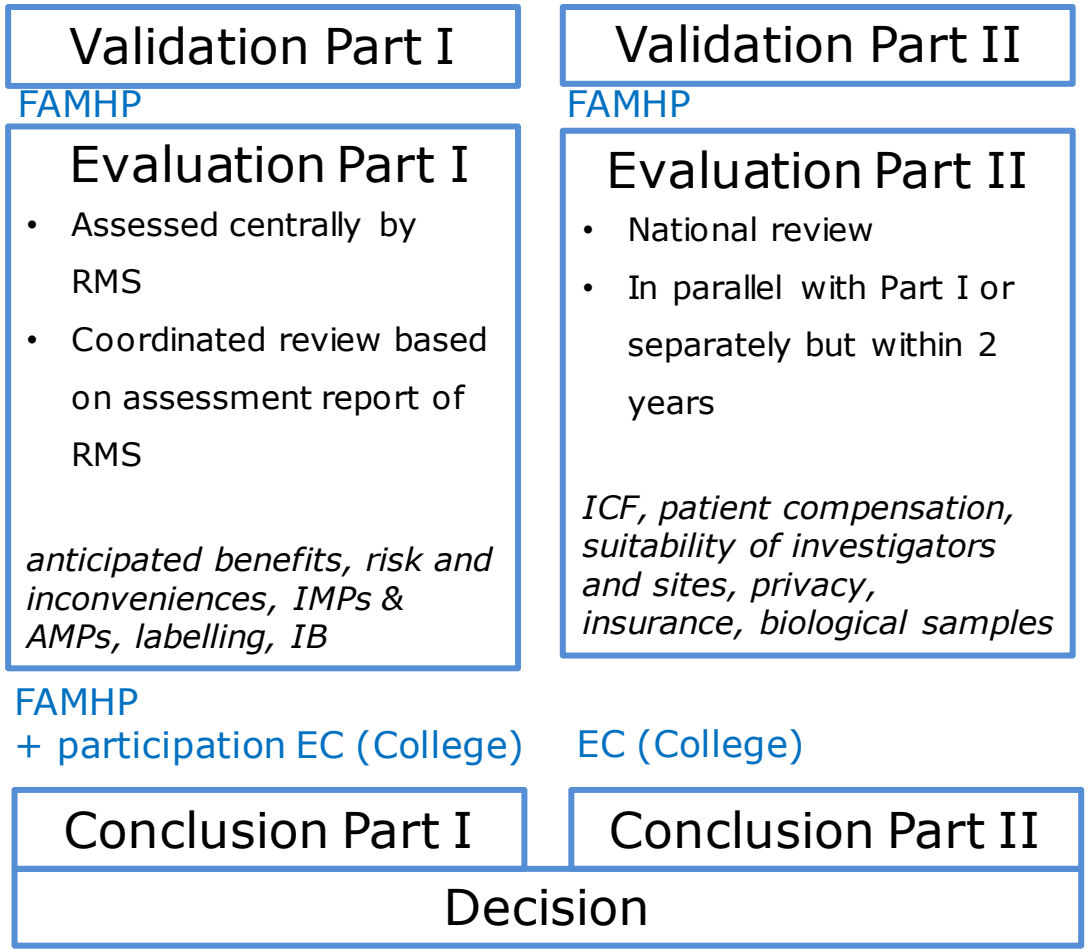
- National contact point :

  - facilitate functioning of the authorisation procedures for a clinical trial
  - designated per Member State , represented at CTAG (Clinical Trial Coordination and Advisory Group)
  - list available at the end of Eudralex volume 10 chapter V (link)

- Determination of appropropriate body / bodies involved in the assessment of clinical trial applications , including the involvement of ethics committees and the organisation of this process is left to each Member State concerned : different models exist :

    - One central ethics committee
    - Several ethics committees: one ethics allocated per CT
    - Ethics committee only involved in part II assessment
    - Ethics committee involved in part I (predefined sections or all) and part II
    - Central coordination by governmental body

Model in Belgium:
Collaboration between NCA and Ethics Comittees

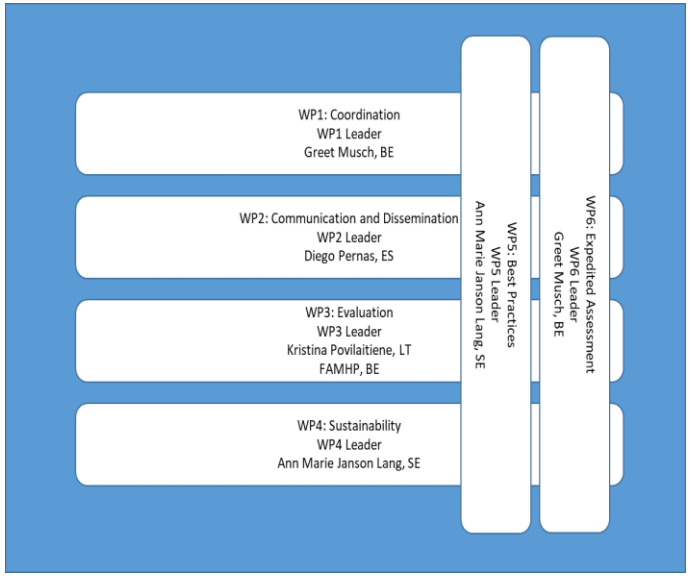


1. CTR - Roles and responsabilities of Member States: general introduction

- Role of the Reporting Member State
- Takes the lead in validation and assessment of the dossier
- Writes the Draft Assessment Report (DAR) on Part I
- Consolidates considerations
- Provides the validation and Part I assessment RFIs to the sponsor
- Provides conclusion on Part I in CTIS
- All this within timelines as defined in CTR/CTIS

- Role of the Member State Concerned
- Provides additional validation or Part I assessment considerations if applicable
- Provides comments on DAR if applicable
- Option to opt out
- All this within timelines as defined in CTR/CTIS

2. Joint Action CT Cure



Participating Member States

Fifteen Member States have confirmed their participation but besides these, other Member States, have expressed interest in joining the expedited assessment.

The JA CT Cure entered into force February 15th 2022 (after the go life CTR , 31 th Jan 2022 , retro-active; grant agreement signed on September 17th 2022)

Website: https://ctcure.eu/

2.1 Joint Action CT Cure - Objectives

- Urgent need for a therapeutic solution in response to the COVID-19 pandemic (4th wave)
- Robust clinical trials are an essential sources of evidence for authorisations of innovative COVID-19 medicines
- There is a need for speeding up and authorize these CT authorisations without compromising the quality of the scientific and ethical review
- The JA CT Cure focusses on providing a harmonized and accelerated assessment of clinical trials with COVID-19 therapeutics, using CTIS

2.2 Joint Action CT Cure - Scope

- Multinational trials investigating the efficacy and safety of novel COVID-19 therapeutics submitted to CTIS under the Regulation (EU) 536/2014 (CTR)

- Novel COVID-19 therapeutics are defined as:

  i) investigational medicinal products (IMPs) without marketing authorisation,

  ii) IMPs with marketing authorisation for a different indication than COVID-19-related indications

  iii) COVID-19 therapeutics with a marketing authorisation used with a new posology or in novel populations, e.g. in children

- The project aims at expedited timelines for the **assessment** of COVID-19 therapeutics in multinational clinical trials

2.2 Joint Action CT Cure - Scope

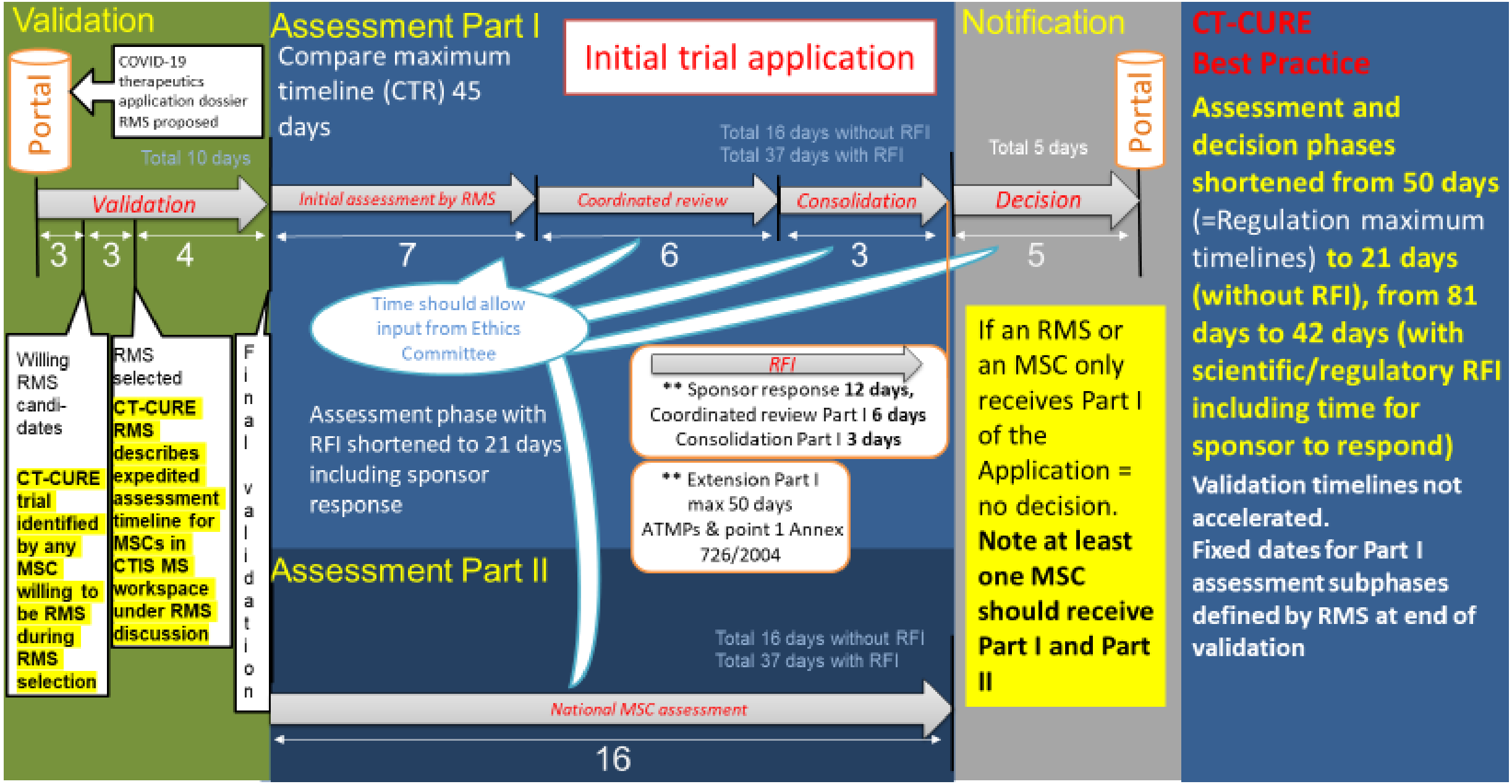
- Initial Best Practice guide has already been developed to enable this work
- Work processes will be optimized by MS (NCAs and Ethics Committees) and sponsors (commercial and non-commercial) at regular basis
- Sponsors are strongly recommended to file excellent applications (e.g. via seeking previously central or (simultaneously) scientific advice
- Sponsors are strongly recommended to plan at least 2 weeks beforehand their applications and to inform the MS (RMS and MSC)

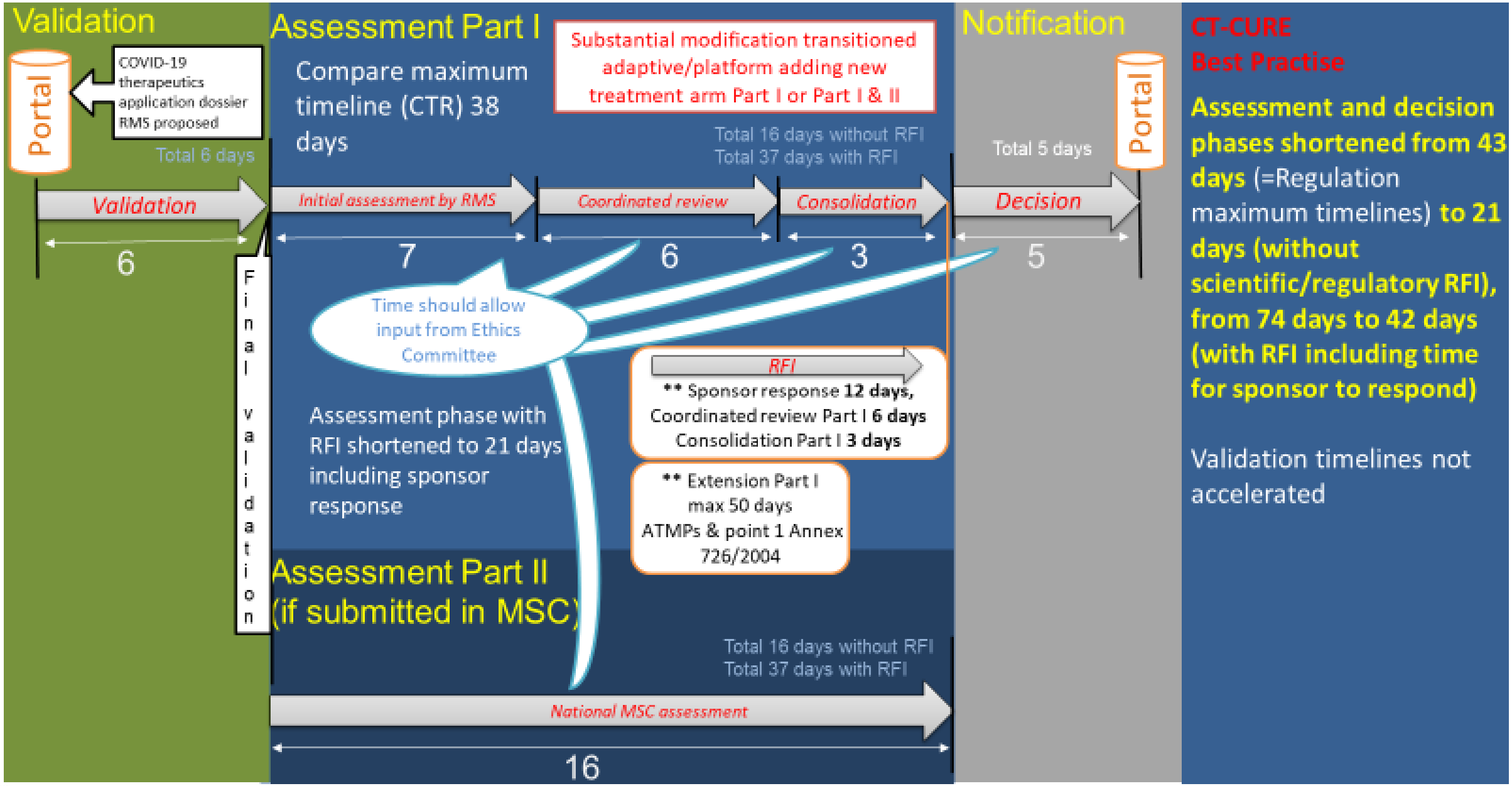
2.3 JA CT Cure - Best practice: identification and assessment of clinical trials on COVID-19 therapeutics

- Basic agreement endorsed by all participating MSs to shorten *assessment timelines* according to graphs (16 days - compared to the regulation maximum timelines for initial applications 45 days) for ***new*** COVID-19 therapeutic trial applications and for ***transitioned adaptive/platform trials for which a new treatment arm is added***

- Timelines for Later Part II submission (CTR Article 11), Additional MSC (CTR Article 14), transition followed by substantial modifications for platform/adaptive trials adding new treatment arms based on similar principles as those for initial application

- ***Sponsors submitting complete trial application dossiers*** (no RFI required) will benefit most from the accelerated assessment. Rolling reviews or similar alterations of trial applications not included in the project
  - After validation, a ***fixed timeline*** applies for the assessment subphases. The assessment timeline shortened to 36-55 % of the CTR maximum timeline depending on procedure (see graph slides later in this presentation)
  - **Expedited assessment should not compromise the quality of the scientific and ethical review as outlined in Article 4 of the CTR**
  - Assessors from ethics committees and NCA's could consider starting assessing the application dossier already during validation in order to meet the short timelines provided.





2.4 Joint Action CT Cure – State of play

- Applications received:
  - Solid Act trial (transition trial), daughter trial and Substantial modifications (SM)
  - Ecraid Prime trial (foreseen to be submitted in June 2023)

- New applications announced but not yet confirmed by sponsor:
  - Easthorn trial, Spikimm trial …

- Planned amendements to the JA:
  - Expanding the scope to "Therapeutics that could potentially be used for COVID-19"
  - Expanding the scope to all types of substantial modifications
  - Organise a training for ethics committees and NCAs on platform trials
  - Include relevant actions derived from the outcome of this workshop

2.4 Joint Action CT Cure – State of play

- All applications have been assessed respecting the timelines of the BPG (except for one MS , non-participating in the JA CT Cure , for the first application)

- Few applications received (very few mono national CTA's received as well ; though sponsors have been activelly asked to inform CT Cure team on future development plans)

  - Pandemic going down
  - Dissemination of the JA needs further optimisation , targetting the academic community in a better way
  - CTIS
  - EU Regulation 2022/123 , 25 th January 2022 : Role of Emergency Task Force at EMA

- Experiences on BPG used for future applications where expedited assessment is needed

2.5 JA CT Cure: Feedback on BPG used for CT Cure applications

- Expediting timelines remain very challenging for RMS/ MSC's

- Workprocess needs to be further optimized by :

  - Only raising blocking issues for Part 1 and Part 2 , based on the considerationsraised by the RMS .
  - National part 2 requirements per MS , should be made available and easily accessible

- Need for improved and harmonized submission via the option of scientific advice/ pre-submission meetings

2.5 JA CT Cure BPG : Feed back related to the experiences gained for M- pox : Mosaic trial)

2.5 Key issues: ETF/MSC (pre-assessment), CTIS

- CT on an outbreak, very URGENT to be assessed, outside CT Cure
- Sponsor lack of CTR knowledge & no experience on CTIS
- Protocol approved in ETF not compliant with CTR requirements. Too short deadlines for certain Ethics Committees
- Difficulties with part II: difficult to find requirements, missing/fake at application time
- Technical problems in CTIS
- No Substantial Modification (no additional trial sites) and no additional MSs before authorisation in all MSCs due to CTR interpretation and CTIS rules

2.5 Improving understanding of legislation and CTIS:

"Kit of first understanding" in every relevant EU website (*)

A Short document giving an overall view on EU CTR requirements in lay language with references to:

- Where part II and national requirements for all MS are placed (i.e. a contact to solve queries related to part II, payment of fee, appeal procedure)
- Summary of CTIS and transparency requirements
- Links to where to get additional information

2.5 MS Communication and Cooperation

- Communication tool for discussions during pre-submission & CTIS assessment (RMS/MSC, RMS/sponsor on part I and MSC/sponsor on part II)
- Place for storage of pre-submission and final Scientific Advice documents
- Presubmission meeting RMS/MSCs including ethics committee representatives and CTCG's ETF members
- Strengthening the RMS role (NCA + EC)
- Restrict considerations by MSC to critical issues!
- Pre-defined calendar from the beginning (CT Cure best practice guide to be used)
- Only involvement of MSC with Ethics Committees able to do expedited assessments: clarify ability per MS

Activities already ongoing supported by CTCG, IT tools pending

2.5 Improvement of collaboration ETF – CTCG (*)

- RMS proposed , is in the lead , attending at earliest stage the ETF meetings , together with MSC's representatives
- CTCG members and alternates , representatives from ethics committees , via the CTCG ethics advisory group are invited , to attend the ETF meetings .

2.5 Less rigid interpretation of CT Regulation could allow:

- A part I SM and an addition of MS after first MS has authorised the CT (part I has concluded for all)
- A part II SM while a part I SM is ongoing (e.g. to add investigators)
- Making feasible transparency reducing the need for redacted documents (e.g. clearer and shorter guidance with focus on what should be rather than what could be deleted?)

2.5 JA CT Cure BPG : Feed back related to the experiences gained for M- pox : Epoxi trial)

From a NCA perspective, accelerating the assessment timelines is not really a problem.

Difficulty is mainly the extensive exchanges via e-mails and outside CTIS before submission (to support the sponsor in preparing the CTIS package and for pre-assessment of protocol) and during submission.

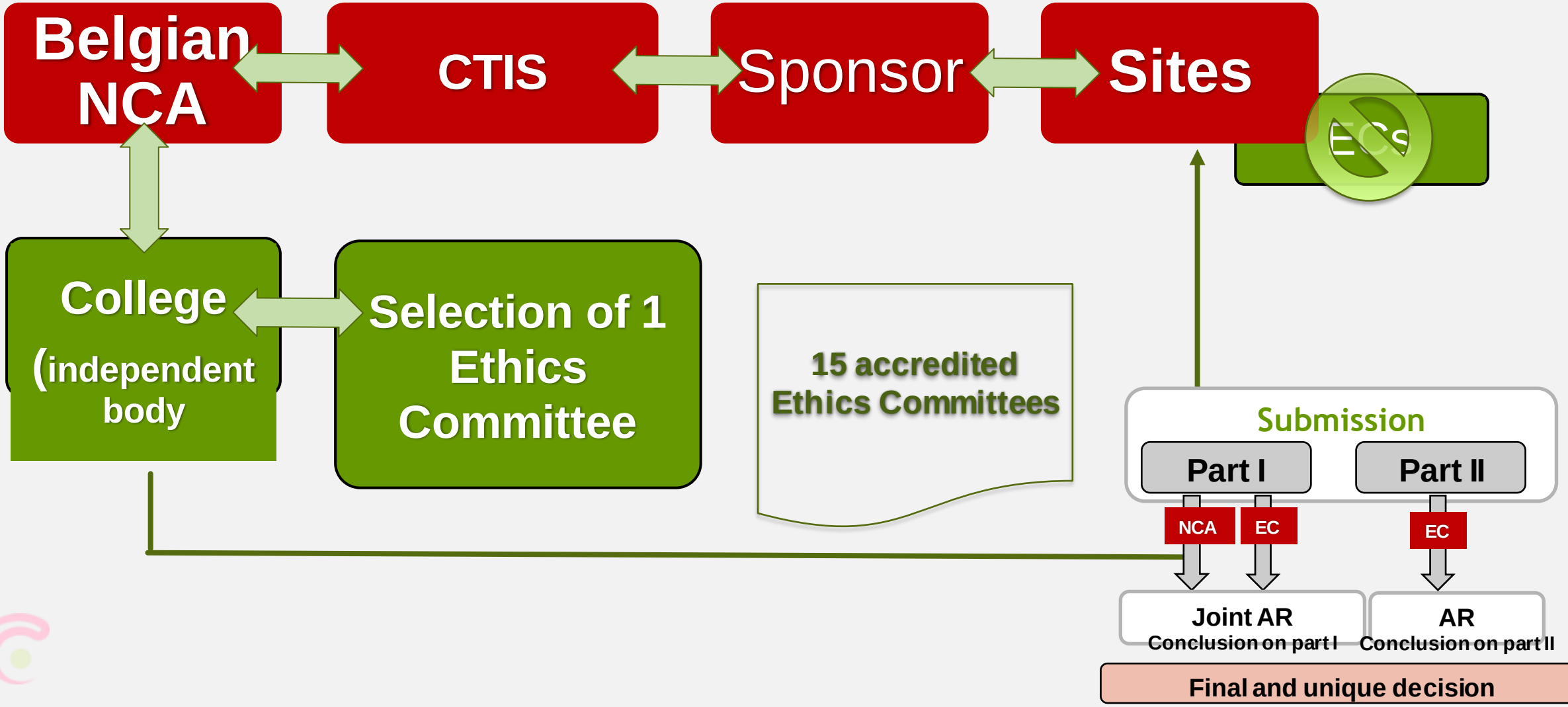
2.6 Feedback from Ethics Committees perspective : BE and NE

Clinical Trial College

Federal Public Service of Health, Food Chain Safety and Environment

ir. Sébastien Vanhiesbecq

Organisation of ethical review in **Belgium**



COVID-19 dossiers - **Pandemy**

- At the beginning of the COVID-19 pandemy, together with the Belgian NCA and the Belgian Ethics Committees, we defined national guidelines and requirements for a COVID-19 dossiers:
  - Required at submission: Most of the part I CTR documents and some part II CTR documents (recruitment, advertising material, subject information and informed consent, informed consent procedure, list of sites, compensation) protocol synopsis & ICF in the language of the participant for the Layperson
  - Required as answers to the RFI (at the latest): rest of the part II documents (CV's & DOI's of PIs, Site suitability statement, Proof of Insurance, Description of the financing, GDPR statement)
- Belgian accelerated assessment procedure : 4 working days (+ 4 working days for the assessment of response to RFI)
- Involvement of 10 voluntary independent Ethics Committees
- Specific information on the websites of the Ethics Committees (prioritization of dossiers)
- Practical consequences of the confinement: quorum not always reached, plenary sessions cancelled,…
- Many Substantial Modifications…

COVID-19 dossiers – **CT-Cure**

- Belgium is member and coordinator of the CT-Cure Joint action
- Discussion between the Member States regarding the protocol before the submission of the CTA - *If we want to involve the Belgian Ethics Committee in the presubmission discussions, we need to know the sites in order to select the independent Ethics Committee*
- CTR requirements at submission of the dossier !
- Additional fee for COVID-19 dossiers (but not for Monkeypox dossiers!)
- Feedback from the Ethics Committees :
  - Too short timelines for the assessment ! (sometimes studies with complex designs)
  - Ethics Committees/NCAs, Researchers and Sponsors should apply the same high quality framework (quality of dossiers, quality of assessment,…)
  - Clear procedure for the accelerated evaluation is needed (who, what, how, criteria,…) + pre-approved templates (before the COVID-19 pandemy, these were missing)

Assessment of MPOX studies
Ethics committee experience from the Netherlands

Lessons-learned workshop on Clinical Trials in Public Health Emergencies
9 June 2023, EMA, Amsterdam

Kaate Vanmolkot, *PhD*

Scientific staff member National Clinical Trial Office
Central Committee on Research Involving Human Subjects (CCMO)

Medical Ethical Review System in the Netherlands

decentral, controlled & integrated peer review system

Decentral:

review by limited number of accredited MRECs

Controlled:

oversight by the CCMO

Integrated:

all documents in one review (part I and part II)

Peer review:

review by experts in accredited MRECs

Limited central review:

by CCMO (e.g. ATMPs, vaccins, non-therapeutic studies with minors/incapacitated subjects)

A national clinical trial office

- one national contact point (CCMO)
- coordination and support

one dossier
[Part I and Part II]
one committee
one integrated assessment
one decision

Experiences in assessment of Mpox clinical trials

Cohort study of treatment outcomes in human Monkeypox virus disease **(MOSAIC)** (2022-501132-42-00)

Spain (RMS), France, Belgium, Ireland, Italy, Portugal, Netherlands, Norway

European Randomised Clinical Trial on MonkeyPOX Infection **(EPOXI)** (2022-501979-10-00)

Netherlands (RMS), France, Belgium, Germany, Portugal, Spain, Norway

- ETF scientific advice – ethics involved at (too) late stage
- Shortened assessment timelines according to CT-CURE best practice
- Central, combined part I and II assessment
- Central ethics committee with required expertise and experience in fast-track procedures
- Established subcommittee with mandate to accelerate assessment
- Part II dossier: published on national website but no central overview requirements per MS in EU
- For EPOXI as RMS: arranged pre-submission meetings with respectively investigators and MSCs →clarification/harmonization in process, requirements (minimal set part II documents), identified contact persons, pre-defined timelines
- Staggered approach, conditional approval
- Open communication: numerous emails around the proceedings, insufficiently supported by CTIS
- Clinical trials authorised within CT-Cure timelines

Lessons learned

- Pre-submission meetings/scientific advice with early involvement of proposed RMS, MSCs and ECs
- Pre-CTA advice with sponsor and proposed RMS in the lead
- Agreement on minimum set of required part II documents – roll over assessment (staggered approach)
- Adherence to fixed timelines – CTIS should facilitate fast track procedure to prevent numerous emails outside CTIS
- Dedicated ethics committees (one per MS) with procedures in place for expedited assessment
- Subcommittee with mandate needed to cope with the shortened timelines
- More flexibility needed in:
  - the use of conditions
  - the timing of submission of substantial modifications part I, part II (should be possible as soon after the first MS has authorised the clinical trial)

3.1 Optimisations on the work process already implemented in general

- CTIS online modular training program on EMA website :link
- Quick guide for sponsors : https://health.ec.europa.eu/system/files/2023-04/mp_ctr-536-2014_guide_en.pdf
- Guidance on transparency : ACT EU_Q&A on protection of Commercially Confidential Information and Personal Data while using CTIS (europa.eu)
- Complex Clinical Trials : Q&A from CTCG: https://www.hma.eu/fileadmin/dateien/HMA_joint/00-_About_HMA/03-Working_Groups/CTCG/2023_03_CTCG_QA_complex_clinical_trials_and_CTIS_v1.0.pdf
- Recommendation paper on Decentralised Clinical trials : https://health.ec.europa.eu/system/files/2022-12/mp_decentralised-elements_clinical-trials_rec_en.pdf
- Improving the workprocess on setting RFIs via Best Practices, Round table for assessors, CTCG Project « CTR Collaborate »

3.2 Focus on harmonisation of the workprocesses

Optimise further the harmonisation of templates

3.3 CTCG and ETF collaboration: pre-CTA advice : work in progress (focus on preparedness for PHE)

See presentation of Manuela Mura

4. Opportunities offered by ACT EU to support academic sponsors in public health emergencies

Actions specific to PHE emergency situations

Foundational support to academic CTs via ACT EU

Support to develop right 1st time fit for purpose dossier

Support to academic sponsors conduct MNCTs

Pilot for consolidated CTA advice and SA

Multi-stakeholder platform

Clinical trials training curriculum

CTCG best practices

Contact

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