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SCIENCE MEDICINES HEALTH

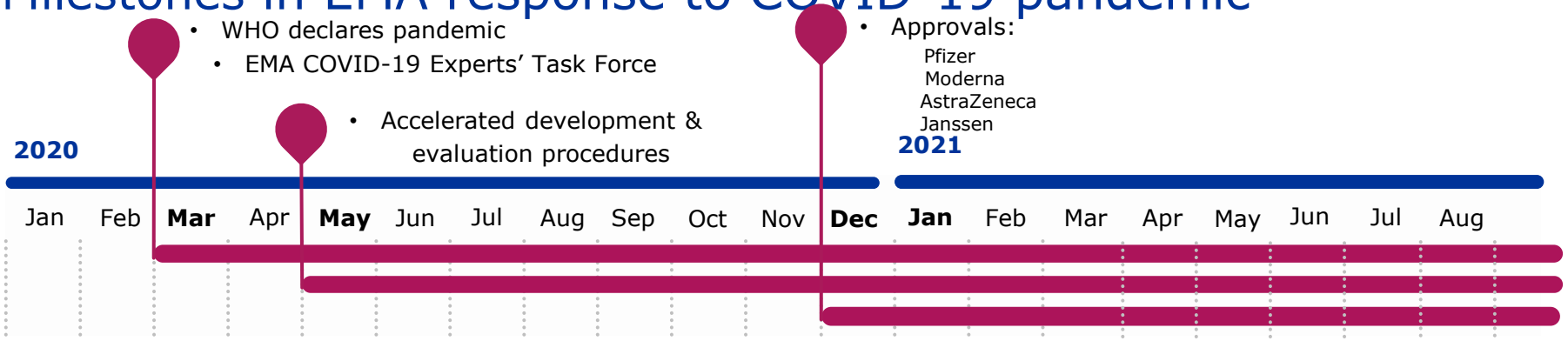
Regulatory process in the COVID-19 era:
how to deal with the organisational and scientific challenges at the European Medicines Agency level

Presented by Fergus Sweeney on 10 December 2021
Head, Clinical Studies and Manufacturing Task Force, European Medicines Agency

Disclaimer

The presenter does not have any conflict of interests.

Milestones in EMA response to COVID-19 pandemic



Scientific & regulatory mobilisation

- EMA Health Threat Plan
- COVID-19 Task Force
  - EU Network
  - International

Development & evaluation

- Guidance to developers
- Early scientific advice
- Rapid procedures

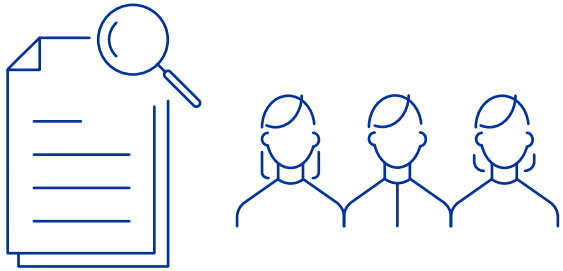
Essential medicines' supplies

- EU coordination
- Preventing shortages

Transparency & outreach

- Public engagement
- Communication

EMA’s scientific experts



COVID-19 vaccines and therapeutics must be approved according to the **same standards** that apply to all medicines in the EU

Evaluation by **EMA's expert scientific committees on human medicines**:

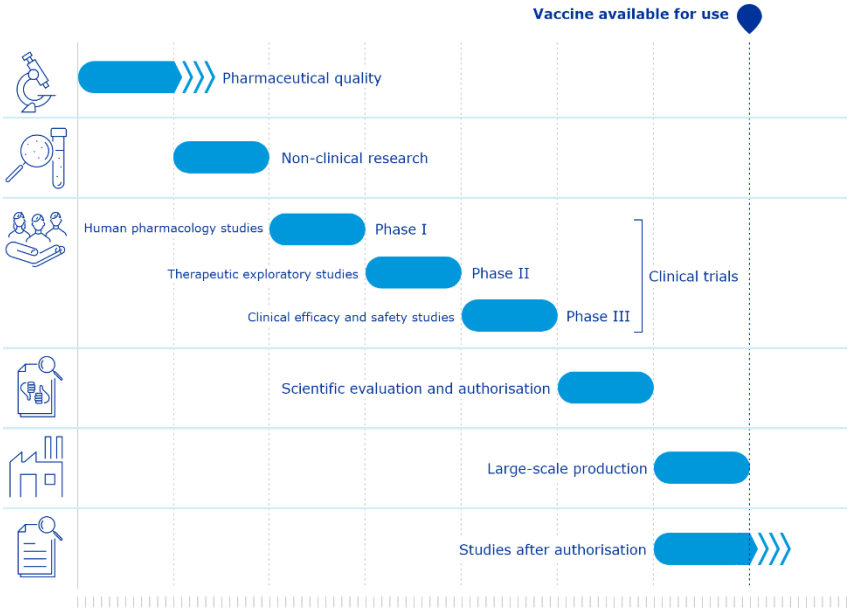
- **CHMP** (all aspects of medicines’ evaluation)
- **PRAC** (safety and risk minimisation)

Unprecedented pooling of expertise in Europe to **reduce timelines**

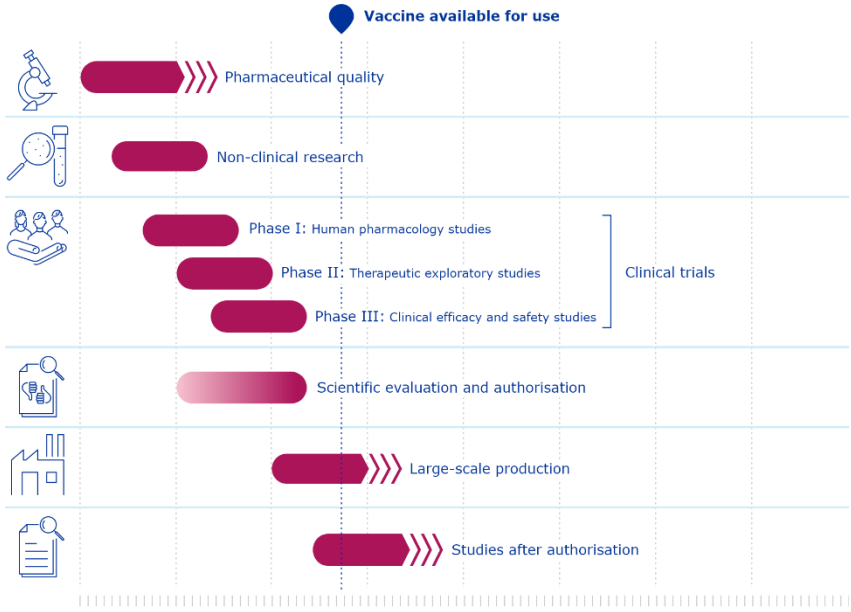
Multidisciplinary **COVID-19 Task Force (ETF)**, **key experts**

- From European medicines regulatory agencies
- Fast and coordinated response to the pandemic

COVID-19 vaccines compared with standard vaccines



Standard Vaccines



COVID-19 Vaccines

Overview

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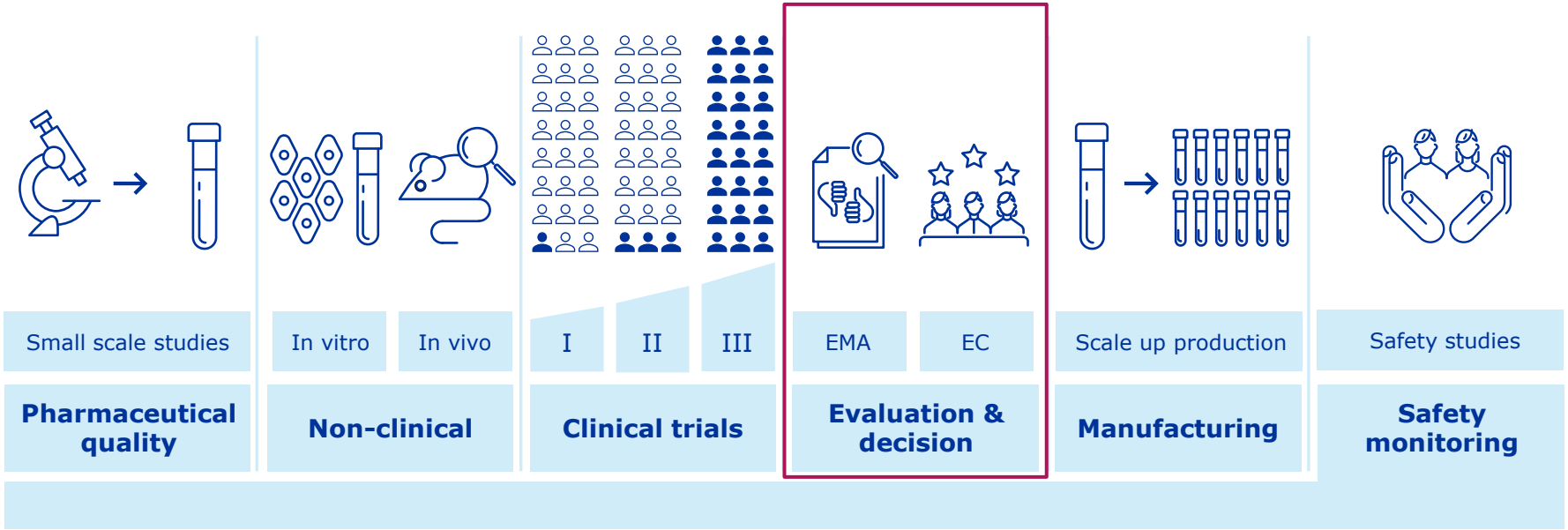
COVID-19 VACCINE DEVELOPMENT, EVALUATION, APPROVAL AND MONITORING



Rolling review

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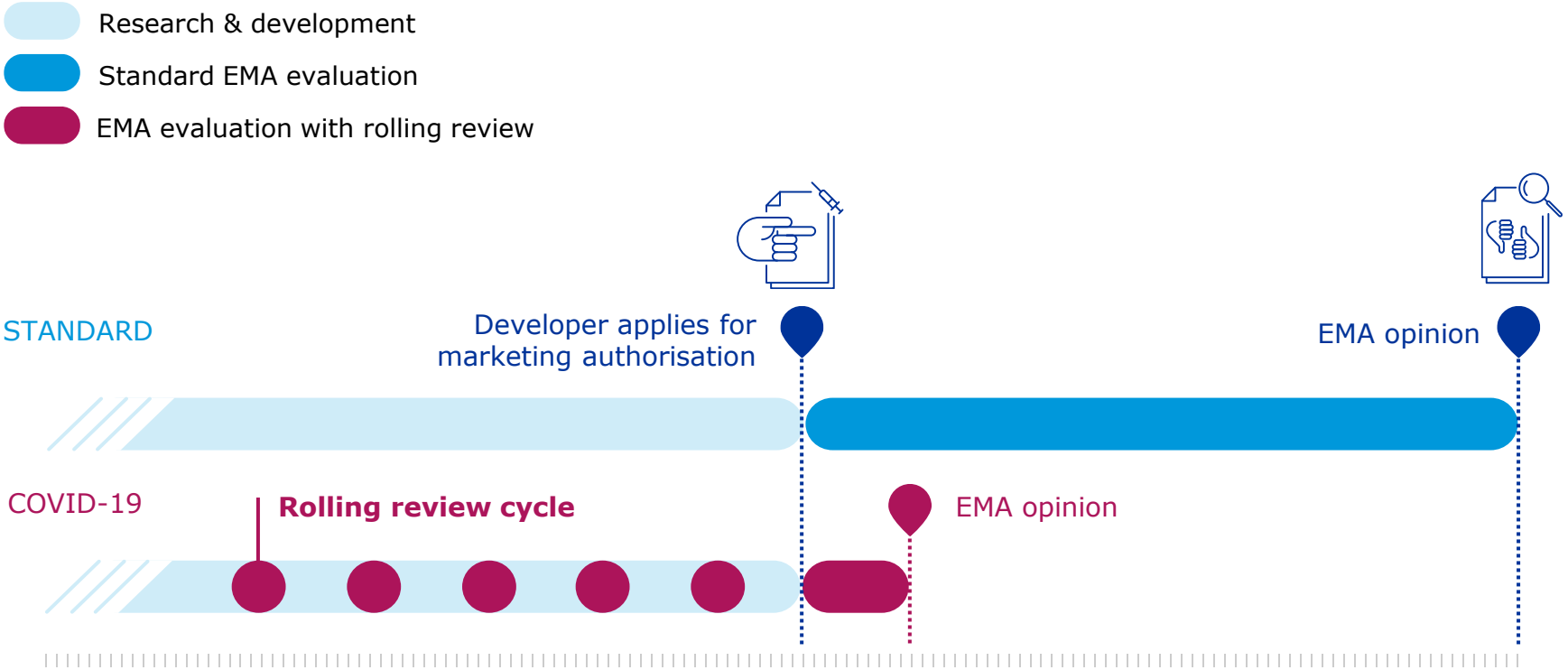

Conditional Marketing Authorisation (CMA)

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- **Formal marketing authorisation approval** of a medicine across the EU: **all member states benefit** from the joint scientific assessment and approval
- It has **all safeguards and controls** in place to ensure high level of protection to citizens during a mass vaccination campaign:

  - A robust **monitoring plan** for managing **safety**
  - Clear **legal framework** for evaluation of **emerging efficacy data**
  - **Manufacturing** controls including **batch controls** for vaccines
  - Full **prescribing information** and **package leaflet** with defined conditions for storage and use of the vaccine
  - A **plan** for **use** of the vaccine **in children**
  - **Additional studies or other data** ('conditions') that the company is **legally obliged** to provide with defined **timelines**

Post Authorisation Change

Ensuring adequate supply for EU market

- Fast scale –up of manufacturing capacity ; availability of necessary ingredients and delivery devices
- Parts of required info not normally part of the submission requirements
- Need for close collaboration and early exchange of information on supply strategy post approval between MAHs and regulators

Manufacturing and GMP - Need for Regulatory flexibility

- EC/EMA/HMA recognised the severity of the current circumstances and proposed regulatory flexibility until the end of the COVID-19 restrictions.
- GMDP IWG developed GMDP flexibilities and EC published in the Q&A on regulatory expectations for medicinal product for human use during the Covid-19 https://ec.europa.eu/health/sites/health/files/human-use/docs/guidance_regulatory_covid19_en.pdf
  - Automatic extension of validity date for the GMP certificates that can be used to support regulatory submissions.
  - Product specific GMP flexibilities for crucial medicines.
  - Non-product specific GMP, GDP and PMF specificities
- …

The challenge

Pandemic has challenged continued supply of some medicines and need for rapid increase in manufacturing capacity of some medicines.

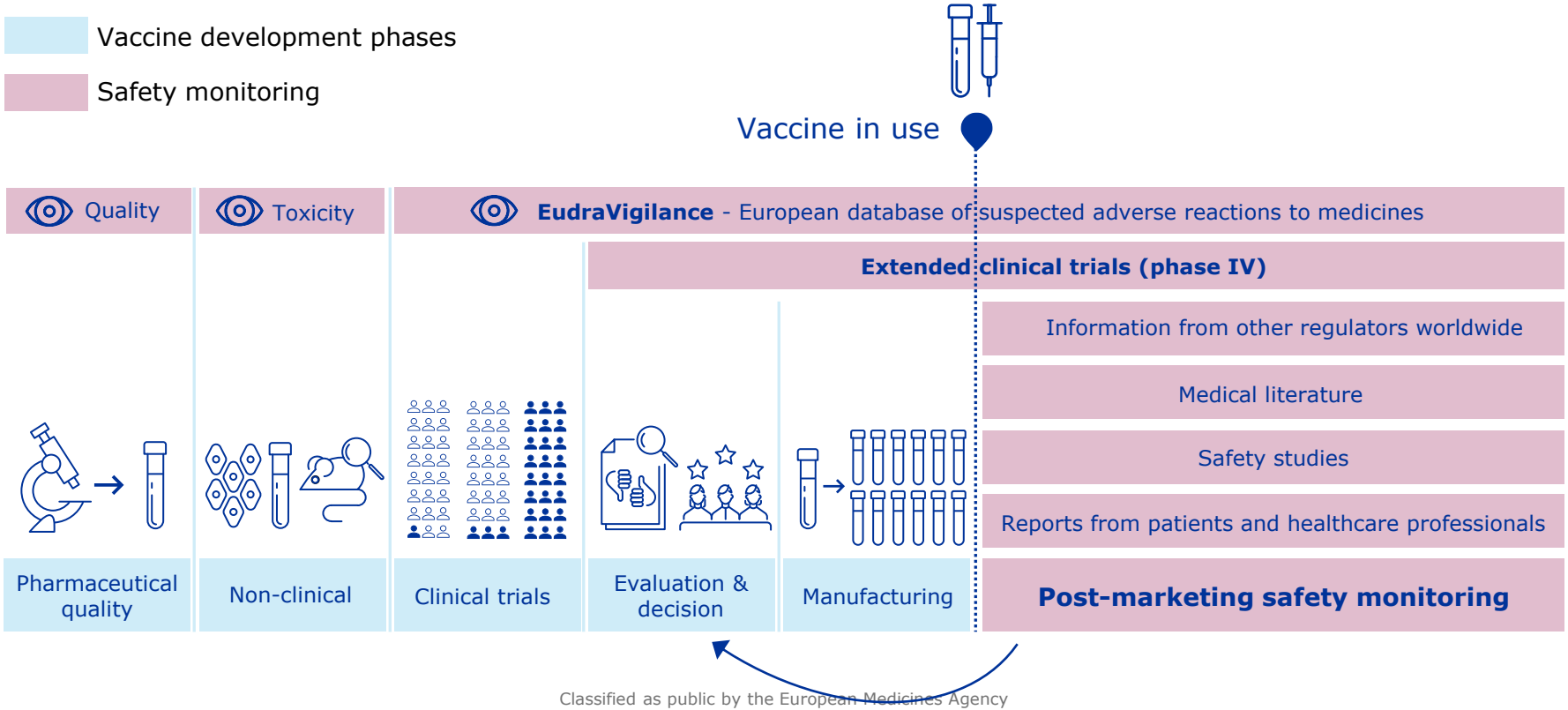
(a) the need for treatments and building rapid manufacturing capacity for COVID-19,

(b) medical innovation driving new products that should be available rapidly and globally,

(c) the global nature of pharmaceutical development and manufacturing

(d) global co-operation between regulators on post-approval changes.

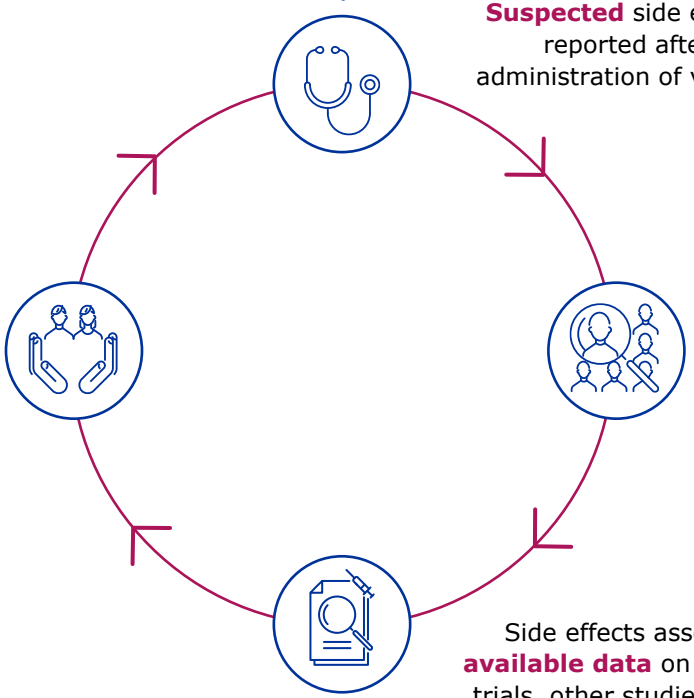
How is safety of vaccines studied from the development stage to use in real life?



How are regulators looking at safety reports?

CONTINUOUS MONITORING OF THE BENEFITS AND RISKS OF THE VACCINE

Suspected side effects reported after administration of vaccine



A **scientific assessment** looks at the suspected side effect in the context of the person's individual case to determine if it may be caused by the vaccine or occur for other reasons

Side effects assessed in the context of **all available data** on the vaccine, including clinical trials, other studies and the scientific literature

Conclusions are drawn on the **benefits and risks** of the vaccine:

Benefits continue to outweigh risks - new/ changing risks could lead to:

- Restrictions of use
- Contraindications
- Warnings or screenings/tests healthcare professionals should do before vaccination

Risks outweigh benefits – vaccine is removed from the market

Enhanced transparency for COVID-19 vaccines

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What information is being published ?

- Medicines that have received **EMA advice** during their development
- Committee **meetings highlights**, minutes and agendas
- Start of rolling review and applications for marketing authorisation
- **Product information** (all EU languages)
- An overview of the vaccine and why it is approved - in plain language (all EU languages)
- European Public **Assessment Report**
- Full **Risk Management Plan**
- **Clinical data** supporting marketing authorisation
- Changes post-authorisation and regular **safety updates**

International coordination needed to encourage conduct of large, decision-relevant COVID-19 clinical trials

Share

Press release 15/05/2020

Regulators are highlighting the need for a comprehensive international coordination mechanism to allow the conduct of adequately powered, randomised controlled trials, which can generate sound evidence on the effects of therapeutics or vaccines against COVID-19. This follows a call made by EMA's Human Medicines Committee (CHMP) for the research community to pool resources into large, well-designed, multi-arm clinical trials to determine which investigational or repurposed medicines would be safe and effective for the treatment or prevention of COVID-19.

Although the scientific community has responded to the COVID-19 challenge in an unprecedented manner, there are concerns about the growing number of COVID-19 stand-alone clinical trials with a small number of participants and observational studies, which might not generate the data required for regulatory decision-making.

Clinical Pharmacology & Therapeutics

REVIEW | Open Access

Clinical trials for Covid-19: can we better use the short window of opportunity?

Hans-Georg Eichler, Marco Cavaleri, Harald Enzmann, Francesca Scotti, Bruno Sepodes, Fergus Sweeney, Spiros Vamvakas, Guido Rasi

First published:14 May 2020 | https://doi.org/10.1002/cpt.1891

GUIDANCE ON THE MANAGEMENT OF CLINICAL TRIALS DURING THE COVID-19 (CORONAVIRUS) PANDEMIC

Guidance on the Management of Clinical Trials during the Covid-19 (Coronavirus) Pandemic

Enable continuation of treatment

Ensure Safety reporting

Ensure reliability of trial results, enable trials to continue

Mitigate burden on clinical site staff and facilities and on participants.

Enable management of clinical trials whilst maintain social distancing.

Use Risk assessment

Changes to:

- informed consent process
- distribution of IMP, diagnostics etc
- monitoring and auditing

Digitalisation - Challenges

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- Establishing Trust
  - Data provenance, validity (technical and scientific)
  - New data sources
  - Personal data protection – ensure protection whilst enabling clinical trial data to be used well – both are legitimate expectations of trial participants
  - Complex landscape or data generation, collection and analysis, digital communication, remote visits, use of wearables, electronic informed consent
- Need to set standards for use of digital tools and information that are universally applicable, future proof, ensure data trust and participant protection but support innovation and new approaches
- EU GCP IWG Draft Guideline on computerised systems and electronic data in clinical trials - open for comment 18 June to 17 Dec 2021

https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/draft-guideline-computerised-systems-electronic-data-clinical-trials_en.pdf

Decentralised Clinical Trials

- Decentralised approaches to clinical trials can be used, for the right research questions, medicines and therapeutic indications, i.e. those which DC approaches are capable of addressing.
- The autonomy and care of the trial participants needs to be assured.
- Sponsor and investigator have clear legal roles and responsibilities
- Build on existing experience with individual trial elements, use combinations that can answer the research questions and can generate trial results suitable to support the decision making required.
- Good guidance is an enabler – ICH E6 rewrite will address digital approaches and any special considerations for decentralised trials

GCP Renovation

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ICH Reflection on "GCP Renovation": Modernization of ICH E8 and Subsequent Renovation of ICH E6

News / Newsroom /

12 January 2017

ICH is inviting public review and comment on a reflection paper on Good Clinical Practice (GCP) "Renovation", which contains the ICH proposal for further modernization of the ICH Guidelines related to clinical trial design, planning, management, and conduct. The scope of the proposed renovation includes the current E8 General Considerations for Clinical Trials and further revision to the E6 Guideline for Good Clinical Practice, which is already undergoing modernization with the recent production of ICH E6(R2).

The reflection paper is available for download via the following link:

- Reflection paper on GCP Renovation

The goal of the potential renovation is to provide updated guidance that is both appropriate and flexible enough to address the increasing diversity of study types and data sources that are being employed to support regulatory and other health policy decisions, as appropriate. The underlying principles of human subject protection and data quality would remain. ICH's decision to invite stakeholder comment on the

E8 clinical trial design principles

E6 GCP clinical trial conduct principles

ICH GCP Renovation

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Redesign our approach to enable innovation in a Rapidly Evolving Ecosystem

Set the foundations to enable innovation by design and not by reaction

Vision for ICH E6(R3) GCP

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- Flexible to allow for and to encourage innovation, while helping ensure the protection of trial participants and reliability of trial results
- Focus resources and efforts on what matters most for participant protection and the reliability of trial results – critical to quality factors
- Focus on the intent and goal of GCP, and allow for the many ways these can be achieved
- Comprehensive principles that remain relevant as technology evolve and clinical trial design advances
- Leveraging and facilitating an increasingly digital ecosystem
- Thoughtful process throughout clinical trial conception, design, conduct and analyses

This is about doing things differently
– change –
We should not just add more to the status quo

Clinical Trial Regulation and CTIS Go-Live 31 Jan 2022

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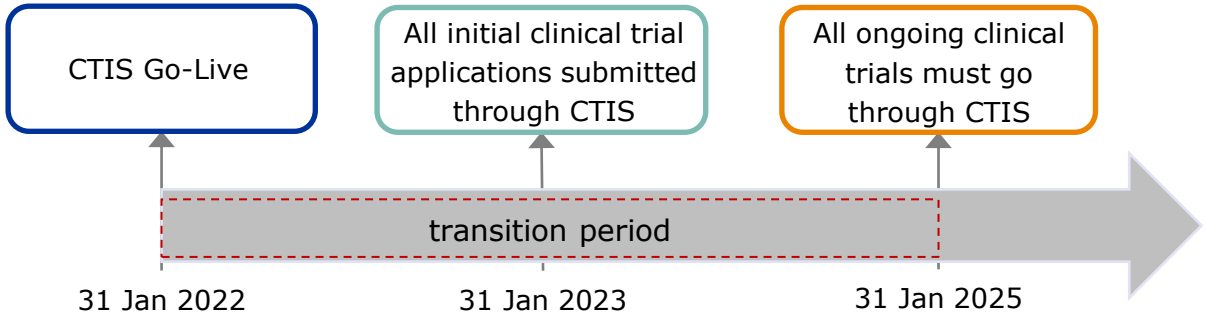
The Clinical Trial Regulation (EU) No 536/2014 and with it the Clinical Trial Information System come into application and use on **31 January 2022**

Member States will use CTIS from go-live. Sponsors can make use of a **transition period** for the submission of clinical trial applications.



Clinical Trials Information System - CTIS

Digitalisation & Improved Efficiency

Increased Transparency

Enhanced Patient Safety

Support to Innovation & Research

- Unique digital tool for harmonised submission, evaluation and supervision and storage of structured data and documents on clinical trials in the European Union.
- End-to-end fully electronic process over the life-cycle of a clinical trial.
- Member States benefit from tools for collaboration and coordination.
- Clinical trial sponsors can submit, manage and report on a trial in one single place throughout the lifecycle of this trial. CTIS allows flexibility to submit dossiers in parts.
- Easy access to structured data and documents on clinical trials for patients, healthcare professionals, scientists and the general public.

Clinical Trials Information System - CTIS

Digitalisation & Improved Efficiency

Increased Transparency

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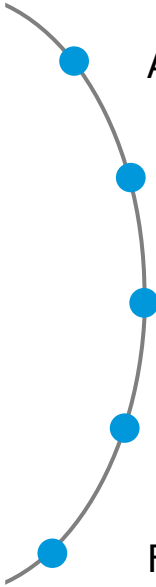
Support to Innovation & Research

- The **single EU entry point** for clinical trial application submissions for sponsors (e-dossier)
  A single application and maintenance process, dossier and timeline; covering clinical trial application to NCA, submission to ethics committee and registration of the clinical trial in a public register; all in one integrated submission
- Harmonised and simplified **end-to-end electronic application procedures** over the life-cycle of clinical trials across the EU
- Collaboration and **coordination in evaluation and supervision of clinical trials** for Member States
- Fully **electronic exchange** of information between sponsors and Member States
- Digital secured **archive** of documents, decisions and information on a clinical trial

CTIS Benefits

With CTIS sponsors can:



- Apply for a clinical trial in up to 30 EU/EEA countries with a **single application**
- Facilitate involvement of trial participants by allowing **easy expansion of trials to other EU/EEA countries**
- **Collaborate across borders** for better results and knowledge sharing
- Ensure the EU/EEA remains an attractive location for **clinical research investment**
- Fulfil all **clinical trial publication requirements** with no additional effort

Learning from Experience

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Rapid responses and regulatory flexibilities, pandemic still ongoing and evolving, fast learning and adaptation

Evolving regulatory landscape:

- Some of the challenges will be addressed through the extension of EMA mandate, other flexibilities and tools may be used, or adapted using the COVID experience,
- Use of digital tools has been accelerated
- Dialogue has been significantly increased along development pathway
- Reflect on experience, improve and select what works
- Need feasible, sustainable, tools for longer term, but it will be a new, different, landscape
- We can change now to act by design, based on experience and less by reaction to necessity
- Keep regulatory standards high along with speed and innovation

Thank you

Further information

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