CAPACITAR | AÇÕES DE FORMAÇÃO E BENCHMARKING

AICIB AGÊNCIA DE INVESTIGAÇÃO CLÍNICA E INOVAÇÃO BIOMÉDICA

Resposta aos desafios do Regulamento de Ensaios Clínicos nas atividades do Centro

Margarida Esteves Santana, ROCHE
Study Start-Up Specialist & Contract Manager
EU Country Submission Lead

TODAY

1. Legal Framework
2. Where are we? – CTR Roadmap
3. CTD versus CTR
4. CTIS
5. CTR Changes impacting how we work
6. Impact on site level
7. Submisison in CTIS / Documentation
8. Transitioning studies
9. Wrap up and Conclusion
10. Q&A

CAPACITAR | AÇÕES DE FORMAÇÃO E BENCHMARKING
AICIB

Legal Framework

Clinical Trials Regulation (Regulation (EU) No 536/2014)

European Union (EU) pharmaceutical legislation known as the Clinical Trials Regulation entered into application on 31 January 2022.

It aims to ensure the EU offers an attractive and favorable environment for carrying out clinical research on a large scale, with high standards of public transparency and safety for clinical trial participants.

REGULATIONS

REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 16 April 2014
on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC
(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on the Functioning of the European Union, and in particular Articles 114 and 168(4)(c) thereof,

Having regard to the proposal from the European Commission,

CTR repealed the Clinical Trials Directive (EC) No. 2001/20/EC and national implementing legislation in the EU Member States, which regulated clinical trials in the EU until the Regulation's entry into application.

CTR harmonises the processes for assessment and supervision of clinical trials throughout the EU.

The Regulation enables sponsors to submit one online application via a single online platform known as the Clinical Trials Information System (CTIS) for approval to run a clinical trial in several European countries, making it more efficient to carry out such multinational trials.

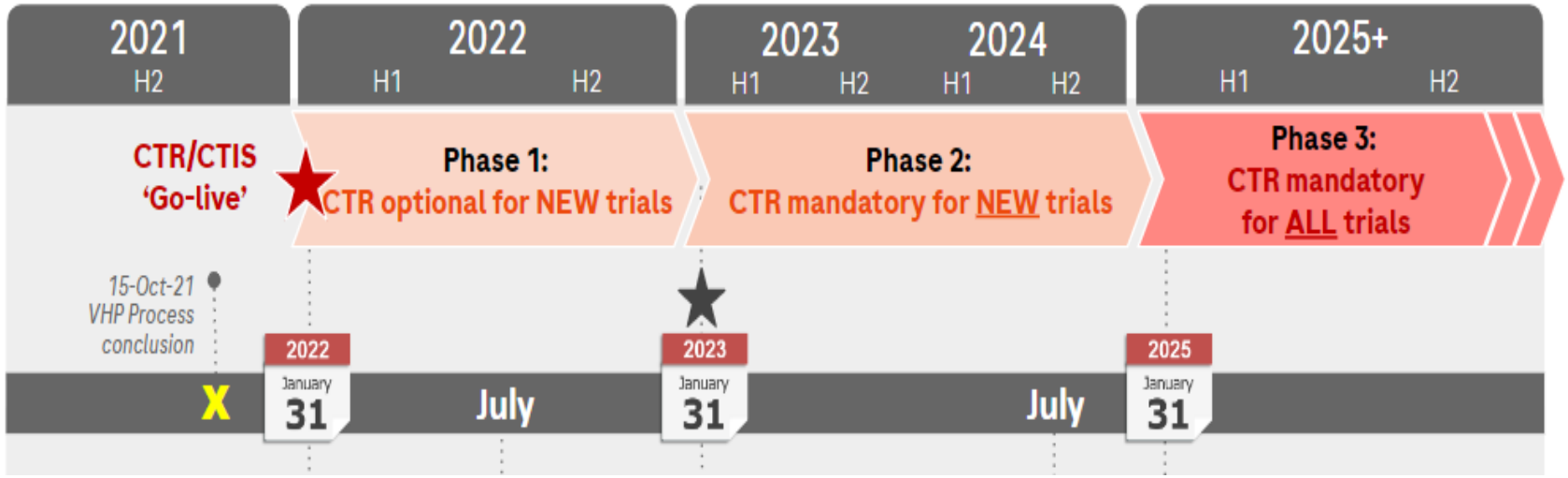
Fonte: EMA

Where are we? – CTR Roadmap

CTR is a new, patient-focused legislative requirement mandated by EMA, offering many benefits:

- ✓ A single, streamlined electronic submission and assessment process for clinical trials
- ✓ Standardized approvals and lifecycle management to reduce overall study timelines and costs
- ✓ Centralized and higher requirements for clinical trials safety
- ✓ Greater transparency for patients on trials data and results
- ✓ Trial modifications to be handled more efficiently and thoughtfully

EMA CTR Phases



- Under the new CTR process, a single dossier will be submitted via EMA's CTIS portal. This means all HA and EC submissions for Part I (common) and Part II (country specific) need to be **ready at the same time for all countries**
- **Greater coordination, oversight, and collaboration is required** to ensure there are no delays

Clinical Trial Regulation

An overview:

WHAT is CTR

The *Clinical Trial Regulation is new legislation* that will replace the Clinical Trial Directive (CTD).

WHY is it needed

The current CTD was associated with challenges that brought an *increased workload* and *administrative burden* for sponsors and regulators, *impacting the EU's attractiveness* for R&D

Scope of Impact

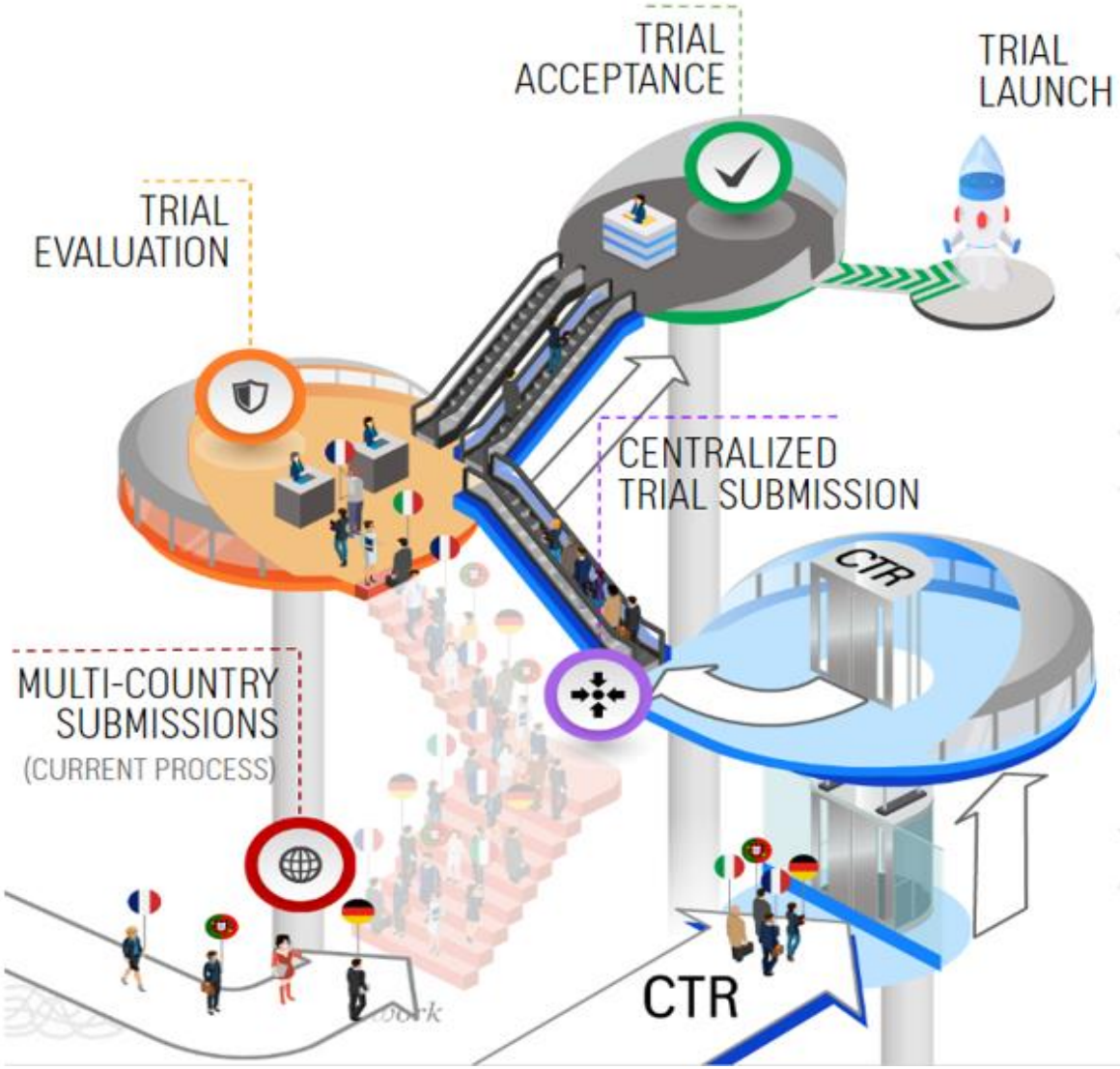
CTR will impact clinical trial *design, application & approval* processes, *safety reporting* and *disclosure requirements* for all EU/EEA states

(30 countries: 27 EU + Lichtenstein, Norway and Iceland - excluding Swiss + UK)

Benefits it will bring

CTR aims to *harmonise submission* and assessment processes, *improve cooperation* and *transparency* in and between Member States and *enhance overall safety standards*

Why CTR?



The Clinical Trial Regulation

Clinical Trial Regulation is **new legislation in the European Economic Area (EU/EEA)**, replacing the Clinical Trial Directive (CTD)

CTR will impact clinical trial design, application, and approval processes, safety reporting and disclosure requirements

CTR aims to harmonize the CTA (Clinical Trial Application) submission and assessment process, improve cooperation and transparency in and between EU/EEA countries, and enhance overall safety standards for patients

As part of CTR, **the EMA Clinical Trial Information System (CTIS) will be the only way to submit CTAs** in the EU/EEA

Clinical Trial Directive

Background:

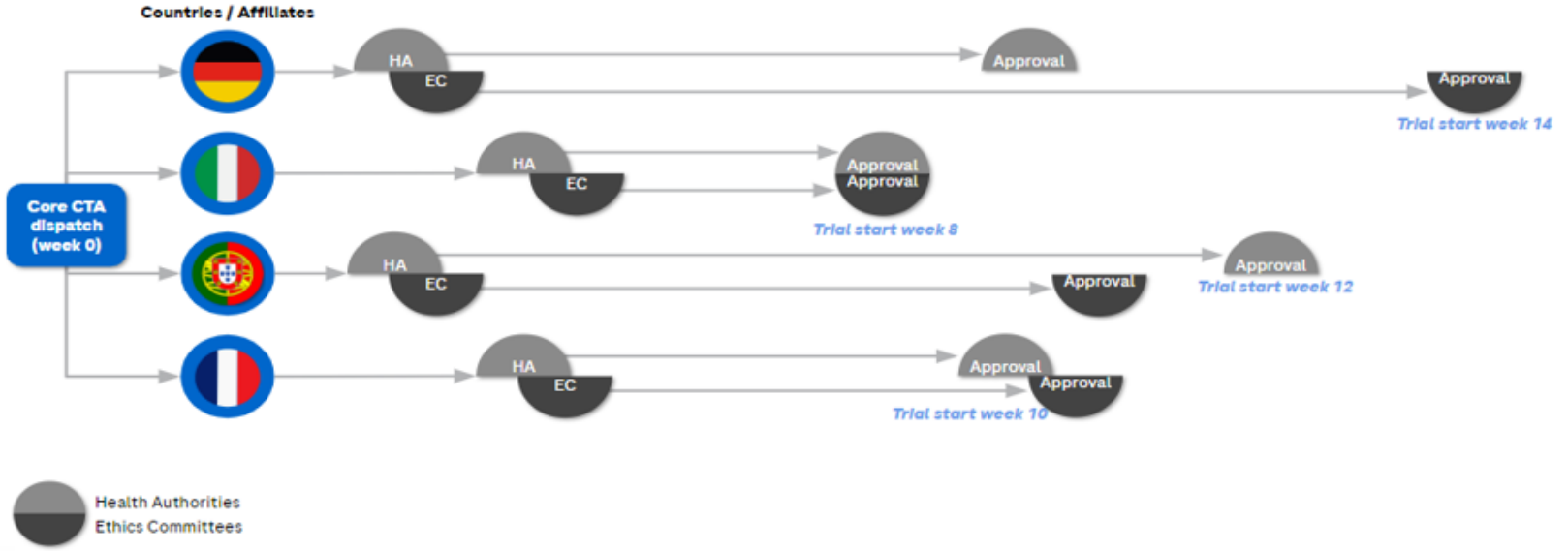
Old Approach: Clinical Trial Directive procedure

What the CTA process looks like under CTD

Large gap in country submission timelines for Health Authority and Ethics Committees submission, review (questions), and decision

Today, **amendments for single country dossiers** can be made - new countries and protocol changes can be added at any time during the trial

No single submission process or electronic system



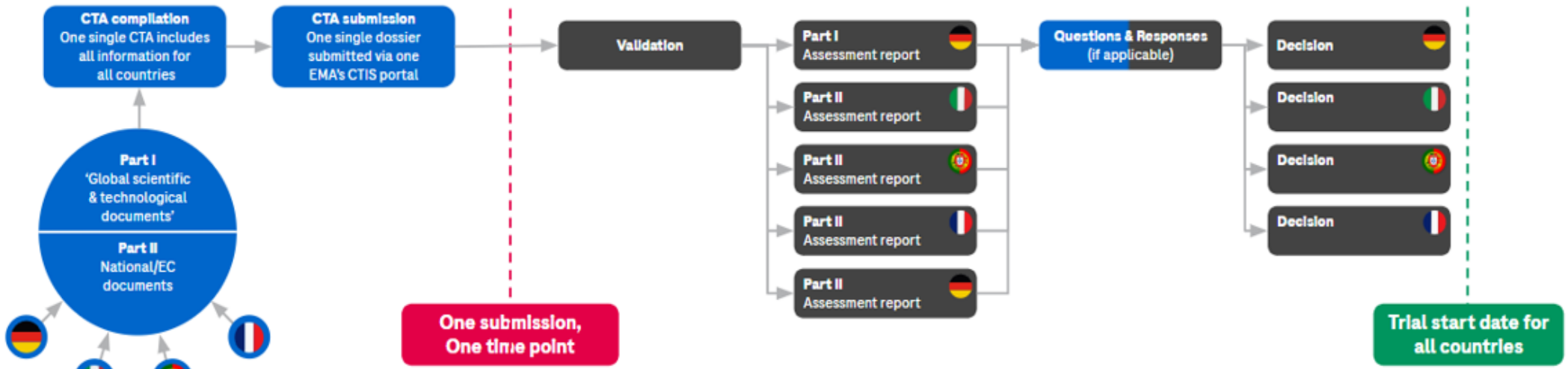
New Approach: CTR Procedure Requirements

What the CTA process looks like under CTR

No gap between HA and EC submission. Part I (common) and Part II (country-specific) need to be ready at the same time for all countries

A single electronic portal, the "Clinical Trial Information System", or "EU Portal", will serve as the single entry point for all CTA submissions

No changes to the dossier or country additions can be made while review is ongoing – review process will need to be stopped (with impact on timelines)



Note for amendments: Any country level change process, e.g. new principle investigator, will put the study on hold for any EU level amendments

Part I review lead by the RMS (reporting member state), issuing a **single part I RFI** (request for information).
Part II reviews are lead by MS (member state), issuing **RFIs per MSC** (member state concerned).
Maximum 12d to respond to RFI. Tacit approval / withdrawal concept.

= Sponsor

= EMA/Authorities

Summary of Key Changes from **CTD**irective to **CTR**egulation

CTR is a new, patient-focused legislative requirement mandated by EMA, offering many benefits:

What changes will EU CTR introduce?

Streamlined submissions

Submission of a single CT dossier to a central Clinical Trial Information System (CTIS), including information for all EU countries involved.

Improved assessment process

Single scientific CTA assessment

Identical standards throughout the EU.

Streamlined approvals for CTAs

Single CT approval for each EU country based on a common scientific review by Health Authority (HA) / Ethics Committee (EC) and national review by EC.

Tacit approval and withdrawal mechanisms in place.

Streamlined and simplified safety reporting

Standardised, single Safety reporting using EudraVigilance.

Transparency

CTIS information will be public unless confidentiality is justified.

under CTD (Clinical Trial Directive - guidance for local/national legislation)		*under CTR* (Clinical Trial Regulation - new central EU legislation)
Large gap in country submission **timelines** for Health Authority and Ethics Committees		**No gap** between HA and EC submission. Part I (common) and Part II (country-specific) ready at the **same time for all countries**
Amendments for single country dossiers - new countries and protocol changes added **at any time** during the trial		**No changes** to the dossier or country additions while HA review is ongoing - review process will need to be stopped (with **impact on timelines**). This will limit the number of amendments possible.
No single submission process or electronic system		**An electronic portal**, the "Clinical Trial Information System", will serve as the **single entry point** for all CTA submissions

What has changed under CTR?

CTR will impact clinical trial design, application and approval processes, safety reporting & disclosure requirements when running clinical trials across the EU/EEA - requiring multiple changes...

Clinical Trial Planning & Design

- Opportunity for **Co-Sponsorship & risk based approach** to trials with lighter regulatory regime (low Interventional CTs & AxMPs)
- **Earlier trial planning** & decision-making to ensure country components for country specific packages are ready in parallel
- **Greater time investment** for robust protocol development, final EU country list & choice of reporting MS

Tacit Approval / Withdrawal

- Objective = **one protocol** approved for all EU countries, with no deviations
- **Adherence to strict timelines** for HA questions to avoid tacit withdrawal
- **Well-defined timelines** will promote better planning and coordination of resources (enabling timely responses to avoid impact on approval timelines)

Amendments Limitation

- **Submissions to CTIS processed one at a time** (parallel filings not possible). This will require 'bundling' of changes for a study and potentially limit the timing and number of protocol amendments.
- Will require **greater appreciation of clinical trials ecosystem** and how decisions impact downstream processes.

Single dossier submission

- **New centralised process** to create and submit a single CTA dossier (for insourced & outsourced studies)
- **Greater coordination** between functions & roles to follow new E2E process
- Revision of impacted procedural documents and related processes

Supported by Technology

- **New IT infrastructure** required to enable
  - Centralised CTA Submission Planning & Tracking
  - Collection and management of EU Portal data
- Enhancements to existing solutions to ensure full compliance with CTR

Transparency

- More robust transparency requirements than current EU policy
- **Information** stored within EMA's CTIS **will be public** unless confidentiality is justified (nearly all Part I docs released, except the QIMPD)
- Disclosure and transparency considerations need to be built into planning

What has changed under CTR?

CTR will impact clinical trial design, application and approval processes, safety reporting & disclosure requirements when running clinical trials across the EU/EEA - requiring multiple changes...

Single dossier submission

- **New centralised process** to create and submit a single CTA dossier (for insourced & outsourced studies)
- **Greater coordination** between functions & roles to follow new E2E process
- Revision of impacted procedural documents and related processes

Study Teams...

- Now require **much greater coordination** between Functions and Affiliates to compile this single dossier
- Local study teams have to prepare the country package - as with CTD - but this is now done in a common system for all countries: **CTIS**

- ✓ Require much greater coordination
- ✓ Need cooperation and Team work
- ✓ Share timelines and expectations
- ✓ Readiness to answer

With this CTR approach, all European patients in participating countries have the same opportunity to access innovative drugs at the same time, via clinical trials, under the same protocol.

What has changed under CTR?

CTR will impact clinical trial design, application and approval processes, safety reporting & disclosure requirements when running clinical trials across the EU/EEA - requiring multiple changes...

Tacit Approval / Withdrawal

- Objective = **one protocol** approved for all EU countries, with no deviations
- **Adherence to strict timelines** for HA questions to avoid tacit withdrawal
- **Well-defined timelines** will promote better planning and coordination of resources (enabling timely responses to avoid impact on approval timelines)

Study Teams...

- Need good collaboration between the different stakeholders to meet the timelines, for ALL (Part I and all Part II) approvals

- ✓ Need cooperation and Team work
- ✓ Share timelines and expectations
- ✓ Communication is key to success
- ✓ Readiness from site – short deadlines to answer (no longer then 12 days)

What has changed under CTR?

CTR will impact clinical trial design, application and approval processes, safety reporting & disclosure requirements when running clinical trials across the EU/EEA - requiring multiple changes...

Amendments Limitation

- **Submissions to CTIS processed one at a time** (parallel filings not possible). This will require 'bundling' of changes for a study and potentially limit the timing and number of protocol amendments.
- Will require **greater appreciation of clinical trials ecosystem** and how decisions impact downstream processes.

- With CTR, **Substantial Modifications (SM) to the approved CTA require early planning** as parallel assessments are not permitted within CTR.
- **This will limit the number of substantial modifications** possible each year – likely a maximum of 3 to 4.

- ✓ Need to optimize how we plan and resource clinical trials
- ✓ Earlier trial planning – forward looking and plan ahead
- ✓ Comunication is crucial
- ✓ No changes to the dossier or country additions is permitted while HA review is ongoing – First Time Right approach
- ✓ Parallel submissions no longer possible
- ✓ New country: can only be added after initial trial approval, and cannot be added while other SM submissions are in progress

What has changed under CTR?

CTR will impact clinical trial design, application and approval processes, safety reporting & disclosure requirements when running clinical trials across the EU/EEA - requiring multiple changes...

Clinical Trial Planning & Design

- Opportunity for **Co-Sponsorship & risk based approach** to trials with lighter regulatory regime (low Interventional CTs & AxMPs)
- **Earlier trial planning** & decision-making to ensure country components for country specific packages are ready in parallel
- **Greater time investment** for robust protocol development, final EU country list & choice of reporting MS

Study Teams...

- Need to be interdependent on each other - **if one Affiliate isn't ready, this may impact everyone**

- ✓ Submission strategy
- ✓ More visibility of countries and sites performance
- ✓ Impact on choosing countries and sites
- ✓ Add country has to be a stand alone process
- ✓ Add sites may cause additional burden and delays
- ✓ Approval of "all or none" sites

What has changed under CTR?

CTR will impact clinical trial design, application and approval processes, safety reporting & disclosure requirements when running clinical trials across the EU/EEA - requiring multiple changes...

Transparency

- More robust transparency requirements than current EU policy
- **Information** stored within EMA's CTIS **will be public** unless confidentiality is justified (nearly all Part I docs released, except the QIMPD)
- Disclosure and transparency considerations need to be built into planning


Clinical Trial Sites

Organisation name	Site location	Site street address	Site city	Site post code	Site country	Title	First name	Last name	Department name	Telephone number	Email
European University Of Madrid	Calle Tajo S/n	Calle Tajo S/n	Villaviciosa De Odon	28670	Spain	2	first	last	xyz	12345	first.last@emat.de

Study Teams...

- Need to know the rules and...
- Build disclosure and transparency considerations into study planning

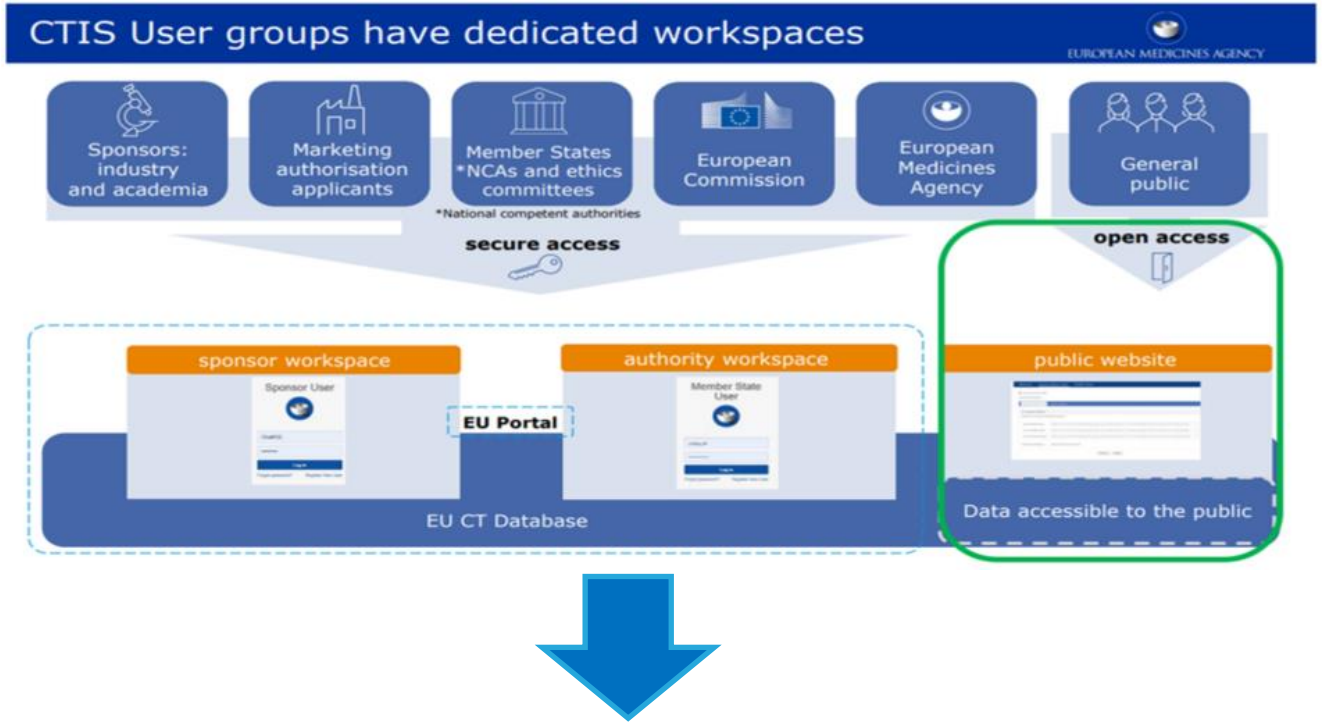
- ✓ Consider the time needed to prepare documentation before upload
- ✓ Submission documents require redaction to remove Company Confidential Information or Protection of Personal Data
- ✓ Redact and sanitize documents
- ✓ Some information will be publicly available after a deferral rule (timelines depend on the phase of the trial). Other information will be made public at the time of decision by the MSC e.g. Principal Investigator CV, Suitability of facilities. Contracts will not be public.

What has changed under CTR?

CTR will impact clinical trial design, application and approval processes, safety reporting & disclosure requirements when running clinical trials across the EU/EEA - requiring multiple changes...

Supported by Technology

- **New IT infrastructure** required to enable
  - Centralised CTA Submission Planning & Tracking
  - Collection and management of EU Portal data
- Enhancements to existing solutions to ensure full compliance with CTR



- ✓ EMA's electronic portal will be the single entry point for initial CTA applications, modifications/amendments, HA questions, Clinical Study Reports etc
- ✓ Need to create access and raise awareness
- ✓ Learn to work in the platform

Pulse check – Question 1

Sabendo que vamos ter um estudo a submeter no nosso centro, qual deverá ser o primeiro passo a realizar?

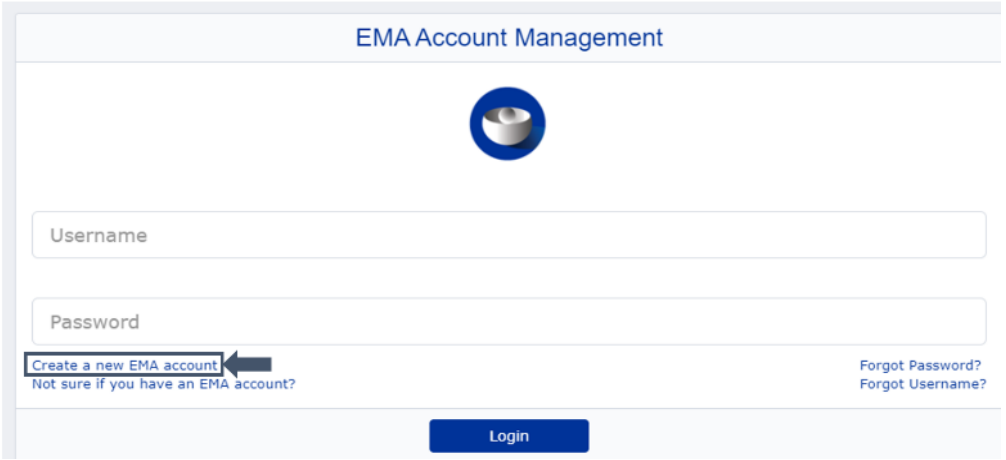
a) Começar a recolher documentação do investigador principal
b) Confirmar acessos: inscrição do centro no site OMS de forma a aparecer no CTIS
c) Recolha de assinaturas nas declarações do centro
d) Nenhuma das anteriores

CTR Changes Impacting how you Work

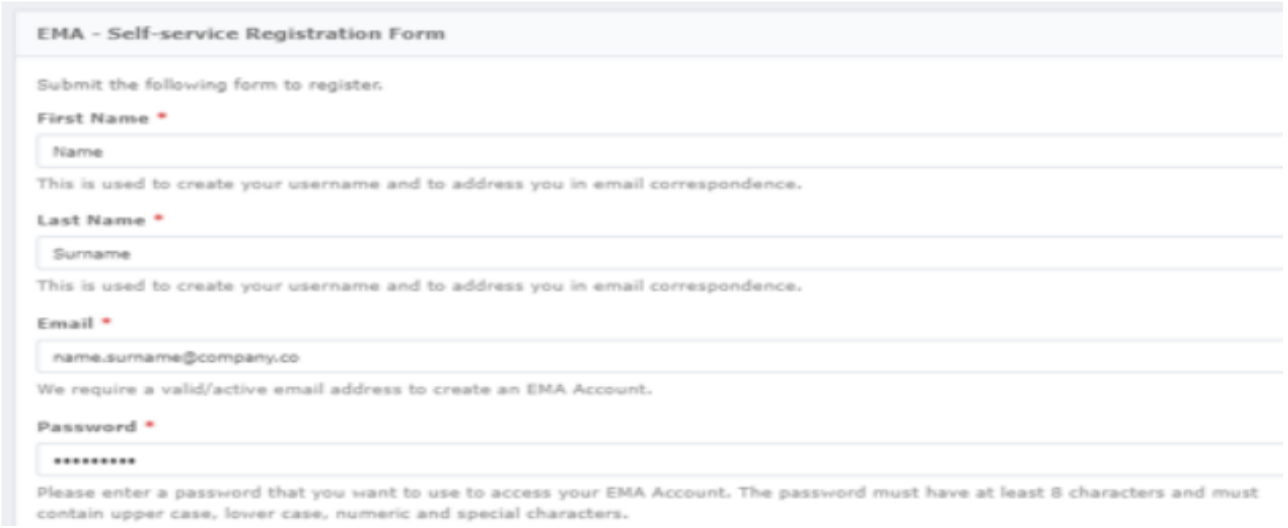
1.1 Create EMA Account

If you don't have an EMA Account, follow these steps to self-register:

1. Go to EMA Acccount Management (https://register.ema.europa.eu)
2. Click on " Create a new EMA account" which will open an "EMA - Self-service registration form";



3. Complete the "EMA – Self-service Registration Form" and click on "Register";



CTR Changes Impacting how we Work

1.2 Checking site availability in Organisation Management Service (OMS)

It is important to check if your site(s) is/are available in OMS. You can do this:
1. via drop-down list and search function in CTIS or

Organisation name	Site location	Site street address	Site city	Site post code	Site country	Title	First name	Last name	Department name	Telephone number	Email
University Of Vienna	Waehringer Strasse 13a, Alsergrund	Waehringer Strasse 13a	Vienna	1090	Austria		First	Last	Alergology	0000111111	investigator@university.com

Search an organisation

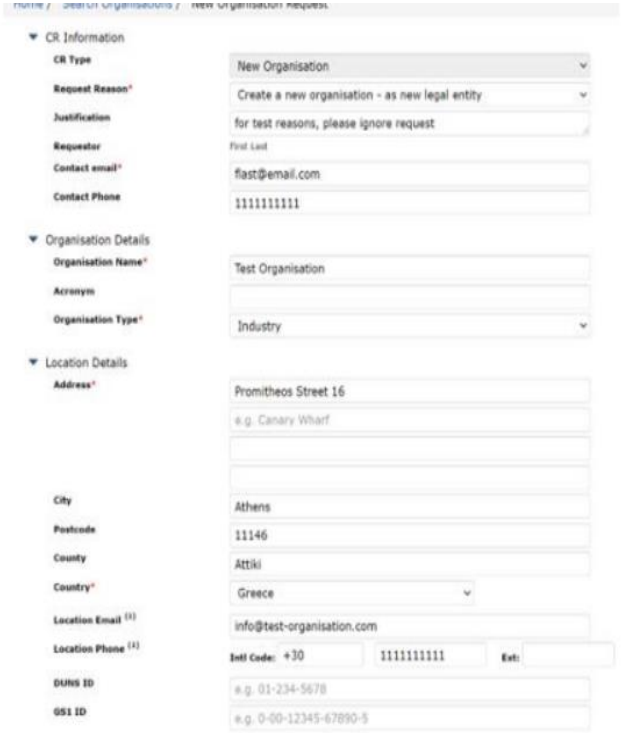
2. How to use the OMS Portal
First, users must log in with EMA account and then search if their organisation exists in the OMS Portal.

3. Ask your site to register themselves in OMS - please see OMS guide

Create a new organisation

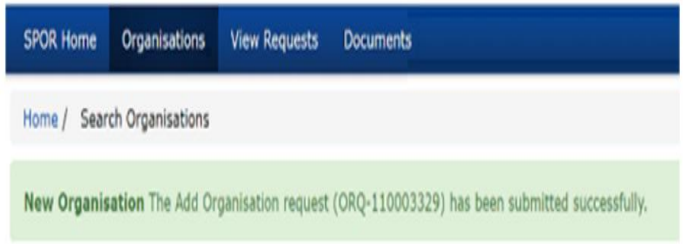
At the same time, a **new button** appears at the **bottom-right corner** of the search fields. Users can click on the '**Request new organisation**' button, which will redirect them to the **registration form**.

Users can then fill in the fields of the registration form accordingly. By default, the email is automatically populated coinciding with the email of the EMA user account of the creator of the organisation. The field can be edited, and the user may populate a different email for further communication during validation.

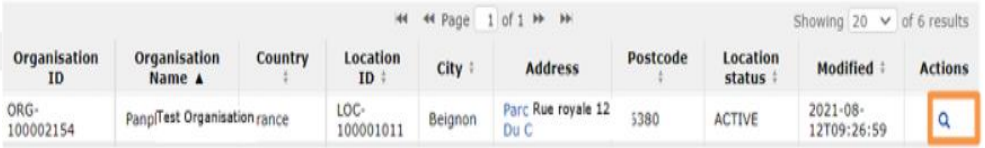


After populating all the information, users are expected to **upload the appropriate documentation in the 'Attachments' placeholders**, next to the populated information, by selecting the '**+**' button. If the documentation attached to the request is not compliant with OMS's requirements, it may lead to the rejection of the request.

After clicking the checkbox, users can select the '**Submit**' button in the **bottom right corner**. This will redirect the users back to the 'Search Organisations' page, in which a **message** above the search fields will appear, informing the user that the request has been submitted successfully and displaying a **Change Request ID**.



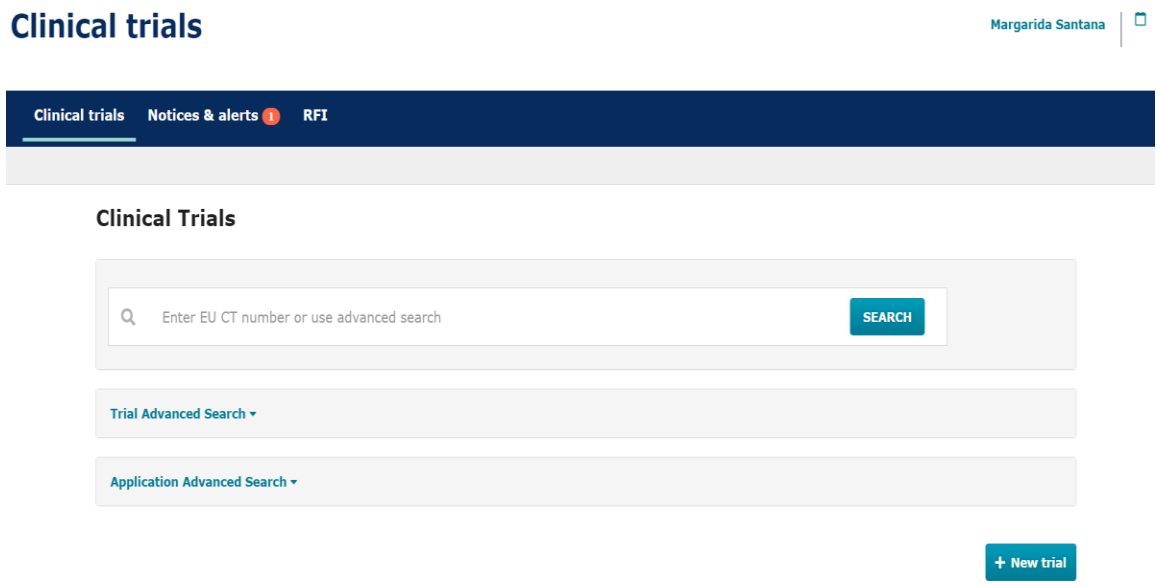
Users can **track** the **status** of their requests by accessing the '**View Request**' sub-tab which will be active once a request has been submitted. Users cannot retrieve a Change Request ID in the search functionality. Therefore, these can only be tracked through the 'View Request' sub-tab.



Submission in CTIS

How to submit an initial CTA in the CTIS?

EMA Tutorial video



https://www.youtube.com/watch?v=jmylMwZFroc

Submission in CTIS

Application Dossier

Application dossier Part I (non-exhaustive list)

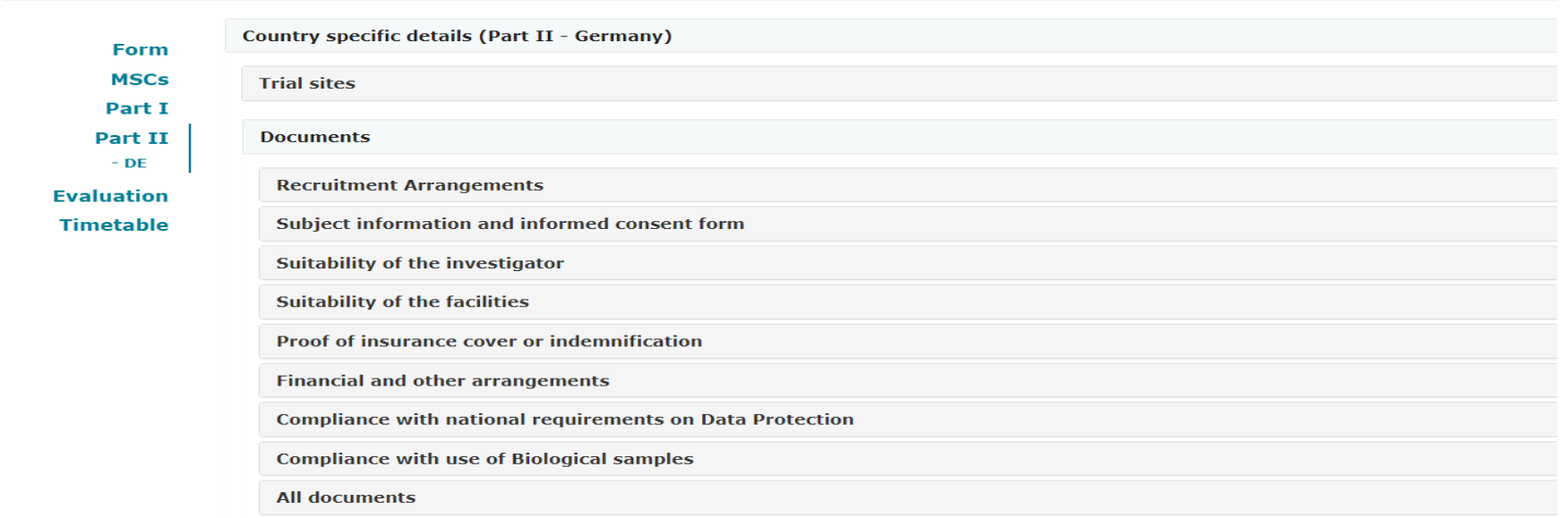
- Unique EU trial number
- Cover letter
- Protocol with synopsis
- Investigator's brochure
- Manufacturing and import (products not authorised in EU/EEA)
- Investigational Medicinal Product Dossier: Quality/Safety and Efficacy
- Auxiliary Medicinal Product (AxMP) - required in the clinical trial but not IMPs
- Scientific advice, Paediatric Investigation Plan (PIP)
- Labelling

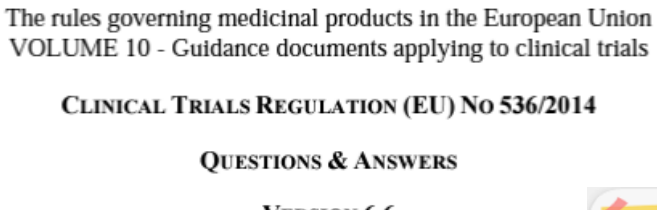
Application dossier Part II (non-exhaustive list under CTR)

- Recruitment arrangements
- Informed consent and subject information
- Subject compensation
- Suitability of investigator and trial facilities
- Proof of insurance/damage compensation
- Proof of payment
- Data protection
- Biobank samples

Country specific documents - Part II

What are the key documents for Part II under CTR?



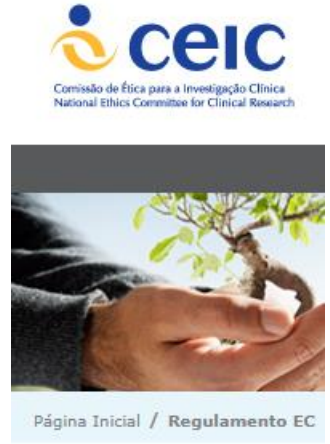

The rules governing medicinal products in the European Union
VOLUME 10 - Guidance documents applying to clinical trials

CLINICAL TRIALS REGULATION (EU) NO 536/2014

QUESTIONS & ANSWERS

VERSION 6.6

- ✓ Q&A 6.6 - Set 2023 - See Annexe II page 125/6 for part I language requirements and Annexe III for the national part II requirements
- ✓ Guidance CEIC / Listas de verificação
- ✓ Guidance CEIC / Contratos



https://www.ceic.pt/regulamento-ec

REPÚBLICA PORTUGUESA
SAÚDE

SNS SERVIÇO NACIONAL DE SAÚDE

ceic
Comissão de Ética para a Investigação Clínica
National Ethics Committee for Clinical Research

LISTA DE VERIFICAÇÃO de DOCUMENTOS

Novo Ensaio – Parte II Regulamento EC

Nº EudraCT (EU CT number):	Título:
Requerente:	

☐ **pedido de elementos a:** Clique ou toque para introduzir uma data.

☐ **resposta a pedido de elementos a:** Clique ou toque para introduzir uma data.

☐ **Modalidade de Recrutamento – Pasta K**

☐ Descrição da modalidade de recrutamento – obrigatória caso não conste do Protocolo

☐ Materiais de Recrutamento

➢ Listar todos os materiais de recrutamento:

Nome do Material	Versão	Observações

☐ **Informação dos Sujeitos do Ensaio – Pasta L**

☐ Assinalar no caso de utilização do *template*:

informedconsent_p
atientrecruitmentpr

➢ Listar todos os formulários de consentimento informado/assentimentos:

Part II
- GR
- BE

Trial sites

Documents

Recruitment Arrangements

Subject information and informed consent form

Suitability of the investigator

Suitability of the facilities

Proof of insurance cover or indemnification

Financial and other arrangements

Proof of payment of fee

Compliance with national requirements on Data Protection

Compliance with use of Biological samples

All documents

Pulse check – Question 2

V ou F:

É mandatório a utilização dos templates da EMA para a documentação do centro de ensaio?

Recruitment arrangements

Recruitment and Informed consent procedure template

How to use this document

It is not mandatory to use this template for describing recruitment arrangements (Annex I K.59) and/or informed consent procedure (Annex I. L) but where this template is not used for this purpose, all the relevant information below should be included in the protocol as a minimum, according to Annex I (D.17.z). This is notwithstanding additional appropriate information also being included in the protocol.

Sections which are not appropriate should either be deleted or marked as Not Appropriate / NA.

This template has been endorsed by the EU Clinical Trials Coordination and Advisory Group (CTAG) to comply with Regulation (EU) No. 536/2014 Clinical Trials on Medicinal Products for Human Use.

EU trial number	
Title of clinical trial	

1. All clinical trials *(This section should be completed for all trials)*

1.1	How will potential participants be identified? *(e.g. publicising the trial or via existing patient lists)*
Click or tap here to enter text.	
1.2	What resources will be used for recruitment? *(Describe the format of the resources, e.g. paper or electronic and how these will be presented to potential participants e.g. via the post, in the clinic, through social media or on the radio)*
Click or tap here to enter text.	
1.3	Will identification of potential participants involve access to identifiable information? If yes, describe what measures will be in place to confirm that access to this information will be lawful *(in accordance with Member State requirements).*
Click or tap here to enter text.	
1.4	Who will be approaching potential participants and who will be obtaining informed consent? *(Describe the professional role and whether there is a prior clinical relationship with potential participants)*
Click or tap here to enter text.	
1.5	When will free and informed consent be obtained? *(Describe when and where informed consent will be obtained and how privacy will be ensured)*
Click or tap here to enter text.	
1.6	How long will potential participants (or their legal representative) be given to decide whether to participate?
Click or tap here to enter text.	
1.7	How will it be assured that potential participants (or their legal representative) have understood the information and that consent is informed? *(This should include how the informational needs of individuals will be identified and addressed)*
Click or tap here to enter text.	
1.8	What arrangements are in place to obtain informed consent from potential participants (or their legal representative) who do not speak the national language?
Click or tap here to enter text.	
1.9	How will it be ensured that participants can withdraw their consent at any point? *(This should include how any potential consequences of consent withdrawal will be dealt with)*
Click or tap here to enter text.	
1.10	Please provide any further information, in relation to the procedure for recruitment and informed consent for the clinical trial, which has not been provided elsewhere in this document. *(It is recommended that you refer to national guidance to ensure that all required information has been provided)*
Click or tap here to enter text.	
1.11	In case this form is used also to describe recruitment arrangements (Annex I K59), please provide a clear indication of what the first act of recruitment is
Click or tap here to enter text.	

2. Clinical trials which will recruit incapacitated adults

Incapacitated adults may be recruited into clinical trials only where consent has been obtained from legally designated representative and data of a comparable validity cannot be obtained in clinical tria involving participants who are competent to give informed consent. Where potential participants do la capacity to consent, arrangements should be in place to involve them as much as possible in th decision to participate in the clinical trial.

2.1	Provide justification for recruiting incapacitated adults *(This should include details of the nature of the condition which has caused the person to be incapacitated and the relevance of this condition to the clinical trial)*
Click or tap here to enter text.	
2.2	Who will assess and confirm whether a potential participant has the capacity to consent?

Suitability of Investigator

Declaration of Interest Template

This template may be used by Sponsors of clinical trials as part of the application dossier. A separate declaration should be completed and submitted for the Principal/Lead Investigator at each site.

This template has been developed and endorsed by the EU Clinical Trials Expert Group to comply with Regulation (EU) No. 536/2014 Clinical Trials on Medicinal Products for Human Use. However, this template is also relevant under Directive 2001/20/EC and may be used in advance of the Regulation applying.

The following declaration is in relation to the following clinical trial [Please insert the full title and reference number below]

Click or tap here to enter text.

Are there any interests, such as economic interests, institutional affiliations or personal interests, which may influence your impartiality?

Yes ☐ No ☐

If Yes, please give details of all interests:

Click or tap here to enter text.

I declare that the information provided above is accurate to the best of my knowledge.

Name of investigator: Click or tap here to enter text.

Name of Institution: Click or tap here to enter text.

Signed: Click or tap here to enter text.

Date: Click or tap to enter a date.

Site Suitability

Site Suitability Template

- This form may be used by Sponsors of clinical trials as part of the application dossier. This is not a mandatory form and different national arrangements may be in place which should be confirmed prior to submission.
- To minimise the number of Request For Information (RFIs) that could be raised during the process and possible rejection, kindly provide detailed and informative responses to each and every question at the best of your knowledge.
- When completing this form, any national guidelines should also be referred to with regards to which sections must be completed. Where no national guidelines exist, the form should be completed in full.
- Where information which is requested in this form is provided elsewhere in the application dossier, the document can just be referenced rather than repeating the information.
- A separate document should be completed and submitted for each site.
- By using this template, the CTR Annex I requirement N.67. is fulfilled.

This template has been endorsed by the EU Clinical Trials Coordination and Advisory Group to comply with Regulation (EU) No. 536/2014 Clinical Trials on Medicinal Products for Human Use.

Section 1	
EU trial number	
Title of clinical trial	
Name of site, city	
If applicable[1], unique identification number of the site	
Name of principal investigator	
Planned number of trial participants at the site	

Section 2
a) Please provide a comprehensive written statement on the suitability of the site adapted to the nature and use of the investigational medicinal product.

[1] This request is only applicable in those countries where sites are identified with a unique identification number. This helps identifying the specific site.

Template site suitability statement, Version 3.0, September 2023

Click or tap here to enter text.
b) Please describe in detail the suitability of the facilities
Click or tap here to enter text.
c) Please describe accurately the suitability of the equipment
Click or tap here to enter text.
d) Please provide a detailed description of all trial procedures which will take place at the site.
Click or tap here to enter text.
e) Please provide a detailed description of Human Resources arrangements and expertise at the site
Click or tap here to enter text.

Section 3
In authorising this document, I confirm that the site has the facilities and equipment to be able to conduct the clinical trial and has suitable arrangements in place to ensure that all investigators and other individuals involved in conducting the trial have the suitable qualifications, expertise and training in relation to their role in the clinical trial, in compliance with EU Regulation 536/2014, and all conditions identified, which might influence the impartiality of any investigators, were addressed. Issued by: Name: Click here to enter text. Position: Click here to enter text. On behalf of the site/organisation Date: Click here to enter a date. **Please ensure that you have consulted with any national guidelines before submitting this form**

NB : The CTR does not require signing individual documents in the clinical trial application – a request for signature could however be subject to national legislation.

Compliance with national requirements on data protection

Statement of compliance with Regulation (EU) 2016/679 (GDPR)

Sponsor	
Title of the clinical trial	
EU CT Number	

The sponsor declares that data have been and will be collected and processed in accordance with the General Data Protection Regulation (EU) 2016/679 (GDPR).

Date:

Name and surname[1] :

Role in the sponsor organisation :

Compliance with use of biological samples

Template version, CTEG 28/01/2022

Compliance with Member State applicable rules for the collection, storage and future use of human biological samples (Article 7.1h)

Full title of the clinical trial	EU trial number
Click or tap here to enter text.	Click or tap here to enter text.
Responsible entity for the samples (legally): Click or tap here to enter text.	

How to use this document

This form may be used by Sponsors of clinical trials in the Part II application dossier to provide information about "compliance with the applicable rules for the collection, storage and future use of biological samples from clinical trial subjects" (Regulation (EU) No 536/2014, Article 7.1 (h)). This is not a mandatory form and different national arrangements may be in place, which should be confirmed prior to submission.

If the information is already provided elsewhere in the Application Dossier, a reference should be provided. To facilitate use of the template, each section can be compressed by clicking on the title.

This Part II template has been developed by the EU Clinical Trials Expert Group to comply with Regulation (EU) No 536/2014 Clinical Trials on Medicinal Products for Human Use.

I - Description of the biological samples involved in the clinical trial
Section 1 - Does this clinical trial involve new sampling of the subjects (newly collected samples)? ☐ **Yes, please fill in the requested information in section 1** ☐ **No, not applicable. Please continue with section 2** **Note: The sponsor needs to fill in *at least one* of the sections 1 or 2**
1.1 What type(s) of samples will be collected from the subject? *State the original material that is collected from the patient e.g. blood, tissue (state type of tissue), urine, saliva etc. Do not include information on the preparation of the sample.* Click or tap here to enter text.
1.2 Total number of samples, fragments (e.g. aliquots, tissue blocks, sections) and the total volume (if applicable) per individual subject: Click or tap here to enter text.
1.3 The maximum number of samples and maximum volume (if applicable) on one single occasion: Click or tap here to enter text.

Contratos - Esclarecimento CEIC relativo a Disposições Financeiras - Destaques

- O promotor deverá celebrar com cada centro de ensaio clínico um contrato, que consagra e corresponde, aos termos e condições do ensaio, **condições financeiras e aspetos económicos** relacionados com o ensaio, designadamente a remuneração do centro e do investigador e custos indiretos associados ao ensaio clínico, e demais aspetos a que se refere a letra P do anexo I do Regulamento, que integraram o pedido e que foram objeto de avaliação e aprovação pela CEIC.

- 2. Sobre a submissão da Parte II no CTIS, no que diz respeito à informação sobre disposições financeiras e outras:

- 2.1. Deverá submeter-se informação de acordo com a informação mínima obrigatória solicitada pela CEIC em anexo a este documento.

 O promotor deverá submeter a informação de modo objetivo e concreto, no formato que entender (*contrato tipo; contrato draft; listagem ou tabela*)

- 2.2. O envio dos *quadros sinóticos* deixa de se aplicar.

- 3. Sobre a designação da equipa de investigação, para cada centro de ensaio, deve ser comunicado à CEIC:

a identificação nominal do Investigador Principal;

a composição (quantitativa e qualitativa) da equipa de investigação prevista, discriminando a diferenciação profissional necessária à condução do ensaio em concreto, não sendo obrigatória a sua identificação nominal.

- 4. A decisão sobre o estudo (parte II) irá incluir a decisão sobre as disposições financeiras que foram submetidas ou alteradas no contexto do pedido de esclarecimentos. Não obstante, o contrato celebrado deve corresponder aos termos e condições que integram o pedido de avaliação e que foram objeto de avaliação pela CEIC.

- 4.1. Sempre que possível, o contrato financeiro celebrado deve conter todas as condições contratuais com todas as partes envolvidas. Excecionalmente poderão aprovar-se outros contratos para centros externos ou outros serviços adicionais ao contrato tipo como tem sido feito até à data.

- 4.2. Quando existam alterações no contrato celebrado, em relação aos termos e condições aprovadas pela CEIC, o promotor deverá submeter o respetivo pedido sob a forma de alteração substancial...

Contratos

Esclarecimento CEIC relativo a Disposições Financeiras - Destaques

- 4.2. Quando existam alterações no contrato celebrado, em relação aos termos e condições aprovadas pela CEIC, o promotor deverá submeter o respetivo pedido sob a forma de alteração substancial...
- 4.3. A título meramente facultativo recomenda-se que seja dado conhecimento à CEIC, por parte dos promotores, dos contratos financeiros celebrados. Não haverá lugar a resposta por parte da CEIC.

Deixa de ser necessário submissão dos contratos assinados, não precisamos de ter o "exequível" para a activação do centro

5.2.1. Constituem alterações que requerem PAS:

- alterações às condições e/ou conteúdos aprovados;
- qualquer nova condição contratual que implique pagamento adicional ao centro de estudo;

  alteração de IP ou da equipa de investigação, por especialidade; isto é, retirada de um especialista, substituição de uma especialidade profissional por outra; alteração da distribuição percentual da verba por função da equipa de investigação, igual ou superior a 20,1%, como por exemplo ajustes aos montantes destinados ao IP e aos co-investigadores;
- alteração na verba total superior a 10,1%; alteração na distribuição entre equipa de investigação e o centro superior a 10,1%;
- alteração que preconize pagamento ao IP (ou equipa) em função do número (e tempo) de doentes recrutados;
- alteração de um elemento coordenador do estudo, que esteja em diferentes condições do coordenador aprovado pela CEIC, como por exemplo substituição de um coordenador que pertence à instituição (e tem número mecanográfico) por outro, externo, que não pertença à instituição;
- modificações na redação do texto relativo ao fornecimento do ME após conclusão do estudo que alterem o sentido;
- modificação das condições/modalidades de reembolso das despesas aos participantes e pagamento de perdas salariais;

5.3. Não obstante a necessidade de o Promotor submeter um PAS para uma alteração igual ou superior a 20,1% por função relativa à distribuição das verbas, ou de igual ou superior a 10,1% em relação à verba total do estudo, ou da distribuição entre equipa de investigação e o centro,

pode o centro iniciar o recrutamento após o ensaio receber autorização às Partes I e II (e antes da aprovação do PAS),

desde que seja submetido à CEIC uma declaração de compromisso do Promotor em como não realizará pagamentos ao centro até que a CEIC se pronuncie sobre esse contrato com as alterações face às disposições financeiras aprovadas.

Contratos

Anexo I

Anexo I - Informação sobre Disposições Financeiras e outras, Letra P do Anexo I do Regulamento de Ensaios Clínicos, cujos elementos integram o pedido de avaliação.

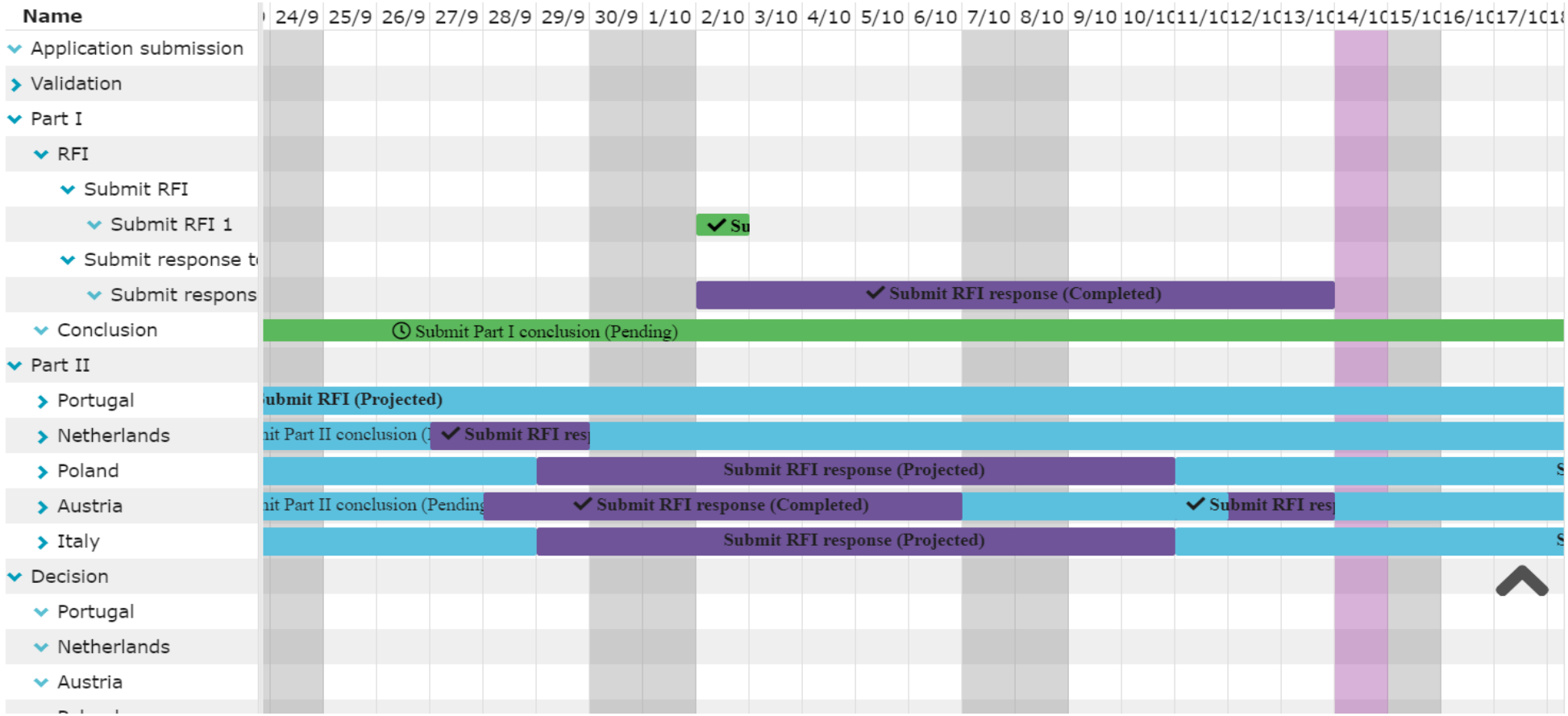
1) Identificação das partes:
   a) Promotor/ou financiador;
   b) Centro Ensaio (Instituição, serviço/unidade);
   c) Investigador Principal (identificação nominal);
   d) Centros Externos para realização de exames imagiológicos ou outros;
   e) Outras entidades prestadoras de serviços (se aplicável);
2) Objeto do acordo;
3) Descrição sucinta do financiamento do ensaio clínico;
4) Condições do centro: serviços e estruturas disponibilizados para realização do estudo (inclui o recurso a centros externos, quando aplicável).
5) Distribuição de verbas:
   a) Encargo total por participante e identificação dos custos diretos e indiretos;
   b) Encargo total do ensaio;
   c) Custos diretos (distribuição da verba, em termos percentuais):
      i. instituição e/ou serviço;
      ii. unidade de investigação (se aplicável);
      iii. equipa de investigação: investigador principal e restante equipa (remuneração identificada em % para o IP e para a restante equipa);
      iv. outras entidades prestadoras de serviços (quando aplicável);
   d) Custos indiretos:
      i. despesas previstas por protocolo (ex: meios complementares de diagnóstico);
      ii. despesas dos participantes e acompanhantes se aplicável (transporte, alimentação, perdas salariais, taxas moderadoras, outras necessárias);
      iii. internamento e/ou outros cuidados médicos não previstos;
      iv. outros encargos/custos com os participantes;
   e) Outros custos (se aplicável): Investigador Coordenador; compensação a participantes saudáveis;
6) Medicação do estudo:
   a) Fornecimento gratuito pelo Promotor do medicamento experimental, outros medicamentos e/ou dispositivos médicos previstos no protocolo; medicação de resgate; medicação utilizada para situações não previstas (exemplo na gestão de eventos adversos);
   b) Fornecimento dos medicamentos de estudo durante o ensaio e após conclusão do estudo (de acordo com a legislação e orientações em vigor), se considerado necessário pelo investigador;
7) Outras disposições:
   a) Condições de reembolso de despesas aos participantes;
   b) Indemnização em caso de danos decorrentes do ensaio;
      i. confidencialidade e privacidade em cumprimento com o Regulamento Geral de Proteção de Dados e Lei 58/2019, de 8 de agosto;
      ii. tempo de armazenamento de dados dos participantes no centro de ensaio e centros externos (quando aplicável);
   c) Fornecimento de equipamento necessário à realização do estudo: ao centro de ensaio e/ou participantes;
   d) Informação prevista sobre Propriedade intelectual; publicações.

Timelines

Submission Type	Clinical Trial Regulation (CTR)
Initial Dossier	60-106 days*
Substantial Amendment/ Modification	49-95 days*
Addition of a new Member State	52-83 days*

If a timeline for responding is not met, the application will lapse!

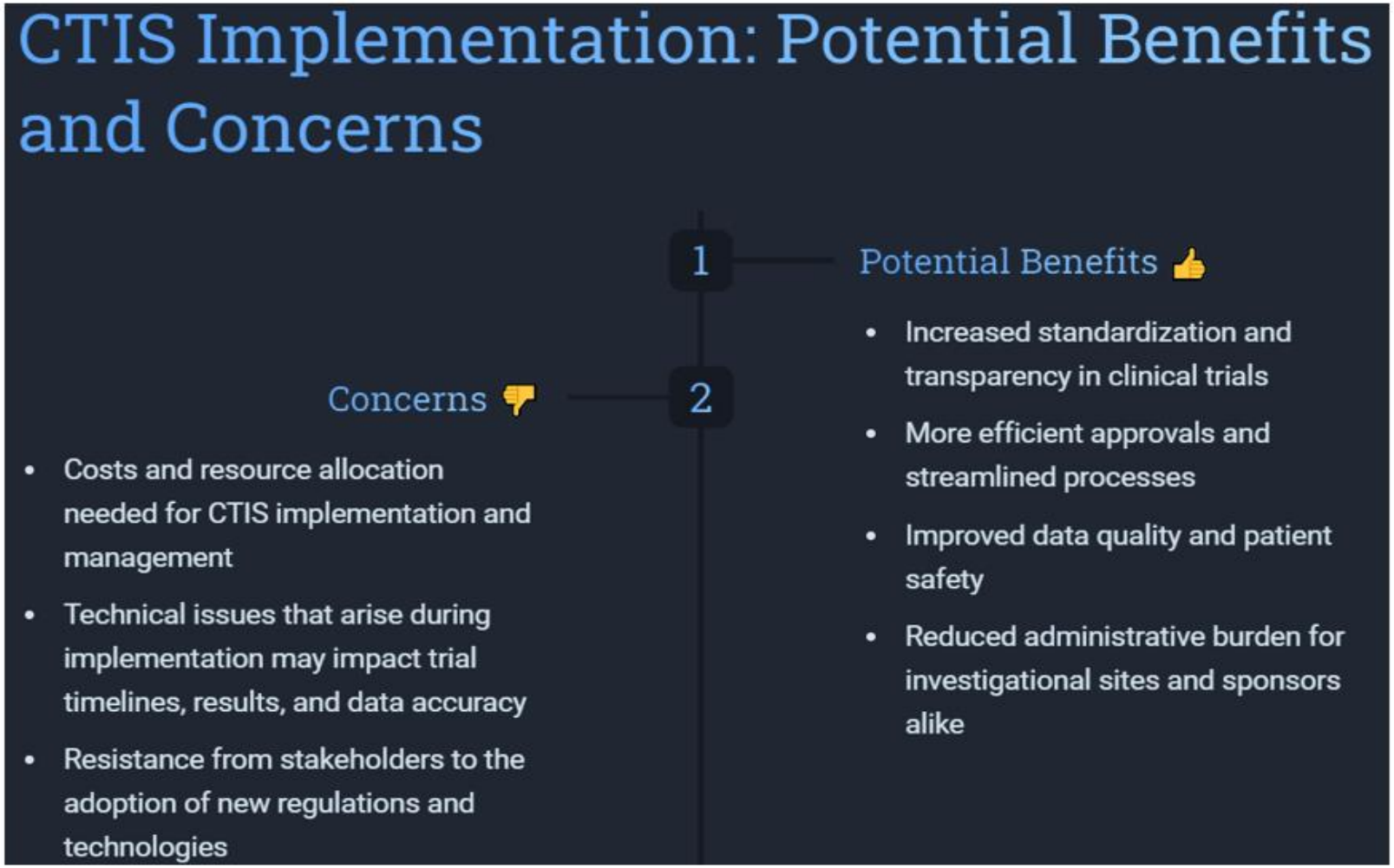
Part I
Part II
Evaluation Timetable



Challenges for Investigational Sites and Investigators

CTR/CTIS Implementation

Potential Benefits and concers



Conclusion

Preparing for a Successful Transition

Conclusion and Preparing for a Successful Transition

Embracing CTIS 🤝

Investigational sites and investigators must recognize the importance of regulatory compliance and embrace the use of CTIS. CTIS implementation may require investments in time and resources, but it will ultimately result in more efficient and effective clinical trials.

A Collaborative Effort 🙌

The successful implementation of CTIS requires a collaborative effort between different stakeholders, including investigators, sponsors, regulators, and CTIS service providers, which will facilitate effective communication and the ability to adapt to new regulations and requirements.

Obrigada!

margarida.santana@roche.com / Tel: 910701205

Links úteis

- Clinical Trial Regulation (EU) No 536/2014
https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32014R0536
- Clinical Trial Directive (EC) No. 2001/20/EC
https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX%3A02001L0020-20090807
- OMS portal
https://spor.ema.europa.eu/omswi/#/
- OMS guide
https://spor.ema.europa.eu/omswi/#/chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.ema.europa.eu/en/documents/other/quick-guide-how-use-organisation-management-service-oms-ctis-training-programme-module-03_en.pdf
- EMA Tutorial video - CTIS
https://www.youtube.com/watch?v=jmylMwZFroc
- EMA Q&A Set 2023
chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://health.ec.europa.eu/system/files/2023-09/regulation5362014_qa_en.pdf
- Lista de verificação CEIC / Esclarecimento CEIC sobre disposições financeiras
https://www.ceic.pt/regulamento-ec
- EudraLex - Vol 10 - Clinical trials guidelines - Set of documents applicable to clinical trials authorised under CTR - Templates
https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-10_en#fragment1
- Guidance for the Transition of Clinical Trials from the CT Directive to the CT Regulation, July 19th 2023
chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://health.ec.europa.eu/system/files/2023-07/transition_ct_dir-reg_guidance_en.pdf
- CTCG Best Practice Guide for sponsors of multinational clinical trials with different protocol versions approved in different Member States under the Directive 2001/20/EC that will transition to the Regulation (EU) No. 536/2014
chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.hma.eu/fileadmin/dateien/HMA_joint/00-_About_HMA/03-Working_Groups/CTCG/2023_07_CTCG_Best_Practice_Guide_for_sponsors.pdf
- FAQs – Transitional trials to CTIS
chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https:/www.ema.europa.eu/en/documents/other/faqs-transition-trials-eudract-ctis-ctis-training-programme-module-23_en.pdf
- CLINICAL TRIALS FACILITATION AND COORDINATION GROUP (CTFG)
https://www.hma.eu/about-hma/working-groups/clinical-trials-facilitation-and-coordination-group.html