Drug Development and Regulation – Europe

"From the lab bench to the bedside – a fantastic voyage of drug development"

Anne Hamel

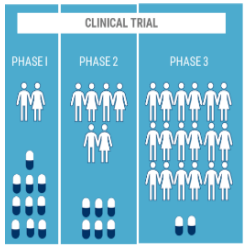
Regulatory Affairs Manager

Drug Development and Regulation - Europe

AGENDA

- Drug development & EU Marketing Authorization (MA)
- Clinical trials - role in drug development and MA
- European regulatory framework for clinical trials
- EU MA procedures and MA types

Drug Development and Marketing Authorization - Europe



Drug discovery
Preclinical development

Research new drugs
Laboratory & animal testing for safety and efficacy

Clinical development
Clinical trials Ph I, Ph II, Ph III

Build knowledge/evidence on the quality, safety and efficacy of the medicinal product in human

Registration

Regulatory assessment
Marketing Authorization Application (MAA)
Marketing Authorization Procedures

Marketing Authorization (MA)

https://www.ema.europa.eu/en/documents/other/laboratory-patient-journey-centrally-authorised-medicine_en.pdf

Clinical trials – background information

What's a clinical trial, why are performed?

- Clinical trials (CT) are a critical element of clinical research and are key to demonstrate that medicines are safe and effective in people
- Generate data & evidence supporting the benefit-risk balance of a medicine and its approval

When a CT could be initiated? Who authorize a CT?

- Before a clinical trial of a medicine can begin, National Competent Authority (NCA) must issue an authorization and Ethics Committee (EC) must give a favourable opinion
- The NCA assess the safety and scientific value of the clinical trial, and the quality of the medicinal product, ensuring that the safety measures are appropriate for the trial
- The EC gives an opinion about whether the research is ethical

Clinical Trial Application dossier

- The Sponsor must submit Clinical Trial Application (CTA) for NCA & EC assessment to obtain the CT authorization. A positive benefit-risk balance must be demonstrated

CT: Clinical trial; CTIS: Clinical Trial Information System; NCA: National Competent Authority; EC: Ethics Committee

Clinical trials – Phases

Phase I

- Focus on the safety and dosage of a drug
- Conducted with healthy volunteers or people with disease (20-100 participants)
- Several months duration

Phase II

- Focus on safety and preliminary data on drug's efficacy in people with a certain condition/disease (up to several hundred participants)
- Several months to 2 years duration

Phase III

- Gather more information about drug's safety and effectiveness (300-3000 participants)
- 1 to 4 years duration

Phase IV

- Clinical trials occurring after marketing authorization
- Gather additional information about a drug's safety, efficacy, or optimal use

Clinical Trials - European regulatory framework

- EU Clinical Trial Regulation No 536/2014 (CTR)
- EU Clinical Trial Directive 2001/20/EC (CTD)
- Guidelines (ICH, EMA)

Compliance with the regulatory framework ensures the rights, safety, and wellbeing of clinical trial participants

https://www.ich.org/
https://ec.europa.eu/health/medicinal-products/eudralex/eudralex-volume-10_en
https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0536&from=EN
https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials-human-medicines

Clinical Trials - EU regulatory framework evolution

BEFORE MAY 2004

- Different **processes and requirements** for clinical trial (CT) authorisations in each Member State (MS)
- …resulted in **delays and complications** detrimental to effective conduct of CT in the EU

EU CLINICAL TRIAL DIRECTIVE 2001/20/EC + NATIONAL REGULATIONS

- Implementation **May 2004**
- First step to **harmonise processes and requirements** for clinical trials authorisations
- Set objectives, **transposed** into national legislations

EU CLINICAL TRIALS REGULATION No 536/2014

- **Binding in its entirety and directly applicable** to all EU Member States (MS)
- Published **May 2014**
- Implemented **31 January 2022**
- **Clinical Trial Information System (CTIS)** a tool to implement CTR provisions
- **Three years transition period** from the Clinical Trial Directive (CTD) to CTR

CT: Clinical Trial; CTIS: Clinical Trial Information System; MSC: Member State Concerned

EU Clinical Trials Regulation (CTR)

New legal frame for the conduct of Clinical Trials in the EU. New submission and authorization process

REGULATION (EU) No 536/2014 (CTR)

Stakeholders concerned

AIMS

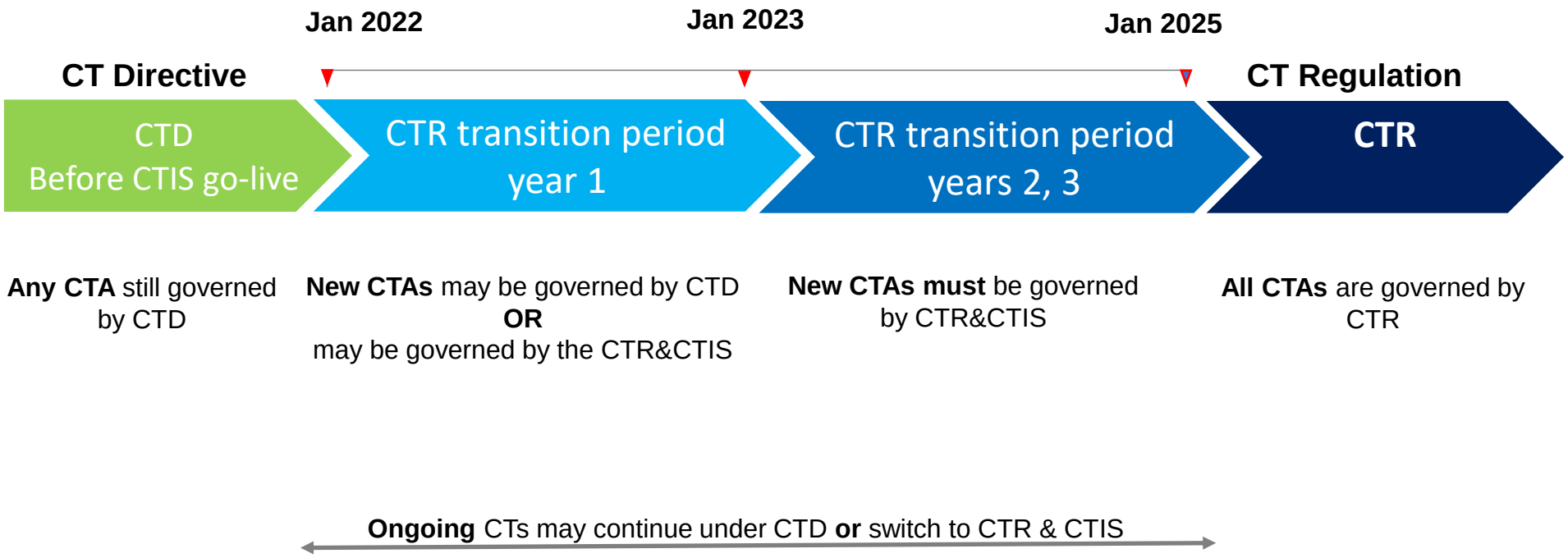
- Create a favourable environment for clinical trials (CT) conduct with the highest safety standards for participants and increased transparency of trial information
- Increase the efficiency of trials (especially multinational)
- Foster innovation and research, while helping avoid unnecessary duplication of CTs or repetition of unsuccessful trials

KEY BENEFITS

- **Simplify, harmonize** the authorization & conduct of CTs across EU
  - New streamlined submission and authorization process: 1) one application for multinational CTs; b) one dossier for HA & EC per MSC; 3) HA&EC combined review, one authorization per MSC
  - CTIS - a single electronic platform for submissions and communication with the HAs and ECs across EU
  - Coordinated safety assessment and streamlined reporting process
- Improve **collaboration, information-sharing and decision-making** between and within Member States Concerned (MSC)
- **Increase transparency** and improve **public access** to CT information

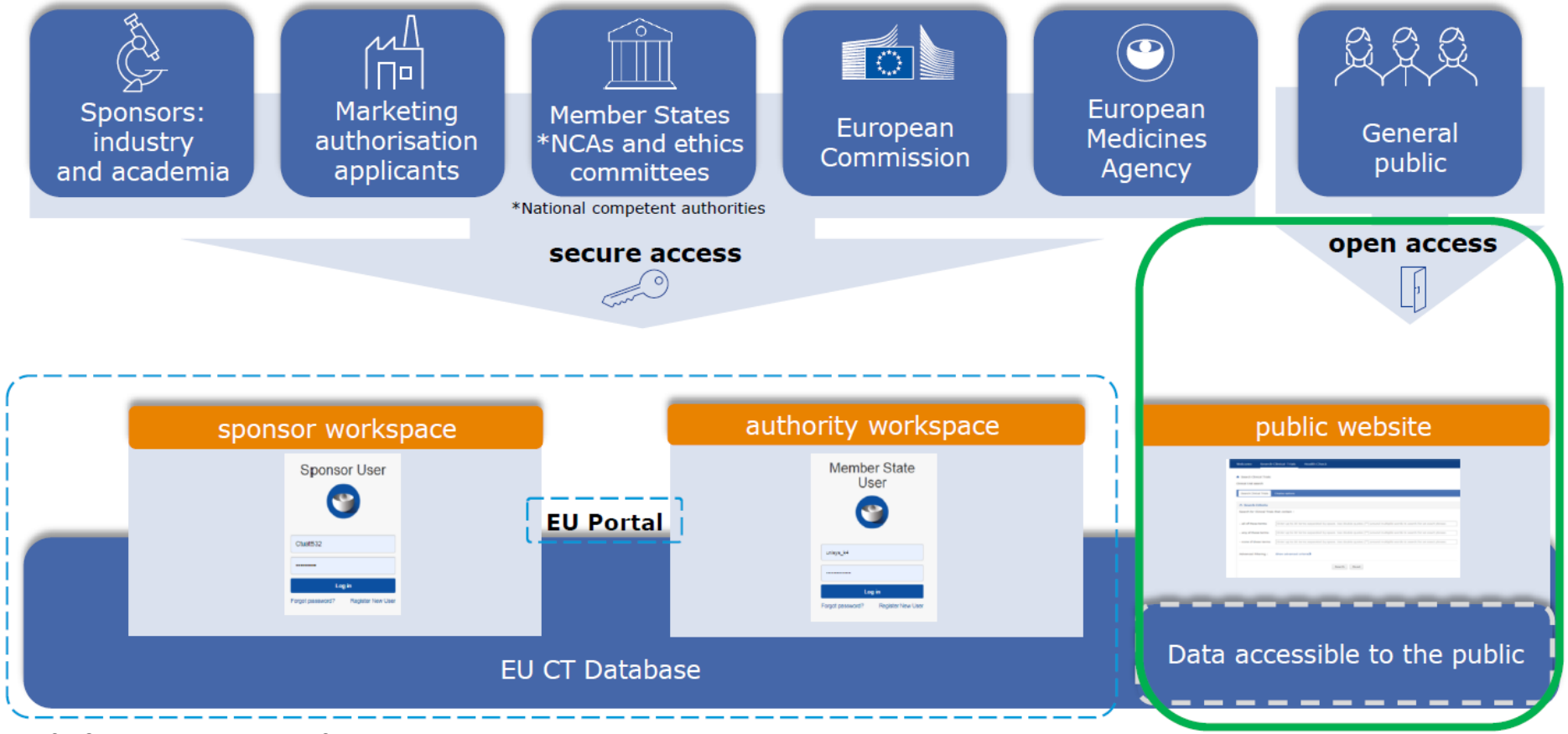
CT: Clinical Trial; CTIS: Clinical Trial Information System; HA: Health Authority; EC: Ethics Committee; MSC: Member State Concerned

Transition period Clinical Trial Directive - Clinical Trials Regulation



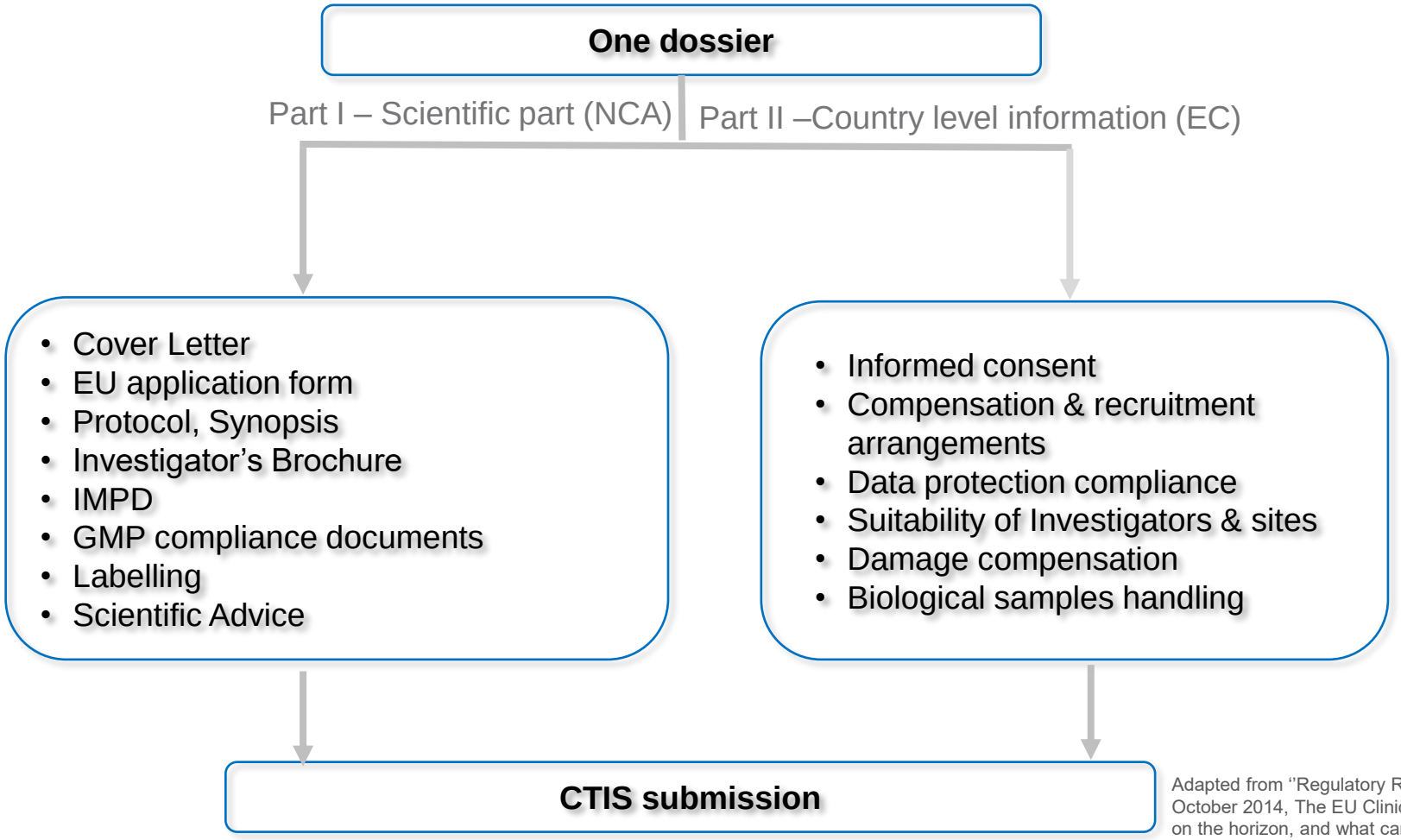
- CTR & CTIS mandatory from January 2023 for new CT and January 2025 for all CT

Clinical Trials Information System (CTIS)



- CTIS is a tool to implement CTR provisions
- CTIS as single-entry point for submission, assessment, authorization, supervision & reporting a clinical trial in all MSC
- CTIS is composed of two workspaces with secured access for sponsors & authorities, and a public website
- Once a decision is reached on CTIS applications, the data & documents are subject to public disclosure (transparency rules)

Clinical Trial Application dossier



Adapted from ''Regulatory Rapporteur – Vol 11, No 10, October 2014, The EU Clinical Trial Regulation: What's on the horizon, and what can sponsors do to prepare?''

Clinical trial application (CTA): a request for authorization of a Clinical Trial (CT) on a medicinal product for human use, submitted to Member States Concerned (MSCs) for their evaluation

Informed consent: a subject's free and voluntary expression of his or her willingness to participate in a particular clinical trial, after having been informed of all aspects of the clinical trial that are relevant to the subject's decision to participate

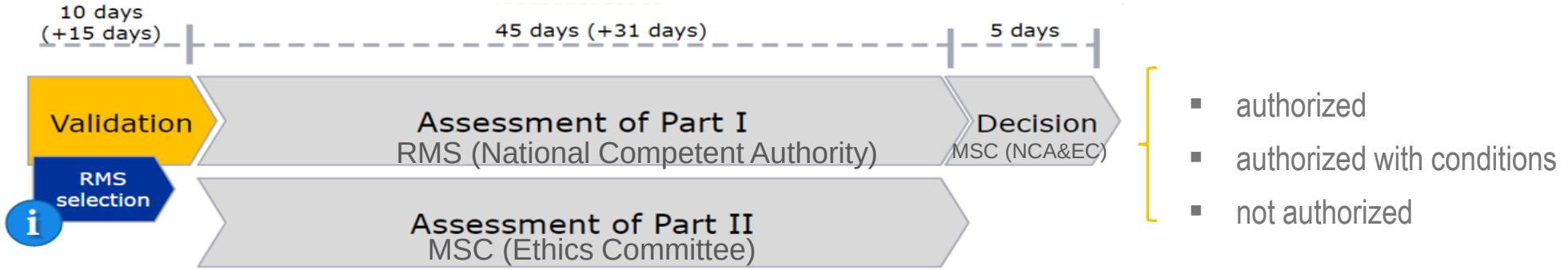
Scientific Advice: Health Authority guidance on the best methods and trial design to generate robust information on the safety, effectiveness and quality of a product

Part I of the CTA is common to all MSC involved in the clinical trial

CTIS: Clinical Trial Information System; IB: Investigator's Brochure; IMPD: Investigational Medicinal Product Dossier; GMP: Good Manufacturing Practice

Initial Clinical Trial Application evaluation process

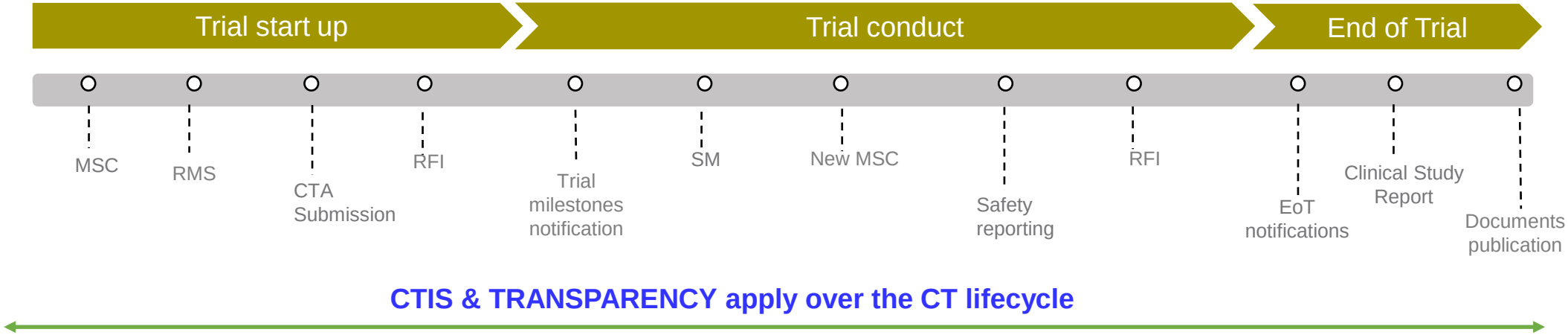
Evaluation process of the initial CTA – validation, assessment and decision



- **Member State concerned (MSC)**: Member State that receives an application concerning a CT intended to be conducted in its territory
- **Reporting Member State (RMS)**: One of the MSC that leads the evaluation and conclusion on Part I assessment
- **Request for Information (RFI)**: request for additional information during the evaluation process of the CTA
- Joint assessment by the NCA & EC, one decision per MSC
- CTA evaluation timelines: 60 - 106 calendar days*
- Part I of the CTA is common to all MSC, and assessed by the NCA of the RMS
- Part II of the CTA assessed by the EC of the MSCs in accordance with the national law within the overall timelines defined by the CTR

EC: Ethics Committee; NCA: National Competent Authority; * The RMS can additionally extend assessment time by 50 days for advanced therapies and products derived from rDNA technology

Clinical Trial Application life cycle



Clinical Trial life cycle submissions

- Trial milestones notification (e.g., start CT, 1st visit of 1st subject, end of recruitment, end of trial)
- Substantial modifications (SM): any change to any aspect of the CT which is likely to have a substantial impact on the safety or rights of the subjects or on the reliability and robustness of the data generated in the CT
- New MSC

CT: Clinical Trial ; CTIS: Clinical Trial Information System; EoT: End of Trial; MSC: Member State Concerned; RFI: Request for Information; RMS: Reporting Member State; SM: Substantial Modifications

Transparency in CTIS [1]

- The CTR sets out requirements for increased transparency of EU clinical trials and describes what data & documents and the timing of the publication
- All data & documents stored in the CTIS database are subject to public disclosure according to the CTR transparency rules, with few exceptions
- The default is always to make public at the first opportunity, e.g., time of decision on initial CTA
- Deferral of the publication timing possible based on the trial category
  - Maximum 7 years from the EoT for **category 1 CT** (Phase I (FIH), PK/PD, BE/BA, Bio similarity)
  - Maximum 5 years from the EoT for **category 2 CT** (Phase II and III)

EoT: End of trial; FIH: First-in-human; PK/PD: Pharmacokinetic/pharmacodynamic; BE/BA: Bioequivalence and bioavailability

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

Transparency in CTIS [2]

Information/data never made public

- Commercially confidential information (CCI): IMPD-Q, RFI-Q, assessment report-Q
- Protected personal data (PPD) (CT participants, Sponsor's staff)
- Draft assessment reports (confidential communication between MS)
- Financial agreements Sponsor-Investigator site

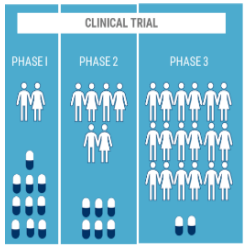
CCI: information which is not in the public domain, or publicly available, and where its disclosure may undermine the legitimate economic interest or competitive position of the owner of the information

Personal data: any information relating to an identified or identifiable natural person (e.g., name, identification number, location data)

IMPD: Investigational Medicinal Product dossier; MS: Member state; RFI: Request for information; Q: Quality

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

Drug Development and Marketing Authorization - Europe



Drug discovery
Preclinical development

Clinical development
Clinical trials Ph 1, Ph 2, Ph 3

Registration

Research new drugs
Laboratory & animal testing
for safety and efficacy

Build knowledge/evidence on the quality, safety and efficacy of the medicinal product in human

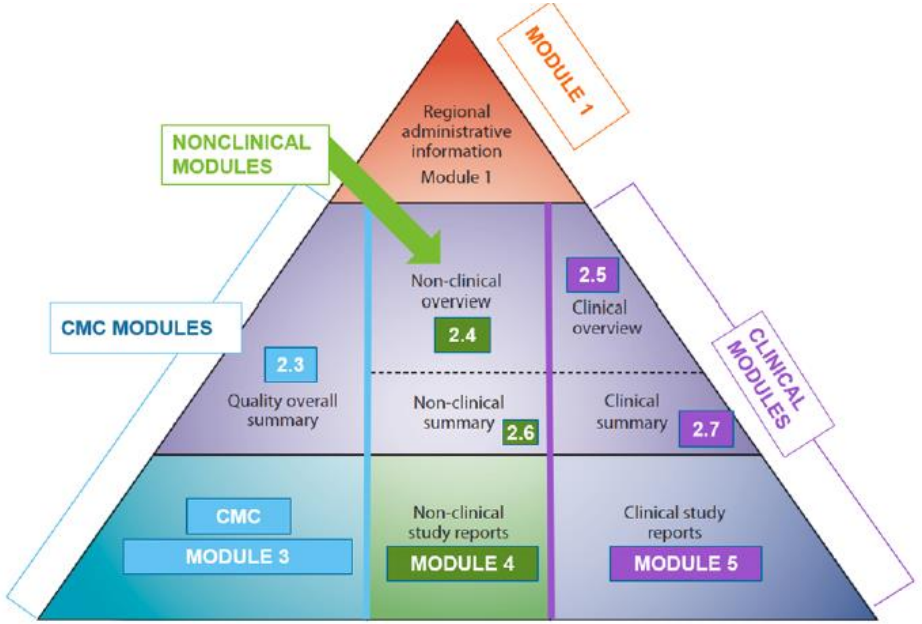
Marketing Authorization

Regulatory assessment
Marketing Authorization Application
Marketing Authorization Procedures

https://www.ema.europa.eu/en/documents/other/laboratory-patient-journey-centrally-authorised-medicine_en.pdf

Marketing Authorization Application dossier

- **Appropriate and robust data package** including non-clinical, quality and clinical development information
- Medicinal product meet the **quality, safety and efficacy** requirements
- **Positive benefit-risk balance** in favor of patients



- MA dossier based on internationally agreed eCTD format (ICH M4)

https://www.ich.org/page/ctd

eCTD: electronic common technical document

Marketing Authorization Procedures - Europe

Centralized Procedure

Centralized procedure (via EMA)

- One MAA assessed by **EMA**
- MA valid in all EU MSs

National Procedures (via NCAs)

National Procedure

Authorization by a single **MS**

Mutual Recognition Procedure

Decentralized Procedure

Authorization by several **MS**s, based on assessment by Reference MS

- Centralized procedure - EMA gives an opinion and it results in a single MA for the whole of the EU
- National procedures - individual MSs authorize the medicines for use in their own territory

https://ec.europa.eu/health/authorisation-procedures-national_en

Marketing Authorization types - Europe

Standard MA

- MA granted based on comprehensive data package
- Post approval commitments (studies) possible
- 5 years validity
- Standard MA at approval

Conditional MA

- MA granted based on a less comprehensive data package
- Comprehensive clinical data expected within defined timeframe
- Post approval commitments (studies) always
- 1 year validity with annual renewal of MA
- Switch to standard MA envisaged

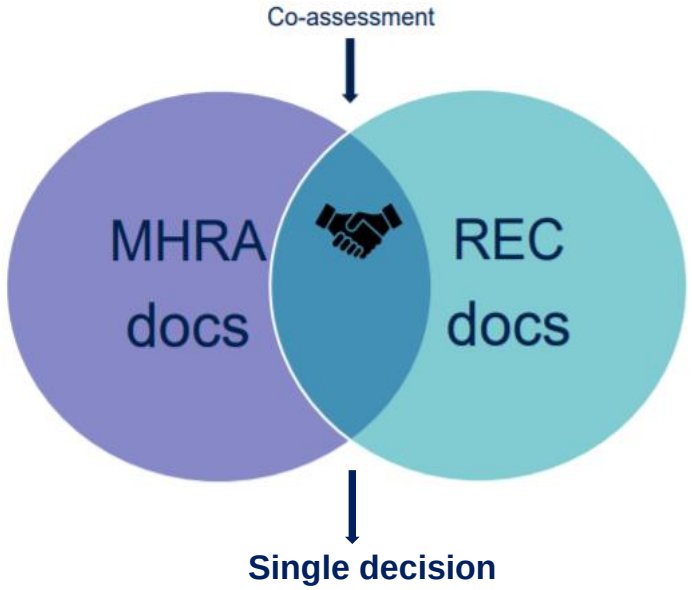
Comirnaty COVID-19 vaccine, granted conditional MA in the interest of public health because the medicine addresses an unmet medical need and the benefit of immediate availability outweighs the risk from less comprehensive data than normally required

MA under exceptional circumstances

- MA granted based on a less comprehensive data package
- Comprehensive clinical data not expected
- Post approval commitments (studies) always
- 5 years validity with annual reassessment of MA
- Standard MA not envisaged

https://ec.europa.eu/health/authorisation-procedures-national_en

UK Clinical Trials Regulation



- Clinical trials are regulated under The Medicines for Human Use (Clinical Trials) (Amendment) (EU Exit) Regulations 2019
- Clinical trials authorized by the NCA (MHRA) & REC
- Co-ordinated combined review of the application leading to a single UK decision, since January 2022
- IRAS platform for submissions to MHRA and REC
- Process to “facilitate rapid startup” of clinical trials so that patients can see earlier benefit from innovative therapies

MHRA: Medicines and Healthcare products Regulatory Agency; IRAS: Integrated Research Application System; REC: Research Ethics Committee

https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/clinical-trials-investigational-medicinal-products-ctimps/combined-ways-working-pilot/step-step-guide-using-iras-combined-ways-working-cwow/#sponsor

Resources

- **Regulation (EU) No.536/2014**

https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf

- **EUDRALEX vol 10 – clinical trials guidelines**

https://ec.europa.eu/health/documents/eudralex/vol-10_en

- **EMA online modular training programme and support on CTIS**

https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trials-information-system-training-support

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