

CTIS GUIDANCE FOR SPONSORS - SPAIN -

Version 1 March 2023

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Abbreviations

AEMPS	Spanish Agency for Medicines and Medical Devices
ASR	Annual Safety Report
AR	Assessment Report
BE/BA	Bioequivalence/Bioavailability
СТ	Clinical Trial
СТА	Clinical Trial Application
CTIS	Clinical Trial Information System
CTR	Clinical Trial Regulation
DAR	Draft Assessment Report
EC	Ethics Committee
EMA	European Medicines Agency
FAR	Final Assessment Report
FIH	First in Humans
GCP	Good Clinical Practice
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
MSC	Member States Concerned
NCAs	National Competent Authorities
OMS	Organisation Management System
PK/PD	Pharmacokinetics/Pharmacodynamics
RFI	Request for Information
RMS	Reporting Member State
RSI	Reference Safety Information
SM	Substantial Modification
SmPC	Summary of Product Characteristics
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction

1.Introduction

The <u>Clinical Trials Regulation (Regulation (EU) No 536/2014)</u> came into application on 31st January 2022 and submission of clinical trials with medicinal products shall no longer be submitted through the ECM Portal; submission has instead to take place via **Clinical Trial Information System (CTIS)**. CTIS is the single-entry point for submitting clinical trials information in the EU, which is stored in the system. All communications, including final decision from the authorities, is received via CTIS. With CTIS, sponsors can apply for clinical trial authorisation in multiple EU/EEA countries with a single application.

CTIS is structured in two restricted and secured workspaces, only accessible to registered EMA account users, and a website with open access to the general public:

- The <u>sponsor</u> workspace, accessible to commercial and non-commercial sponsors. It supports the preparation, compilation and submission of clinical trial data for its assessment by Member States.
- The <u>authority</u> workspace, accessible to national competent authorities, ethics committees, the European Commission, and the European Medicines Agency (EMA). It supports the activities of Member States and the European Commission in assessing and overseeing clinical trials.
- The **public** website, accessible to patients, healthcare professionals, scientists, clinical research associations, media, and members of the public. It supports the open access to clinical trials data in the European Union, in line with the transparency goal set out in Regulation (EU) No 536/2014 (Clinical Trials Regulation, CTR).



This guidance covers the process on how to start up, complete and maintain a clinical trial application (CTA) as a sponsor, using the **trial-centric approach** or **the organization-centric approach**, as well as management of relevant notifications and information throughout the life cycle of clinical trials.

There are two possible approaches to user management in CTIS and sponsors should carefully consider which user management approach best fits their organisation:

- **Organisation-centric approach**: intended to serve the needs of organisations and/or sponsors that run multiple clinical trials. This approach means that user management is done at organisation level.
- Trial-centric approach: intended to serve the needs of small organisations and specifically academic

sponsors, which may initiate trials on an ad-hoc basis. It allows the management of a smaller number of users and one or very limited numbers of clinical trials. This approach allows a faster process (no need for registration of a high-level sponsor administrator) when submitting a first initial, and subsequent application. Further allocation of other CT Administrator (CT Admin) roles or business roles is assigned to users at the clinical trial level. The CT Admin can manage users only for the particular trial(s) of his/her concern and can perform all sponsor business activities in CTIS related only to the particular trial.

For further information regarding management of users and organisations in CTIS, please see the <u>Handbook</u> for clinical trials sponsors and this <u>video</u>.

This guidance is based on and can be used as a supplement to the following CTIS training guides from EMA:

- <u>Clinical Trials Information System (CTIS) Online modular training programme</u>
- <u>Clinical Trials Coordination Group (CTCG) Key Document List</u>
- Documents published on Chapter V of <u>EudraLex Volume 10 CT guidelines</u>, with special attention to:
 - \circ $\;$ Quick guide for sponsors Regulation 536/2014 in practice
 - o Questions and Answers Document Regulation (EU) 536/2014

How to get started for working in CTIS

In order to access the CTIS Sponsor workspace, a user will need to have an active EMA Account. If the user already uses other EMA applications (e.g. Eudralink, SPOR, IRIS, EudraVigilance, OMS or the EU Clinical Trials Database), the user already has an EMA Account and can access the CTIS Sponsor workspace using his/her existing EMA Account credentials. If the user does not have an active EMA Account, please consult these instructions on how to create a new one.

In addition, organisations must be registered in EMA's Organisation Management System (OMS). For instructions on how to register organizations in OMS, please consult this <u>guide</u>.



Access to CTIS

When a Sponsor User logs into the system and initiates a new CTA in CTIS, the system will automatically check if a high-level sponsor administrator has been appointed for the sponsor organisation selected (this happens in the organization-centric approach).

In case of trial-centric approach, the user will be able to proceed becoming the CT Administrator for that particular trial and can then assign other roles in the particular trial to other users also holding an EMA account.

TIP: all EMA accounts are automatically disabled after 6 months of inactivity. Prior to disabling the account, the system sends three reminders to the user (two weeks, one week and one day before the account is disabled).

To re-activate your account you will need to use the Forgot Password? process. By re-setting your

password your account will be re-activated and a notification sent to your email address. If you are affiliated to an organisation, your 'User Administrator' will also be notified that your account has been re-activated.

To find out more about how to re-activate your account reference the guidance <u>Recover your</u> <u>credentials - Re-activate your account - Forgot Password?</u>



The sponsor workspace comprises 13 different business roles:

More information on this topic can be found in:

- <u>Video</u> and supporting materials: <u>Step-by-step guide</u> and <u>Frequently asked questions (FAQs)</u> in EMA training **Module 7**.
- For additional information concerning business roles please consult **Module 7** <u>Roles and permissions</u> <u>matrix summary - Sponsors Workspace</u> and <u>Sponsors Business Processes and Roles</u>.
- Academic sponsors can consult the <u>quick guide</u> and <u>the step-by-step guide</u> in **Module 19: CTIS for SMEs and academia.**

2.RMS selection process

To select the RMS between all the MSC involved in the assessment of a CTA, there are three possible scenarios:

Scenario 1: Only one MSC is willing to be RMS at day 3

That MSC will be selected as RMS at day 3 (or even before if the task "Express willingness/unwillingness" is set as completed by the rest of MSCs).

	Day 1	Day 2	Day 3		Day 4		Day 5	Day 6	RMS Selected
	Express Willingnes	ss/Unwillingness							
1.	1. 1 MSC express Wi		llingness						
		RI	Willing RMS	RMS	Candidate RMS	RMS	Sponsor proposed RMS		

Scenario 2: More than one MSC is willing to be RMS at day 3

The MSC that has expressed willingness and has the lowest workload will become assignor:

- The assignor will select one of the MSCs (pull of willing) to be RMS at day 5. This MSC selected by the assignor is called candidate. This candidate will be appointed RMS at day 6 if there is not disagreement.
- If assignor does not select any MSC as candidate or if there is a disagreement among the MSCs, the MSC proposed by the sponsor will become RMS at day 6.



Scenario 3: No MSC has expressed willingness at day 3

In this case, at day 3 the task re-express willingness is triggered. MSC proposed to be RMS by the sponsor will become assignor. This MSC will become RMS if there is not any MSC express willingness or if there is disagreement among the MSCs.



When does the MSC proposed by the sponsor become RMS?

- It is the only willing RMS.
- More than one MSC expresses willingness but there is disagreement among MSCs.
- None of the MSCs wants to become RMS.

For further information on this topic, please see <u>Step-by-step guide</u> in **Module 6**.

3.How to create and submit an initial Clinical Trial Application (CTA)

Before creating a CTA which involves Spain, **the sponsor must select an Ethics Committee** in Spain between those which figure in the list that can be consulted in the <u>AEMPS website</u>. This Ethics Committee has to agree to assess the CTA on the submission date, whether or not Spain is going to be proposed as RMS. In all CTAs submitted through CTIS, the sponsor must indicate in the cover letter the selected Ethics Committee in Spain. It is important that if sponsor asks several CEIms to assess their CTA, they should inform the non-selected ones.

The cover letter must also include a list of medical devices (including in vitro diagnostic medical devices) which are to be investigated in the clinical trial but which are not part of the IMP, together with a statement as to whether the medical devices are CE-marked for the intended use or not. For specific instructions for submission of this type of applications please see Annex 1.

If the IMPs are manufactured in a hospital pharmacy service (please see <u>Instruction document of the AEMPS</u> <u>for conducting clinical trials in Spain</u> and Article 34 of the <u>Royal Decree 1090/2015</u>), the sponsor must indicate it in the cover letter.

For clinical trials concerning COVID-19 treatments (not vaccines), it is possible to request an expedited assessment in the context of the **Joint Action CT_CURE of the program EU4Health**. These clinical trials must involve several member states in the UE and the expedited assessment has to be requested during the CTA submission. For further information please visit website <u>CT Cure |</u> and <u>AEMPS website</u>. For any consultation on this topic please contact <u>EU4HEALTH_CT-CURE@fagg-afmps.be</u>.

For a better understanding of the following section, please consult EMA training material of <u>Module 10 on</u> <u>how to Create, submit and withdraw a clinical trial.</u>

Dossier for the initial application content

The content of the application dossier for the initial CTA is collected in <u>Annex I of the CTR.</u>

Available European templates can be found in Chapter I of <u>EudraLex - Volume 10 - Clinical trials guidelines</u> and available national templates can be found in the Annexes to the Instruction document of the AEMPS for conducting clinical trials in Spain located in the section "Guías" of the <u>AEMPS website</u>.

Language requirements for Part I documents can be found in the Questions and Answers Document - Regulation (EU) 536/2014, published in the Chapter V of <u>EudraLex - Volume 10 - Clinical trials guidelines</u>. Documents can be in Spanish for trials running only in Spain, and for which no additional member state application is foreseen.

Language requirements for Part II documents are described in Table 1 of this document.

Please notice that it is acceptable to include the EU CT Number without the last two digits (2022-123456-12 instead of 2022-123456-12-00) in the documents submitted with the application. This is useful in order to prevent the necessity of updating the EU CT Number in all documents in case of resubmission, as in a resubmission the final digits change (for example, -01 instead of -00).

How to create a CTA

CTIS fields should be completed initially in English, adding the translations indicated in section 2.1 – Part I: EU application form.

When you are logged into CTIS, click on the tab **New Trial** to create a new CTA:

cal trials	
al trials Notices & alerts 🛑 RFT User administration	
Clinical Trials	
Q. Enter EU CT number or use advanced search	SLARCH
Trial Advanced Search •	
Application Advanced Search •	
	+ Rew trial
	3

In the generated pop-up, type the full title of the trial in English and indicate your organization.

TIP: Remember to click Save on the top of the page. This should be done often as there will be no automatic saving.

This point is further explained in CTIS Training Module 10, <u>Step-by-step guide</u>.

	glish)*							
ID	organisat (starts with Name A	ion in in in in ddress Cl	starts with ¥	city city e count	starts with	a v Country All de Clear Sear ne email	v ch organisation Actions	_
Full t Cl Se Nam Ter	itte (English)* inical Trial for arch orga e con st Organisation	the CTIS Traini Inisation tains	ng Programme P 2 st	arts with 🗸	1 City	starts with	Country All	
	ID	Name	Address	City	+ New o	country	dt Clear Search or phone	ganisation email
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			Tart	3		Antarctica		
0	ORG- 100023032	Test organisation	employer address					
0	ORG- 100023032 ORG- 100022987	Test organisation Test Organisation 1	employer address 980 Great West Road Address line 2,Address line 3,Address line 4,	London		United Kingdom		
0	ORG- 100023032 ORG- 100022987 ORG- 100023057	Test organisation Test Organisation 1 Test Organisation Demo	esk employer address 960 Great West Road Address line 2,Address line 3,Address line 4, Berlinstrasse 12	London Berlin	1045GA	United Kingdom Germany	004952255564545	sponsort@e
0	ORG- 100023032 ORG- 100022987 ORG- 100023057 ORG- 10002305	Test organisation Test Organisation 1 Test Organisation Demo ist rganisation emo1	ess employer address 960 Great West Road Address line 2,Address line 4, Berlinstrasse 12 Berlinstrasse 12	London Berlin Berlin	1045GA 1010GB	United Kingdom Germany Germany	004952255564645 004952255564645	sponsor1@4

When the two fields are filled in, click on the **Create** button and the draft CTA will be created.

When creating the draft CTA, on the top right side of the screen there are four buttons:

- Check: Identifies the mandatory fields in the sections which have not been filled in.
- Save: Save the data which have been filled in up to that moment.
- **Cancel:** To cancel your application. This can only be done while your trial is an "draft" mode.
- Submit: Submit the application when all information is entered and it is completely ready.
 - TIP: <u>The lock button</u> needs to be **locked** to enter data. Remember to unlock after uploading data in each section. Save the data before going to the next section.

The four different sections of the application which needs to be filled in with data and documents are: Form, MSCs, Part I and Part II.

Clinical trials Notices & alerts 👩 RFI Us	er administration	
Rease note that data and documents provided in the second seco	ne EU Database are subject to publication rules (including the protection of personal data and comm	erdałły confidential information), as per Regulation (BU) 538/2014, Anticle 81(4).
Form MSCs Part I Part II Evaluation Timetable The four sections that need to be	cation details er the asterisk * = mandatory fields	Click on the "lock button" to be able to enter data in the form
filled in Deferral pub Publish da Short title / Justification	lication dates tes of trial information Trial category * for trial category / Trial category *	8 •

In CTIS it is possible to upload two versions of the same document: one **for publication** (it will be public, and it should not contain confidential or personal data \rightarrow <u>redacted</u>) and other one **not for publication** (unredacted).

By default, the first uploaded version is "For publication".

Form	Form details	
MSCs Part I Part II	Initial Application details	A
Evaluation	Cover letter	~
Timetable	Cover letter *	Add document
	Cover letter 2022-503832-14-00 🛓 💉 🗈 🖻 💿 English · Cover letter (for publication) · System version 1.00 · Version 1 · 12/05/2022	

Because of that, sponsor will have to upload the redacted version (for publication: without personal or confidential data) first. After that, the unredacted version (not for publication) has to be uploaded using the

				_
	Title*	Type**		
	Protocol 2022-503832-14-00	Protocol (not for publication)		
	Language	Version*	System version	
	English 🗸	1	1.00	
	Date*			
	20/04/2022			
	Comment			
			11	
			â Remove	
	The above document(s) will not be published.			
			× Cancel Attach	
Part I	Protocol information			~
Part II	Clinical trial protocol			
Evaluation	Protocol *			
Timetable				Add documen
	Protocol 2022-503832-1	14-00 🗻 🥒 📔 🔲 🖸		
	Version 1 · 20/04/2022	ication) · System version 1.00		
	Protocol 2022-503832-1	14-00 🛓 🖉 🖺 🛅		
	English · Protocol (not for p · Version 1 · 20/04/2022	publication) · System version 1.00		

tab "Add". Title ("Title" field in CTIS) must be the same in both versions of the document.

TIP: The Check button can be used to validate for missing sections at all times during completion. The asterisk* in CTIS indicates mandatory fields to be filled in or mandatory upload of documents.

Form

- Cover letter (section B in Regulation Annex I) containing a reference to the selected Ethics Committee in Spain, a list of medical devices investigated in the CT and an indication if the IMPs are manufactured in a hospital pharmacy service.
- Compliance with Regulation (EU) 2016/679: Template available in Eudralex Volume 10 (R)
- Proof of payment (Q). Unique fee applies either if Spain acts as RMS or as MSC.
- Deferral publication dates: section where the sponsor has to establish the trial category (in relation with transparency rules) and possible deferrals. See the <u>Draft guidance document on how to</u> approach the protection of personal data and commercially confidential information in documents uploaded and published in the Clinical Trial Information System (CTIS).

Add the cover letter and category of the trial in relation with transparency rules. To select the trial category you must use the drop down menu. The category can be from 1 to 3. Thereafter you need to add the "justification for the trial category".

Available video on this topic in EMA training module 10: <u>Training video: Fill in the Form and the MSC sections</u>.

MSCs Part I Part II	Form details Initial Application details Cover letter	Add the cover letter		
Evaluation Timetable	Cover letter *			Add docum at
	Deferral publication dates Publish dates of trial information	Add the trial category and		8
	Sheet little / Trial category * Justification for trial category / Trial category *	justification for the category		

The "deferral publication dates" section must only be filled in if the sponsor has applied for a deferral date of the publication of the documents in the application.

In the following table the different categories and possible deferrals are shown in relation to the different types of structured data and documents contained in CTIS (please see also <u>EMA's Appendix</u>, specially points 4.3.3 and 4.3.4):

	Grouping	Category 1 FIH, PK/PD, BE/BA, Bio similarity	Category 2 Phase II and III	Category 3 Phase IV Low interventional CT
•	Main Characteristics	Publication of final summary of results		
	Notifications	Publication of final summary of results		
•	Subject information sheet	Up to 7 years after the end of the trial in EU/EEA	Up to 5 years after the end of the trial in EU/EEA	
	Protocol	Up to 7 years after the end of the trial in EU/EEA	Up to 5 years after the end of the trial in EU/EEA	Publication of final summary of results
•	IMPD S&E sections and Investigator Brochure	Up to 7 years after the end of the trial in EU/EEA	Up to 5 years after the end of the trial in EU/EEA	Publication of final summary of results
	Responses to RFI	Up to 7 years after the end of the trial in EU/EEA	Up to 5 years after the end of the trial in EU/EEA	Publication of final summary of results
•	Clinical trial results summary for an intermediate data analysis	 12 months after interim analysis date up to 30 months after the end of the trial in the EU/EEA 		
•	Clinical trial results summary and lay person summary	 1. 12 months after the end of trial date in the EU/EEA 2. Up to 30 months after the end of trial in the EEA 		

Table 2. Trial categories and deferrals information

MSCs

Member states concerned. Add the countries (member states) where the trial application should be submitted, and the number of subjects that are expected to participate in each country. If there are more than one country participating in the trial, sponsor have to propose a country as RMS, which is the country that will be responsible for the overall scientific assessment.

Add member states				×
Member State		Subjects*	Proposed RMS	
			۲	Î
Spain	~	16		
			0	Ī
Italy	*	8		
			+ Ad	ld another
			Cancel	✓ Add

Available video on this topic in EMA training module 10: Training video: Fill in the Form and the MSC sections.

Part I

• EU Application form (C): data entered directly in CTIS.

According to transparency rules, a translation into Spanish of the fields to be published in REEC (Spanish Clinical Studies Registry) shall be included: Title, investigated disease, objectives, endpoints and inclusion and exclusion criteria.

		🗸 Check 🛛 🕅 Save 🖉 Cancel 🕻 🏠 Submit
Form	Trial specific information (Part I)	
Part I	Trial details	
Part II	Trial identifiers	*
Evaluation	Full title (English) *	
Timetable	LL - SANDBOX MOCK SUBMISSION SPAIN IL3 (1)	4
		+ Add translation

- Protocol (D)
- Patient facing documents linked to the CT endpoints shall be provided together with the protocol in part I of the CTA (D14 and D17I)
- Protocol synopsis (D.24): it must content all the information described in question number 5.8 of the Questions and Answers Document - Regulation (EU) 536/2014, published in the Chapter V of <u>EudraLex - Volume 10 - Clinical trials guidelines</u>. Spanish version of the protocol synopsis is required.
- The two pages requirement is only orientative. Sponsors should consider to make the synopsis understandable to a layperson. If a lay person version is created by sponsor, only this version is to be submitted.
- Charter of the Data Safety Monitoring Committee, if applicable (D.23)
- Investigator's Brochure/Summary of Product Characteristics (E)
- Documentation relating to compliance with good manufacturing practice for the IMP (F)
- IMPD quality, safety and efficacy/Simplified IMPD with reference to the valid SmPC (G)
- Auxiliary medicinal product dossier (H)
- Scientific advice and paediatric investigation plan (PIP) if available (I)

• Content of the labelling of the IMPs in local languages (J)

Fill in the Part I section

Available videos on this topic in EMA training module 10:

- Training video: Fill in the Part I section
- Training video: Fill in the trial details of Part I section
- Training video: Fill in the Sponsor details of Part I section
- Training video: Fill in the Product details of Part I section

Trial details

Medical condition, trial objective, inclusion and exclusion criteria, end points, trial duration, population of trial subjects and upload of protocol.

Clinical trials Notices & al	erts 🕘 RFI User admi	nistration									
O Please note that data an	d documents provisied in the BJ Detabas	are subject to publication re	Jes (including the p	estaction of paras	rnal data i	nd commercially co	eddaetal idornal	ion), as per Regulati	on (BU) 536/2014, Ar	ficta #1(4).	
								🗸 (he	s B Save	O Cancel	a Submit
						-		_			
Form	Trial specific information	(Part I)									
MSCs	Trial details										
Part II	Trial Identifian										
Evaluation	Trial information						>				
Timetable	Protocol information					-					
	Scientific advice and I	Andiatric Investiga	tion Plan (PII	21		-					>
	Associated clinical tri	ds		<i>'</i>		-					>
	References										>
	Countries outside the	European Economic	Area								>
					_	_					
	Sponsors										
											<u>a</u>
	Name 0	rganisation type	Country Typ	pe 51a	tus Le	gal representa	tive Scientif	ic contact point	Public contact	point Th	ind parties
	Test Organisation Demo P	armaceutical company	Germany Con	nmercial Acti	ive .					0	~

Sponsor details

Includes sponsor information which was added when the application was first created. All these contacts must also be registered in OMS. This information is not registered directly in CTIS but it is retrieved from OMS.

At first, contact point for union must be added. This person will be the contact point for sponsor. AEMPS will contact this person for urgent issues (e.g. if Ethics Committee has not been defined in the cover letter).

Part I	Sponsors									
Part II	Sponsor must be provide	ed .					+ Add	sponsor 🖉 Cha	nge contact point	for union
aluation	Name	Organisation type	Country	Type	Status	Legal representative	Scientific contact point	Public contact point	Third Parties	Actions
	Test Organisation Demo	Pharmaceutical company	Germany	Commercial	Active				0	
	Contact point fo	or union*								
	Organisation na Test Organisation	me Demo		L3						
	Address line 1* Berlinstrasse 12					Address lin	e 2			
	Address line 3					Address lin	e 4			
	Town/City*					Post code				
	Berlin					1045GA				
	Country*					Functional	contact point name			
	Germany									~



Click on the sponsor line and add:

- Legal representative: an EU contact that only needs to be added if sponsor is located outside EU.
- Scientific contact point and public contact point: they must be added for all trials and they can be the same person.
- Third party (only if tasks or functions in the trial have been delegated to third parties). This is e.g. monitoring (the GCP unit) or laboratory facilities. All third parties must be registered in OMS.



TIP: The full information (inlcuding Legal representative, scientific contact point and third parties) on section Sponsors will not be visible until the user clicks on the Sponsor line.

Product details

Information on the medicinal products used in the trial must be added. If the products have a marketing authorisation you need to click on the "Add" tab. Select the role of the product. It is mandatory to include at least one test product (investigational medicinal product (IMP)) in the application.

Inical trials Notices & alerts 🚳 RFI User adminis	tration		
MSCs Products Part I Part II			A Segister
Evaluation Timetable	11 No sorting ~	+ Add 🖪 Regis	ter
Documents Part 1	Click "Add" for products	Test	
P	already registered in teh Eudravigilance	Comparator Auxiliary	Click "Register" if
Outform, Cover English - Cover - - Version 1 - 0	database	Placebo	you compound is new
O.Part1_CT_Pr- English - Protocol Version 1 - 08/22	u januttettu – System versen 1 12020	_	_
Product			
Content labeling			~

The Investigator's Brochure (IB) or the SmPC, contanining the reference safety information (RSI) must also be uploaded.

According to the Article 67 of the <u>CTR</u>, the labelling must also be uploaded except in case the IMP has a marketing authorization, it is used according to its authorization and the clinical trial is not blinded.

All documents uploaded for the Part I can be found at the end of the section, in subsection "All documents".

Part II

Section in CTIS (section in <u>Regulation</u> Annex I)	European template (<u>Eudralex</u> vol10, Chapter I)	Spanish template (<u>AEMPS</u> , Annexes to Instruction Document)	Accepted template	Accepted language	Need for signature
Recruitment arrangements (K)	Recruitment and Informed consent procedure template	No specific template for recruitment arrangements available	European template	Spanish or English	No
Subject information and informed consent form (L)	Not available	Annex VIIIA, which includes instructions for personal data protection section in its Appendix 1 Annex VIIIB	Spanish Annexes	Spanish	No
Suitability of the principal investigator (M65 and M66)	Investigator CV template Declaration of Interest template	Not available	European templates Investigator CV must be uploaded in CTIS subsection "Investigator CV*". CV must have been updated within the previous two years. It is not mandatory to indicate the EU CT Number in the CV. Dol must be uploaded in CTIS subsection "Suitability of the investigator". Dol must have been updated within the previous year. Dol submission is mandatory, whether or not there is a conflict of interests.	Spanish or English	No

Section in CTIS (section in <u>Regulation</u> Annex I)	European template (<u>Eudralex</u> vol10, Chapter I)	Spanish template (<u>AEMPS</u> , Annexes to Instruction Document)	Accepted template	Accepted language	Need for signature
Suitability of the facilities (M64 and N)	Site suitability form template	Annex IV	European template or Spanish Annex IV	Spanish or English	Yes
Proof of insurance cover or indemnification (O)	Not available	Annex VA Annex VB Annex VI in cases where the waiver to present the insurance within 30 days after the CT authorisaton applies, as per art. 9.3 of Royal Decree 1090/2015 Annex VII	Spanish Annexes	Spanish	No
Financial and other arrangements (P)	Compensation for trial participants	Financial budget according to Instruction Document's specific section	Financial budget according to Spanish instructions. European template for compensation for trial participants is acceptable.	Spanish or English	No
Compliance with national requirements on Data Protection	Not available. There is a Template statement on compliance Regulation (EU) 2016/679 to be uploaded in CTIS section "Form"	Covered already in Appendix 1 of Annex VIIIA	Spanish Annex VIIIA. To be uploaded only in CTIS subsection "Subject information and informed consent form"	Spanish	No

Section in CTIS (section in <u>Regulation</u> Annex I)	European template (<u>Eudralex</u> vol10, Chapter I)	Spanish template (<u>AEMPS</u> , Annexes to Instruction Document)	Accepted template	Accepted language	Need for signature
Compliance with use of Biological samples	Compliance with applicable rules for biological samples template	Annex XIII, which is the European template including a paragraph referent to Spanish legislation in section 5.1	Spanish Annex XIII	Spanish or English	No

Table 1. Spanish requirements for part II documents.

Requirements for part II documents for each MSC will be collected in a single point that will be available in EMA Website. When available, we will provide the link for access to this information.

When uploading documents in CTIS be aware not to use date and version in the file name on your documents as this will be transferred to the "Title field" in CTIS and that "Title" will be the same during the entire life cycle of the clinical trial even if there are substantial modification updates. In any case, you can rename your documents in CTIS after upload.

For instructions on filling the field "Title" when uploading documents in CTIS, please see the Best Practice Guide for Sponsors of document naming in CTIS. It can be found in the <u>CTCG Key Documents List</u>. Names of documents on sponsors files can follow sponsor's SOP.

Fill in the Part II section

Available video on this topic in EMA training module 10: Training video: Fill in the Part II section.

Individual information for each country to be assessed by the selected Ethics Committee. Part II documentation is listed in Annex I of CTR, points K to P. For clarification about acceptable templates (Spanish vs European) for Part II documents, please see **Table 1**.

MSCs Part I Part II	Trial sites					-			Frial si cour	ites fo ntry ca addec	r each n be I	_	→ 🖪	Add sit
- AT - DE	Organisation ID	Organisation name	Site location	Site street address	Site city	post code	Site Country	Title	First name	Last name	Department	Phone	Email	Actio
Evaluation Timetable	8285	Medizinische Universitat Innsbruck	Schopfstrase 41, Wilten	Schopfstrase 41	Innsbruck	6020	Austria	Dr.	First	Last	Chest Clinic	4234242424	flast@email.com	-
	Subject info Suitability o Suitability o	ormation and in of the investiga of the facilities	nformed conser	nt form										
possible	Suitability o	of the facilities	r indemnificati	on										3
upload all	Financial ar	nd other arrang	jements											;
cuments	i munchur un													

The name and address of the organisation must be registered in OMS before you can search and add the organisation (site) on the application in CTIS. If the organisation is not already part of the OMS system, the organisation must be added to OMS. This can be done by sponsor or by the organisation itself.

Information about the department and the investigator responsible for a specific clinical trial has to be registered directly in CTIS.

Trial sites												
Organisation ID	Organisation name	Site location	Site street address	Site city	Site post code	Site country	Title	First name	Last name	Department	Phone	Email
2537	University Clinic Of Navarra	Avenida Pio XII 36	Avenida Pio XII 36	Pampiona	31008	Spain		Juan	Luis	Cardiologia	+123456789	juan.luis@navarra.e
DA	TA RETR	IEVED	FROM		6		D/ D	ata (Epar	ON II TME	NVESTIG/ NT TO BE	ATOR AN	D ETED IN CTIS

Organizations (sites) that are not included in the sites and hospitals catalogue of the National Health System can be included directly in CTIS when completing the CTA. For instruction on how to do it, please see <u>Annex</u> <u>II</u>.

For further instructions on this topic, please see the <u>guide How to use the Organisation Management Service</u> (<u>OMS</u>) and the <u>OMS website</u>, when further instructions can be downloaded clicking on "Help" and on "About OMS".

There is not a permanent connection between CTIS and OMS. CTIS takes the information from OMS at the moment the application is created, but it is not automatically updated. Sponsor will be able to update this information in CTIS with the subsequent SM submitted for the clinical trial.

The address indicated in OMS has to be aligned with the information contained in the sites and hospitals catalogue of the National Health System.

Plane note that data are	orts 💿 RFI	Select trial sit	stration e								×
Form	Country sp	Search orga	nisation tains v 10	starts with w	City	starts	with v]	Ceuritry Austria			
MSCs	Trial sites				+ 54	w irgeniseth	a di Cin	- Sea	N erse	nisəti	inn
Part I Part II - AT - DE	Trial site	ED ORG- 100307200	Name Department of Nuclear Medicines, MJ Isenbruck	Address Anichstrasse 35	City Innsbruck	postCode 6020	Austria	phane	and a	Action X	+
Evaluation Timetable	1D	O 08G- 100322556	Medizinische Universitat Inmabruck	Schopfstrase 41 Wilten,	Innsbruck	6020	Austria			×	+
	Documen	1-2 of 2			1						
	Recruit										
	Subject						×	ancel	V 844	trnail s	

When the organisation is found via the search function, the details of the investigators must be added (first and last name, department, email address, phone).

Teasue roots that there a	and documents provided in	If a EV Database an	Investigator info	mation		×	e artisenation
			1814		First name*		
		-	None	*			
Form	Country specif	ic details (Pa	Last name*		Department*		
MSCs Part I Part II	Trial sites Trial sites		Prove		trai ⁿ		
AT DE	Organisation ID	Organisation			* Cancel 🗸 Canto		Title ou
Timetable	10 8295	Organisation Heducesche Un	verstet Schepheras	41, Schopfstra	ne Senstruck 6020 Au	stra	Title

Click on the **Save** button to save all uploaded documents and click on the **Check** to see if any documents or information are missing. The green message shows when the application is valid.

Clinical trials		Green message shows when the application is valid	Application is valid
Clinical trials Notices & a	lerts 👩 RFI User administration		
Please note that data a	nd documents provided in the EU Database are subject to publication rules (including the p	protection of personal data and commercially confidential information), as per Regul	ation (EU) 536/2014, Article 81(4).
િ Clinical Trial for the C	TIS Training Programme 2020-501643-14-00 / Initia	al ID: IN Draft	eck 🔯 Save 🗿 Cancel 🕰 Submit
Form	Country specific details (Part II - DE)		A
Part I	Trial sites		>
Part II	Documents		
- DE	Recruitment Arrangements		~
Evaluation Timetable	Recruitment arrangements *:		Add document

Remember to upload the Part II information relevant for each country. Part I is always included by default in the submission for all countries.

Pb	ease select the application parts you	wish to submit.	
8	Part I		
	Part II Austria Part II Germany		
Ì			

Applications limited to part I: Article 11 of the CTR

It is possible for sponsors to submit a partial application, according to Article 11 of the CTR. In these cases, CTA assessment and conclusion shall be limited to the aspects covered by Part I. After the notification of the conclusion on Part I, the sponsor may apply for an authorisation limited to aspects covered by Part II withing the next two years. Otherwise, the application on the aspects covered by Part I shall be deemed to have lapsed.

Nevertheless, this functionality is still not fully implemented and presents some disadvantages for the submission of subsequent substantial modifications (SM). With current implementation, if Sponsor needs to submit an SM once the clinical trial has been authorized in the full dossier MSCs, the sponsor needs to withdraw the application in the partial dossier MSCs in order to proceed with the SM application. Then sponsor needs to submit an additional MSC application once the SM is approved to add the MSCs previously withdrawn. As this "Workaround" brings a lot of workload for both parts (sponsor and NCAs) we recommend not to use this Article 11 until an IT solution is built in the CTIS.

For further information on this topic, please see questions 2.1, 2.2, 2.14, 3.6, 3.8, 3.9, and 4.1 of the Questions and Answers Document - Regulation (EU) 536/2014, published in the Chapter V of EudraLex - Volume 10 - Clinical trials guidelines, and Article 11 of the <u>CTR</u>.

Transition trials

If the application is for a transition trial from CTD to CTR, the Transition trial box must be checked before creating the draft CTA. In Form section, the former EUDRA CT number must be indicated in the Transition Trial subsection.

For transition trials, it is mandatory to submit the documents listed in questions 11.6 and 11.7 of the Questions and Answers Document - Regulation (EU) 536/2014, published in the Chapter V of EudraLex - Volume 10 - Clinical trials guidelines.

In order to harmonize document versions for a transition trial application, it is necessary to submit a previous substantial modification in each MSC. The document versions must be the same in all MSCs at the moment of submitting the transition CTA trough CTIS, even if the differences between versions are non substantial. For this reason in some cases a version containing non substantial changes versus the previous version authorised in Spain should be submitted as a substantial modification through <u>ECM portal</u> before submitting the transition application in CTIS (in this case, please explain in the cover letter that the changes are non-substantial but they are neccesary to obtain an harmonized dossier for latter transition of the application to CTR/CTIS).

4. Request for Further Information (RFI)

A request for further information (RFI) contains the considerations (questions or additional requirements) from authorities to sponsor. RFIs can be sent to sponsor during the validation, assessment, ASR assessment ad-hoc assessment, additional MSC applications, etc. The system is prepared for the submission of more than one RFI.

How to access and view a request for further information (RFI)

<u>Step-by-step guide</u> and videos on this topic in EMA training module 11:

- How to access and view an RFI in CTIS
- How to change a Clinical Trial Application as part of an RFI response
- How to respond to RFI considerations and submit an RFI response

In the sponsors workspace you will be able to see incoming RFIs in the "Notices and alerts" tab.

Clinical trials	Notices & alerts RFI User administration					وعري والمساور		
-	L.S.							
1	Notices & alerts 👩							
/	Q Enter EU CT ID or ASR ID (Business Keys) or use advanced search.	Access by click of ti	the RF on eac	ls ch	SEARC	эн	Advance	d Search *
	Showing 1 - 8 of 8 items				1 of 1 pa	iges	· 1	>
	Sort by: 12 Received ~							
	Newi 🧿 Ali 🛛		1					
	Alert RFI sent to sponsor	Ref number	Source type	Evaluation process	Received	ІМР	RMS	Sponsor
	An RFI has been sent by Austria for the Initial application, Validation .	2021-500027-47-00	Initial	Validation	03/02/2021	Paracetamol Tablets 500mg	Austria	Test Organisation Demo
	Alert RFI sent to sponsor	Ref number	Source	Evaluation	Received	ІМР	RMS	Sponsor
	An RFI has been sent by Austria for the Initial application. Validation .	2021-500027-47-00	Initial	Validation	03/02/2021	Paracetamol Tablets 500mg	Austria	Test Organisation Demo

You can access the RFI by clicking on each of the alerts. They can also be accessed from the RFI tab next the "Notices and alerts" tab. Click on the RFI and you will be redirected to the "Evaluation" section where the RFI is shown.

Please note that da	ta and documents provided in the EU	Database are subject to publication rules, which take	e into account the need to protect personal data and commercially confidential information. Once available, a redacted version of the documents
will be made public	ly available in accordance with these	rules.	
CTIS Training Program	me test CT for Dem	2021-500027-47-00 / Initial ID: IN	Under evaluation / RMS: Austria
		Validation section	● Withdraw
Form MSCs	Evaluation Validation	shows the number of RFIs	
Part I Part II	RFI 🕖		~
Evaluation			Expand all 🛩
Timetable	REI-CT-2021-5000	027-47-00-IN-001 Doe: 15/02/2021	~
	MSC: Austria Submiss	ion date: 03/02/2021 Due date: 15/02/2021	
Click on the	Reason	Incomplete	
lock to be able to upload	No changes have been ma	de to the application.	
response to	Constant in the second	-	
RFI	Supporting documenta	alon -	

When you have clicked on the lock button you can see the documents that the authorities have attached to

the RFI. The RFI can be related to "quality" or "non quality". Considerations and responses related to quality questions will not be subject of publication in CTIS public portal.

Clinical trials Notices & alerts	0 RFI User administration	
Please note that data and will be made publicly ava	d documents provided in the EU Database are subject to publication rules, which take into account the need to protect personal data and ilable in accordance with these rules.	commercially confidential information. Once available, a redacted version of the documen
Will be made publicly vol MSCs Part I Part II Evaluation Timetable	RFI-CT-2021-500027-47-00-IN-001 0mm: 15/107/2021 MSC: Austria Submission date: 03/02/2021 Due date: 15/02/2021 Reason Incomplete Supporting documentation	Expand all V Change application
RFIs from authorities or	HS: Quality RF1_Submission_Quality English - Supporting document from MS - Quality - System version 1.00 submission date 03/02/2021 - Version 1 - 03/02/2021 Non-Quality	the application if required in RFI
Ethics commitees	RF1_Submission_nonQuality English - Supporting document from MS - Non Quality (for publication) - System version 1.00 jubmission date 03/02/2021 Version 1 - 03/02/2021	
	General documentation Quality related documentation	Add document

In the "Add document" tab you can upload supporting documentation for the RFI or for an specific consideration.

Part I *			
Part II * Evaluation Timetable RFI	Consideration number RFI-CT-2021-500027-47-00-IN-004-01 Application section parts Part I - Non-clinical Consideration Austria - Part I Assessment consideration nr3 Sponsor response Response Austria - Part I Assessment consideration nr3 Documents related to the response ResponseRFI1	Application section and document Pro	tocol
nsideration must be	English - Supporting documentation for Consideration (for publication) - System version 1.00 Submission date 05/02/2021 - Version 1 - 05/02/2021		
nsideration must be answered	English - Supporting documentation for Consideration (for publication) - System version 1.00 submission date 05/02/2021 - Version 1 - 05/02/2021 Consideration number PELCT-2021-500027-47-00-IN-004-02 Application section parts Part 1 - Non-clinical	Application section and document CO	ver letter
nsideration must be answered	English - Supporting documentation for Consideration (for publication) - System version 1.00 submission date 05/02/2021 - Version 1 - 05/02/2021 Consideration number RFI-CT-2021-500027-47-00-IN-004-02 Application section parts Part I - Non-clinical Consideration Germany - Part I Assessment consideration nr5	Application section and document Co	ver letter
RFI 2	English - Supporting documentation for Consideration (for publication) - System version 1.00 submission date 05/02/2021 - Version 1 - 05/02/2021 Consideration number RFI-CT-2021-500027-47-00-IN-004-02 Application section parts Part I - Non-clinical Consideration Germany - Part I Assessment consideration nr5 Response Response to Austria - Part I Assessment consideration nr5	Application section and document Co	ver letter

If core documents of the CTA should be updated as a consequence of a response of a RFI, the option "Change application" must be used and the updated documents must not be uploaded as supporting documentation.

How to change a Clinical Trial Application as part of a RFI response

To change the application, you must click on the change application button. Each RFI must be answered

Please note that data and	d documents provided in the EU Database are subject to p	publication rules, which take into account the need to protect personal da	sta and commercially confidential information. Once ava	ilable, a redacted version of the documents
will be made publicly ava	ilable in accordance with these rules.			
MSCs	Protocol information	click on the upload		~
Parti	Clinical trial protocol	button to upload	Add new	
Part II	Protocol *	new versions of	document	
Evaluation		the documents		Add document
Timetable				
New version	0_Part1_CT_Protocol 🛓 🧪			Previous versions
of the	English · Protocol (for publication) · Sy submission date 05/02/2021	ystem version 2.00		
protocol	- Version 2 · 02/02/2021			
	Comment new version of the docume	ent - RFI change		
Previous	0 Part1 CT Protocol			
version of the	Version 1 · 02/02/2021 · En	glish - Protod (for publication) - System version 1.00		
protocol		43		
	Synopsis of the protocol			
				Add document
	Data safety monitoring committee charter			
				Add document
	Study design			
	-			
	aroal activity			Add document
	Period details			+Add period
	New ID Title Description Allo	cation method Blinding used Roles blinded	Blinding implementation details	Arm details Actions

separately. You can make changes in the sections Form, Part I and Part II.

If there are RFIs from different countries concerning part II, it is necessary to make a draft application for each Part II RFI. During the assessment phase, there could be for example one RFI for Part I (all MSCs) and one RFI for Part II from each MSC.

nical trials Notices & al	erts 🗿 RFI User administration		
Please note that dat will be made publich	a and documents provided in the EU Database are subject to pub v available in accordance with these rules.	olication rules, which take into account the need to protect personal data and commercially confidential information. One	e available, a redacted version of the docur
MSCs Part I	Assessment Part I	Draft 1 for	
Part II	RFI 🕲	Assessment Part I	>
Timetable	Conclusion		>
	Intended Disagreements		>
Application in draft for Part I	Assessment Part II	Draft 2 for Assessment Part II - Austria	• •
and Part II.	RFI 2		>
be one	Conclusion		>
answer from each RFI.	DE	Draft 3 for Assessment	v
	RFI 🚺	Part II - Germany	>

* <u>TIP</u>: Remember to unlock each section after completing the relevant information of each consideration.

How to respond to RFI considerations and submit an RFI response

Sponsor must reply to each of the RFI received from the authorities. In case of sponsor changes the application when answering the RFI, it is mandatory to upload a response document that describes the changes to the application.

Please note that data will be made publicly	and documents provided in the EU Database are subje available in accordance with these rules.	ect to publication rules, which take into account the need to protect p	ersonal data and commercially confidential information. Once available, a redacted version of the do
MSCs Part I * Part II * Evaluation Timetable	Assessment Part I		open the REL country
	RFI-CT-2021-500027-47-00-IN-6	003 Responded: 03/02/2021 004 Juni: 15/02/2021	C Discard chang
click on the	MSCAtria Submission date: 03/02/202 Changes to the application *	J Due date: 15/02/2021	Add docume
be able to answer the RFI	No document has been uploaded. Supporting documentation MS: Quality	Remember to tick the "includes application	Add a response
	No document available Non-Quality	are changes to sections in the	document
	No document available	application	

Each consideration of the RFI must be responded separately in order to be able to send the final RFI response.

Click on the lock button		
Consideration number RFI-CT-2021-500027-47-00-IN-004-01 Application	on section parts Part I - Non-clinical	Application section and document Protocol
Consideration Austria - Part I Assessment consideration nr3		
Sponsor response Response Austria - Part I Assessment consideration nr3	Consideration	1
Documents related to the response	L	
ResponseRFI1 L English - Supporting documentation for Consideration (for public submission date 05/02/2021 - Version 1 - 05/02/2021	ation) · System version 1.00	Here you can upload additional documents for the
		consideration
Consideration number RFI-CT-2021-500027-47-00-IN-004-02 Application	on section parts Part I - Non-clinical	Application section and document Cover letter
Consideration Germany - Part I Assessment consideration nr5 Response	Consideration	2
Response to Austria - Part I Assessment consideration nr5		
Documents related to the response	Type your response in the field	Add docum A
	Click on the lock button Consideration number RFI-CT-2021-500027-47-00-IN-004-01 Application Consideration Austria - Part I Assessment consideration nr3 Sponsor response Response Austria - Part I Assessment consideration nr3 Sponsor response Response Austria - Part I Assessment consideration nr3 Documents related to the response Provide State Stat	 Click on the lock button Conderation number RFI-CT-2021-500027-47-00-1N-004 2 Conderation Austria - Part I Assessment consideration nr3 Consideration Austria - Part I Assessment consideration nr3 Consideration Construction Partice Consideration for Consideration (for publication) - System version 1.00 Consideration number RFI-CT-2021-500027-47-00-IN-004-20 Consideration number RFI-CT-2021-500027-47-00-IN-004-20 Consideration Germany - Part I Assessment consideration nr5 Response to Austria - Part I Assessment consideration nr5 Consideration Germany - Part I Assessment consideration nr5 Consected to the response Consected to the response

The "Submit response" button will be active when the changes have been saved on "Save response".

5.Timetable

In the timetable tab on the left side of the page, CTIS shows the dates for the assessment schedule.







All these days are natural days. If a due date falls in a weekend or a bank holiday, this date is moved forward to the next working day.

These timelines cannot be extended except in CT involving an advanced therapy IMP or a medicinal product as defined in point 1 of the Annex to Regulation (EC) No 726/2004, for the purpose of consulting with experts. In such cases, the RMS may extend the assessment phase by a maximum of 50 days.

During the validation bank holidays from all MSCs are considered, until the RMS is selected. From that day, the calendar of RMS applies.

For further information on this topic, please see <u>this video</u> on the use of Timetable, this <u>step-by-step guide</u> and the <u>CTIS Evaluation Timelines</u> document.

6.Authorisation

In the assessment overview at the "Evaluation" page it is shown which countries have authorised the trial.

MSCs	Decision					
Part I	Part I Disagreement	s				
Part II Evaluation	Part I conclusion Part II conclusion	Accep	stable	· \		
Timetable	Decision	Autho	orised			
	ASSESSMENT OVER	RVIEW				
	MSCs	Validation	Assessment Part 1	Assessment Part II	Decision	+AB
	AUSTRIA	Valid (30/10/2020)	Acceptable (04/11/2020)	Acceptable (04/11/2020)	Authorised (05/11/2020)	+
•						

The sponsor will receive a notice indicating that the decision has been submitted in each MSC:

Notices & alerts (1651) Annual safety reporting	RFI User admir	nistratio	n 				
Sort by: 12 Received ~							
New! 0 All 3							
Notice Decision submitted	Ref number	Source type	Evaluation process	Received	IMP DENUBII	RMS	Sponsor
Italy has submitted a decision of Authorized on the Initial. The current trial status is Authorized in Italy.	2023-503321-19-00	Initial	Decision	14/02/2023	250 mg/180 mg solución oral	France	Achilles - testcompany
Notice Decision submitted	Ref number	Source	Evaluation	Received	IMP	RMS	Sponsor
Greece has submitted a decision of Authorized on the Initial. The current trial status is Authorized in Greece.	2023-503321-19-00	Initial	Decision	14/02/2023	DENUBIL 250 mg/180 mg solución oral	France	Achilles - testcompany
Notice Decision submitted	Ref number	Source type	Evaluation process	Received	ІМР	RMS	Sponsor
France has submitted a decision of Authorized on the Initial. The current trial status is Authorized in France.	2023-503321-19-00	Initial	Decision	14/02/2023	DENUBIL 250 mg/180 mg solución oral	France	Achilles - testcompany

Clicking on the Notice title, sponsor will access to the CTA and will be able to download the Final Assessment Reports for part I and Part II in the conclusion sections of Assessment part I and Assessment part II tabs. Therefore, neither AEMPS nor EC will send any document to sponsor.

Please notice that the FAR for part II submitted by Spanish EC will not contain signatures, document versions nor a list of the EC members.

For transitioned trials, only simplified FARs will be uploaded by AEMPS and ECs.

In Spain, national authorization (or not authorization) letters are not going to be submitted. If necessary, the sponsor can **download the Decision document from CTIS** following these steps:

1- Search the Clinical trial and access to the summary page of the application. Click on the "Download" button.

Clinical trials	Notices & alerts (160984)	Annual safety reporting RFI User admin	istration			
0	Please note that, in accordance information. It is the responsibi	with Regulation (EU) No 536/2014, all data and documents pro ility of each user to ensure compliance with Regulation (EU) 20	vided in the EU database are s 16/679 and Regulation (EU) 2	ubject to publication rules , aiming am D18/1725 when uploading documents	nongst other things at protecting and processing personal data in (personal data and commercially confidential CTIS.
						Download + CREATE -
	IT - TRAINING Authorised 2022-500515-	G - TEST - TRIAL 3 - Corrective I 	4easure - Do no	ot touch		
	Summary	Full Trial Information Notifications	Trial results	Corrective measures	Ad Hoc assessments	Users
	TRIAL INFORM	ATION				
	Sponsor	Achilles - testcompany		Member states concerned	ES · IT	
	Trial phase	Therapeutic confirmatory (Phase III)		Medical conditions	Inserire qui medical	condition - testo libero
	Therapeutic area	Diseases [C] - Cardiovascular Disease	s [C14]	Low intervention study	No	
	Medical device	140		Population type	Patients (Women of	child bearing potential using contraception)
				Transitioned Trial	No	
	ІМР					
						Expand all 💌
	UENUBIL	250 mg/180 mg solución oral				

2- Select Applications \rightarrow INITIAL IN \rightarrow Evaluation --> Structured data in PDF and Documents. Click on the Start **Download** button.

Summary	Full Trial Information	Notifications	Trial results	Corrective	measures	Ad Hoc assessments	Users
							start Download Cancel
Applications 1 Application t	ype Application ID	Membe	er states concerned		Application Part	Submission	date Decision date
) INITIAL IN	648	IT (Auth ES (Aut	horised with condition) horised)		Part I Part II	01 Aug 2022	01 Aug 2022
Contents for Dow	/nload:	Inc	lude the following :				
Form		⊠st ©De	ructured data in PDF* ocuments*				
		the	application	ersion related to			
🗆 Part I							
Part II		>					
Evaluation		~					
Select all							
	DN						

3- A zip file will be downloaded and the sponsor will find a folder called "Evaluation", and other one called "Decision" inside it. Finally, going into the "Spain" folder, there will be a PDF file with the decision for Spain and the date in which it was submitted.

7.Withdrawal of an application

The sponsor has the option to withdraw an application for a clinical trial at any time until the decision is made.

In cases of withdrawal of an application before the reporting date, the withdrawal will apply to the entire application in all MSCs. If the withdrawal is done after the reporting date, but before the decision is taken by a particular MSC, the sponsor has the option to withdraw the application in one, two or all MSCs.

Additional information on withdrawal rules can be found in section 4 of the Questions and Answers Document - Regulation (EU) 536/2014, published in the Chapter V of <u>EudraLex - Volume 10 - Clinical trials</u> <u>guidelines</u>.

After opening the initial trial application which is under evaluation, select the "withdraw" button. A justification for the withdrawal should be provided.

CT for training test 2021-501399-27-00 /	Initial ID: IN Under evaluation				
		✓ Check	0) Save	• Withdraw	Copy

The sponsor has the option to withdraw an application for a clinical trial at any time until the decision is made. However, in cases of withdrawal of an application before the reporting date, the withdrawal will apply to the entire application in all MSCs. After the reporting date, but before the decision is taken by a particular MSC, the sponsor has the option to withdraw the application in one, two or all MSCs.

8.How to submit an additional member state concerned (MSC) application (add a new country)

Available video and step-by-step guide on this topic in EMA training module 10.

To add a new member state (MSC) to an already approved application, in the page of the authorised clinical trial click on the **Create** button and choose "Additional MSC".

Clinical trials	Notices & alerts 🧔 🛛	Annual safety reporting RFI User	r administration		
1	Trial title Webin 2003-50075-71 Summary Fill T TRIAL INFORMAT	nar 21 09 2020 20 RMS: Austria Ital Information Notifications TION	Trial results. Carrective measure	es Ad Picc assessments	Consider Single Cold relations Refl: Solid relations Refl: Solid solidated at modification Non-substantial modification Additional MSC
	Sponsor Trial phase Therapeutic area Medical device	Test Organisation I Therapeutic exploratory (Phase II) Deceases [C] - Respiratory Test Disco No	Hember states (Medical condition Low intervention Population type	concerned AT - 56 ms Aproex n study Yes Healthy Volume	13
					Expand all +

In the next pop-up window you can select one or several MSCs to add at the same time and specify for each country the number of subjects. Each application will be assessed individually by the country that has received the new application.

In the Form section a new cover letter and a proof of payment of fee (if applicable) must be uploaded for each added MSC.

In the Part I section you can provide translations if required by the new MSC. If you need to upload translations for documents, you can choose the document type on a list and thereafter upload the new document and add the language.

MSCs Part I	Bigibility criteria	Ψ
- Translations	Eligibility criteria	
Part II Evaluation Timetable	Principal inclusion criteria * New ID Principal inclusion criteria (English)	Principal inclusion criteria (Languages)
	Protocol Synopsis of the protocol Data subty monitoring committee charter Study detign Investigates brockner Summary of Societtic advice Authorisation of manufacturing and import QF DMP contribution DMD Quality Simplified DMD-Q DMD - Safety and Efficacy Simplified DMD-Q Solety Intel Efficiency Content babelling of the DMS AMPO - Full Attochment of gluteRication of low interventional clinical trial PSP Queien	Principal exclusion criteria (Languages)

In the Part II you can add the site details for the new MSC.

It is possible that the sponsor receives RFI from the additional MSC during the process.

9.Notifications after authorisation

The notification tab can be found in each clinical trial in the sponsor workspace. Sponsors use the notification tab to inform each member state of important milestones in the clinical trial:

- Start of recruitment
- Start of inclusion
- Temporary halt of the clinical trial
- Temporarily halted clinical trial is resumed
- End of recruitment
- End of inclusion
- End of trial

The deadline for reporting these notifications in CTIS is 15 days. The notifications should be made for each member state where the clinical trial is approved. The specific country must be selected and then click on the notification tab you want to enter.

All buttons found in the notification tab will be active once the clinical trial is authorized.

100	Authorised 2020-500-	438-88-00 RMS: Bulgar	ia	-					
	Summary	Full Trial Information	Notifications	Trial results	Corrective r	neasures Ad Hoc assessments	Users		Amend
	Trial & Recruitn	nent Periods		_					
	_		_						
	Start Trial E	nd Trial Restart Tria	d Temporary Ha	dr.		2 Start Recruitment End Re	cruitment	Restart I	Recruitment
		11		T-i-1	-		-	Description	
				Trial				Recruit	ment
	 Select all 	Current status	Start date	Trial Temporary Halt	Restart	End (or early termination)	Start	Recruit	Restart
	Select all Austria	Current status	Start date	Trial Temporary Halt	Restart	End (or early termination)	Start	Recruit End	Restart
	Select all Austria Germany	Current status Authorised Authorised	Start date -	Trial Temporary Halt	Restart -	End (or early termination)	Start -	Recruit End	Restart -

Select the specific country where you want to make a notification.

Click on the notification tab you want to enter either Start Trial, End Trial, Restart trial, Temporary Halt, Start recruitment, End recruitment or Restart recruitment. For example:

Notices & aler	S 🔕 Clinical study New star	reporte Annue t of recruitment	notifica	tion	rtin		RET	IIse	er ad	mini	strat	ion	×		
Summary	Full Trial			Bulga	aria								5		Amend
Trial & Recru	itment Peri Start of re	cruitment date*		_								L 1			
Start Trial	End Trial Related docur	ment(s)		<			Augus	1 2020			>	-	10	Restart	Recruitment
				31	Sun	Mon 27	Тие 28	2.9	Thu 30	Fri 31	Sat	Add document	2	Recruit	ment
				32					0						
Select all	Curre			33								×Cancel ✓Sub	nit srt	End	Restart
🗆 Austria	✓ Authorised			34							22				
🗇 Germany	✓ Authorised		-	35				26		- 211	- 255				
🖬 Bulgaria	✓ Authorised	26/08/2020		10	tay	Clear	01	10	.03	04	one				

Choose the country where you want to notify about recruitment start. Enter the date where the recruitment will start and then click submit.

For further information on this topic, please see the <u>Training Video: How to manage a CT in the CTIS sponsors</u> workspace – <u>Trial and recruitment periods notifications</u> and the <u>Step by step guide</u> in EMA training module

For instructions on how to notify Unexpected events, Serious Breaches, Urgent Safety Measures or 3rd Country inspectorate inspections, please watch this <u>video</u>.

RFI mechanisms have also been implemented in the system to enable exchange of information between MSC and sponsors as part of an ad hoc assessment, following for example a notification of a serious breach, in case of evaluation of an annual safety report (ASR) or when a sponsor opinion needs to be provided in the context of a corrective measure.

For additional information on responding RFIs during the ASR assessment, please see the <u>step-by-step</u> guide and <u>this video</u>.

Sponsor can find further information on Clinical study reports submissions in this <u>step-by-step</u> guide in EMA training module 13.

10. How to create and submit a Substantial Modification (SM)

To create and submit a substantial modification after the clinical trial has been authorised, users can select the '+ CREATE' button in the sponsors workspace at the top-right corner of the Clinical Trial page.

Clinical trials	Notices & alerts 🚳 🛛 An	nual safety reporting RFI User administral	tion			
		ß			Lownload + CREATE -	1
	Trial title Webina	ar 21 09 2020 RMS: Austria			Single trial substantial modification Multi trial substantial modification Non-substantial modification	
	Summary Full Trial	Information Notifications Trial results	Corrective measures Ad Hoc a	assessments	Additional MSC	click on the create tab to make a
Go to the summary	TRIAL INFORMATIO	ON				substantial modification
section in	Sponsor	Test Organisation 1	Member states concerned	AT · BE		
the sponsors workspace	Trial phase Therapeutic area Medical device	Therapeutic exploratory (Phase II) Diseases [C] - Respiratory Tract Diseases [C08] No	Medical conditions Low intervention study Population type	Apnoea Yes Healthy Voluntee	rs	
	ІМР					

This will enable to select which type of modification you want to submit:

<u>Single trial substantial modification:</u> to update information for only one trial.

<u>Multi trial substantial modification</u>: to update information for trials that have the same IMP and the same sponsor. In this case it is possible to submit a single application covering several trials.

More information in question 3.8 of the Q&A Document - Regulation (EU) 536/2014, published in the Chapter V of <u>EudraLex</u> -<u>Volume 10 - Clinical trials guidelines</u>.





If you click on the **"Single trial substantial modification"** you will be redirected to a window where you need to enter the scope of the substantial modification. Thereby you will define the part which will be modified (Part I and/or II).

In the "Form" section, cover letter should be uploaded and additionally it is mandatory to upload a general description of changes in the field Modification description.

Clinical trials Notices & a	lerts 🕘 Annual safety reporting RFI User administration
Please note that data a	na documents provobal in the su batabase are subject to publication rules (inclusing the protection of personal data and commercially confidential information), as per Regulation (EU) 536/2014, Article #1(4).
Trial title Webinar 21 / RMS: Austria	you can upload cover letter and description of the 1-00 / Substantial modification ID: SM-1 Draft New version draft SM-1 = O View submitted application modification and other supporting information
Form MSCs	Form details
Part I Part II Evaluation Timetable	Substantial modification details
	Add document Supporting information

If you scroll down, the reason and the scope for the substantial modification must be added here.

				de 81(4).
MSCs				Add o
Part I Part II Evaluation Timetable	C_Modification_Description_Details ▲ ✓ English · Modification Description (for publication) · · Version 1 · 13/09/2020 Supporting information	System version 1	Choose a reason for the substantial modification. If none of the reasons are applicable you can choose "other".	
	Supporting information documents		Substantial modification score	Add d
	End of trial in MS End of trial in EEA Global end of trial	₿ ·		
	trial in HS trial in EA Global and of trial Anticipated date of summary of results Unexpected Event Change in B/R Serious Breech Urgant Safety Heasure	₹		

In the "MSCs section" only subject numbers (number of planned trial subject) can be modified.

Clinical trials Notices & al	erts 🔕 Annual safety reporting RF	I User administration			The button "add member state" is
Please note that data an	id documents provided in the EU Database are subject to p	ublication rules (including the protec	tion of personal data and commercially confidential info	ormation), as per Regulation (EU) 5.	inactive as this
In the MSCs					application.
the number of Inar 21 0	09 2020 2020-500275-71-00 / Subs	tantial modification	ID: SM-1 Draft New version of	draft SM-1 👘 🕕 View	submitted application
be changed					
				🗸 Check 🛛 🕅	Save 🛛 Cance 🗛 Submit
	3				
Form	Member states concerned				
MSCs					+ Add member states
Part I	Member states concerned	RMS	First submissions date	Subjects	Atctions
Part II	Austria	Selected		20 \$	
Evaluation	Belgium			20	
Timetable	and control of the second s			120	1

Form	Trial specific information (Part I)	
MSCs Part I	Trial details	
Part II	Trial identifiers	>
Evaluation	Trial information	>
Timetable	Protocol information	~
	Clinical trial protocol	
	Protocol * I_1_Part1_CT_Protocol Image: Comparison of the second se	Add document
	English · Protocol (for publication) · System version 1 · Version 1 · 13/09/2020	

When all data and documents have been modified and uploaded, click on **Submit**. Then select the parts of the application you want to submit and click on the **Confirm** button.

Clinical trials		Submit confirmation	×	UAT CT	1.
Clinical trials Notices & alert	ts 📵 Annual safety repor	Please select the application parts you wish to submit.			
O Please note that data and d	ocuments provided in the EU Database ar	Part I Part II Austria Part II Belgium	\searrow	ai information), as per Regulation (EU) 536/2014, article 81(4).	
Trial title Webinar 21 09 / RMS: Austria	2020 2020-500275-71-00	_	× Cancel ✓ Confirm	in draft 5H-1 = 0 View submitted application	
-				Check 🗈 Save 🔍 Candel 🛆 Su	bmit
Form	Trial specific information (Par	t I)			
Part I	Trial details				A
Barris TT	Transfer a week concerned				

In the Summary page you can scroll down and see the status of the substantial modification.

▼ Paracetamol	I Tablets 500	mg	Kri Userauminis	uation					
OVERALL TRIAL STATUS Member State	Overall Tria	Status	First decision date	Start of t	rial End of t	rial	Recruitme	nt start d	ate
AT BE	Authorised	0	11/09/2020 11/09/2020	It is shown the subs modificati been auth and by v	whether tantial on has torised vhich		It is po additio	ossible nal info	to view ormation
APPLICATION AND	ID NON-SUB	Parts	MSCs	member Submission date	States	Reason	Scope	Link	
Substantial modification	<u>SM-1</u>	Part 1 Part 1	AT(Authonsed) BE(Authorised)	13/09/2020	13/09/2020	+	+	ß,	+ INFO
Initial	Ш	Part I & Part II Part I & Part II	AT(Authorised) BE(Authorised)	11/09/2020	11/09/2020	·	1	1.50	+ INFO
*	_	_			_	_	_	-	_

Additional information can be found in this training video and step-by-step guide in EMA training module 10.

Non-substantial modifications

Non-substantial modification (NSM, i.e. without substantial impact on the safety or rights of the subjects and/or the reliability and robustness of the data and when the information is not necessary for oversight) should not be notified as such. Correction of typos and other administrative changes with no impact on the content and meaning of the information are always expected to be updated as non-substantial modifications. NSM can be submitted with a SM application. These NSMs need to be listed and identified as NSMs in the cover letter of the SM application. We do not expect to receive NSMs notifications on a regular basis. Sponsor should accumulate non substantial changes and notify them within the next substantial modification submitted for the clinical trial.

For further information on this topic please see question 3.4 of the Q&A Document - Regulation (EU) 536/2014, published in the Chapter V of <u>EudraLex - Volume 10 - Clinical trials guidelines</u>.

Changes to a clinical trial which are not SM but are relevant for the supervision of the trial (Art. 81.9)

Information on any changes to a clinical trial, which are not SMs but are relevant for the supervision of the clinical trials by the MSC, shall be permanently updated in CTIS by the sponsor, in line with Article 81.9 of the CTR. This route can be used to update information to fulfil a condition, depending on the instructions of the RMS (part I conditions) or the MSC (part II conditions).

For further information on this topic please question 3.3 of the Q&A Document - Regulation (EU) 536/2014, published in the Chapter V of <u>EudraLex - Volume 10 - Clinical trials guidelines</u>.

11.Create and submit an Annual Safety Report (ASR)

To create and submit an Annual Safety Report users can open "the Annual Safety Reporting form" by clicking on the '+New ASR' button in the sponsor's workspace.

Clinical t	rials		UAT CT 0 0 0 0
Clinical trials	Notices & alerts 🕘 Annual safety reporting RFI User administration		
	Annual safety reports		
	Q. Enter EU CT or ASR ID or use advanced search. To search for multiple IDs, separate them with commas.	SEARCH Advanced Search *	
	Search results		R ,
	Showing 1 - 3 of 3 items	1 of 1 pages (1)	

TIP: Make sure to have the <u>ASR document in PDF</u> prepared and all the relevant information ready (e.g. Investigational medicinal products, relevant events that occurred, reporting period, etc) before starting.

An ASR form opens:

Clinical trials	UAT CT 🛛 🗖 🕇 EN 🗸
Clinical trials Notices & alerts 🧑 Annual safety reporting RFI User administration	
Submit ASR	₫ CLEAR ✓ CHECK Ø CANCEL SUBMIT
1 2 Sponsor information Clinical Trial detail	ASR reporting period details Supporting documents and submit
 Step 1 Sponsor information 	Expand all V
 Step 2 Clinical Trial Detail 	
 Step 3 ASR Reporting Period details 	
 ▼ Step 4 Supporting Documents and Submit 	

Fill in the information for the four steps (Sponsor information, Clinical trial details, ASR reporting period details and supporting documents) and submit on the **Submit** button. The ASR form has to be filled in and submitted in one go. You need to have all information ready because it cannot be saved.

Step 1: Sponsor information

+
+
Next

Fill in Organisation details of the selected sponsor and the contact details for the person who is responsible for the submission and can be contacted with an email address and or phone number.

Step 2: Clinical trial details

Search for the Clinical Trial (CT) to which you want to submit an ASR. You search for clinical trials that are authorised for the selected sponsor organisation and select the trial for which you want to submit an ASR.

< Try a	trial results based on your search criteria mother search				
2	CT for training test EU CT number 2021-501398-35-00	Decision date 20/05/2021	Sponsor Test organisation	MS (Attistria) (Cormany)	
0	CT for training test EU CT number 2021-501535-14-00	Decision date 01/06/2021	Sponsor Test organisation	MS (Germany)	
howing 1	- 2 of 2 items		1 of 1 pages	(1)	

When the form opens you can click on the related IMP or IMPs for the clinical trial you want to submit an ASR.

this the sponsor's first ASR for any of the IMP(s) selected?	O Yes Q No		
f yes, indicate which IMPs	Paracetamol 500 mg Soluble Table	ets	
bata lock point			
SR reporting period *	dd/mm/yyyy	dd/mm/yyyy	
SI Updated during the reporting period *	○ Yes ○ No		
substantial modification on RSI submitted and approved during the reporting period *	⊖ Yes ⊖ No		
During the reporting period ASR includes *	Select		14

In this section you need to select and fill in the data lock point (DLP). That is the cut-off date of selecting data

for the ASR. The DLP must be as close as possible to the approval date.

If this is the first ASR in the clinical trial the ASR reporting period starts the date where the clinical trial is first authorised.

The deadline for submission of ASR is 60 calendar days after the date of the first authorisation. The following should also be answered:

- Has the RSI (reference safety information) been updated during the reporting period?
- Has a SM on the RSI been submitted and approved during the reporting period?

In most cases the answer would be no.

From the drop-down menu it is possible to choose what the ASR includes.

Step 3: Supporting documents and submit

Step 4	
Supporting Documents and Submit	
SR Document *	Add document
SmPC	Add document
if the SmPC includes RSI and not submitted as part of the ASR document)	
nvestigator's Brochure	Add document
if the Investigator's Brochure includes RSI and not submitted as part of the iSR document)	
Other	Add document
Submit	

In step 3 you add the ASR report document and you can also add other supporting documents. The ASR report should be uploaded as a PDF.

Then you can check if all information is valid or anything is missing by using the **Check** button and then you can submit. Once submitted you see this page where all the information that was populated will appear.

Clinical trials	Notices & alerts 🧿 Annual safety reporting RFI User administration						
		0					
	< Go to search ASR-2021-00183						
	Test organisation IMP: Paracetamol 500 mg Soluble Tablets Submitted: 11/06/2021	MSC AT, DE	saMS	ASR reporting period 01/04/2020 - 30/04/2021	Submitted 11/06/2021		
	ASR Submission Assessment SPONSOR DETAILS						
	ORGANISATION DETAILS FOR SPONSOR Test organisation Dun Karm Street, 2 Floor, Orange Point Building, BKR 9037, Birkirkara, Malta	CONTACT FOR ASR SUBMISSION Full name test Test organisation Dun Karm Street, 2 Hoor,Orange Point Building,, BKR 9037, Birkirkara, Malta 123123123 testmail@mail.com					

SUSAR reporting must be done only through Eudravigilance_CTM. It is not necessary the submission of semiannual SUSAR reports. It is not neccessary to report ASRs or SUSARs to the sanitary authorities of the Spanish Autonomous Communities (CCAA).

For more information on this topic, please see <u>this training video</u> in in EMA training module 18.

12. Summary of results and summary for laypersons

The sponsor shall submit a scientific summary of results of the Clinical Trial and a summary of results for laypersons. The deadline for uploading the results in CTIS is one year after the end of trial.

The content of the summary of results is set out in <u>Annex IV of the CTR</u>. It shall be accompanied by a summary written in a manner that is understandable to laypersons, whose content is described in <u>Annex V of the CTR</u>. Summary of results for laypersons must be submitted at least in Spanish, while scientific summary of results may be submitted in English and/or Spanish.

To submit the summary of results, go to Clinical Trials page and search for the clinical trial by entering the "EU CT number" or use advanced search.

inical triats	Notices & alerts 💿	Annual safety reporting	RFI	User administration
Clinic	al Trials			
9	Titler Tol CT number or the			SLAKER
Trial Ad	warend Saarch *		E	Enter the CT number or
Applica	tion Advanced Search +		ļ	use advanced search

Select the trial from the results page and click on the **Confirm** button.

EU CT number	Trial title	Lead sponsor	Product	Member states concerned	Submission date	Decision date
2021-500030- 26-00	Trial test	Test org	Test product	DE(Authorised) GR(Authorised)	03/03/2021	04/03/202
1-1 of 1	Select	the	< 1 >		-	
	trial				× Cancel	🗸 Confirm

When the trial is selected a window will show where the "summary of results" and "layperson summary of results" can be uploaded.

f for trai	Ining test					
Summary	Pull Trial Information	Notifications	Trial results	Corrective measures	Ad Hoc assessments	Users
UMMARY OF	FRESULTS					
				_	→ I	+ New
AY PERSON	SUMMARY OF RESULTS	E.				+ Now
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Select Add document. Then Save and Submit.

Summary of results	<u>^</u>	Lay person summary of results	×
Title 1: Vero Table of summary of sector Dise	ter tupe ni	10a 1	Territor Type:
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Barrenary of results 🗼 🥓 🖹 📑 O Brightsh - Survivary of results (for publication) - Systems ve - Version 1 - 22/07/2021	raine 1.00		1

For further information on this topic please see this <u>step-by-step guide</u> in EMA training Module 5, and this <u>training video</u>.

Annex I. Instructions for clinical trials with medical devices

Clinical trials with medicinal products and medical devices without CE marking

In clinical trials whith medical devices to be investigated but which are not a part of the investigational medicinal product or products, and are not CE-marked for the intended use, documents listed in Annex I of the CTR must be submitted through CTIS. The statement of the use of the medical device must be included in the cover letter (CTR, Annex I, B.i). In the Medical device structured field of CTIS, the sponsor has to indicate "Yes".

A Phase 1/2 o investigate the	pen-label, mu e safety,	lticentre, dos	e escalation and e	xpansio	n study to		
Under evaluation 2022-5019	41-63-00 RMS: Polan	d					
Summary Full Trial Info	ormatior Notifications	Trial results Correct	tive measure:Ad hoc assessments	Users	Inspections		
TRIAL INFORMA	TION						
Sponsor	Glaxosmithkline Re Limited	search & Development	Member states concerned	I PL			
Trial phase	Phase I and Phase	II (Integrated)- First	Medical conditions	Multiple myeloma No			
•	administration to h	umans	Low intervention study				
Therapeutic area	Diseases [C] - Neo	plasms [C04]	Population type	Patients (Inca	pacitated population, Subjects		
FIH	Yes			Women of chi	jiving consent personally, Id bearing potential using		
Medical device	Yes			contraception potential not	, Women of child bearing using contraception)		
			Transitioned Trial	No			

The documents required for the authorization of a clinical investigation with a medical device or a performance study for in vitro diagnostics must be submitted through the general electronic registry of the General Spanish Administration, attaching additionally in this submission the clinical trial protocol. In case the electronic submission is not available for the sponsor, these documents can be physically submitted (on paper or on CD/USB) through the General Registry of the AEMPS: C/ Campezo, 1; edificio 8; 28022 Madrid.

Both applications must be simultaneously submitted for their assessment, that will be performed in paralell. The Ethics Committee appointed in Spain must be the same.

The sponsor has to pay two different fees: one regarding the clinical trial application, and other regarding the clinical investigation with a medical device or the performance study for in vitro diagnostics.

Two separate authorizations will be granted. To start the clinical trial, it is essential that the sponsor has both authorizations.

Clinical trial with an integrated product

In clinical trials investigating an integrated product that has components which, used separately, could be considered a medical device or a medicine, two situations can be differentiated:

a) In case the main action is due to the medicinal product, the sponsor should submit a CTA through CTIS,

marking "Yes" in the Medical Device section of the general information of the trial and indicating this in the cover letter.

It should also be specified that a medical device associated with the investigational medicinal product is used in the structured field of CTIS (Part I - Products):

Part I * Part II Evaluation Timetable	EU MP number	Marketing authorisation number	Product authorisation	Product name	Pharmaceutical form	Strength	Sponsors product code	Active substance name	EU substance number	ATC Name	ATC Code	ATC Level	Sponsors substance code	Active substance other descriptive name
	PRD9979206	-	Unauthorised	Gedatolisib	Powder for infusion	Gedatolisib 180mg	PF- 05212384	Gedatolisib	SUB189009	-	-	-		-
	Cetails for Product with EU MP number: PRD9979206												•	
	Medicinal product details												>	
	Product characteristics												>	
	Dosage and administration details												>	
	Product Classification												>	
	Orphan Designation												>	
	Active sub	stance												>
	Advanced	Therapy Med	icinal Product											>
	Device ass	ociated with	medicinal pro	duct										Ŷ
	No devices con	nbined with the p	roduct											

In this case, it is not necessary to submit an application to the Medical Devices Department, and only the fee for the clinical trial with medicinal products has to be paid.

The part of the product that separately could be considered a medical device must comply with the safety and performance requirements set out in Annex I of Regulation 2017/745 on medical devices.

b) In case <u>the main action is due to the medical device</u>, it would be a clinical investigation with medical devices that must comply with the provisions of its legislation. The application must be sent through the General Register of the AEMPS addressed to the Department of Medical Devices and only the fee corresponding to clinical investigation involving medical devices shall be paid.

Annex II. How to register sites in CTIS

It is possible to create organisations locally in CTIS, without the need to register them in OMS, in the following five areas of the system:

- Part I: Sponsor section "Third-party organisations"
- Part II: "Trial sites"
- Serious Breach Notification: "Details of the site where the serious breach occurred"
- Third Country inspectorate Notification: "Third country inspection site"
- MS Inspections: "Inspected site"

The registration only requires the population of structured data as per the process explained below. There is no validation required apart from the completion of the mandatory fields and users can add the new site as soon as it has been registered in CTIS.

Organisations created locally in CTIS behave and function in the same way as the ones sourced from the Organisation Management Service (OMS) and can be searched and selected once they have been registered in CTIS.

Step-by-step instructions: How to register sites in CTIS

The following example refers to the registration of an investigational site. Please note the process is also applicable to the other four CTIS areas where this functionality has been enabled (see above).

Step 1

The user must first search OMS, as the "Search in OMS" radio button is ticked by default.

Clinical trials Notices & alerts Clinical study report	Select trial site	Secting presend data and commercial but on presend data and commercial but on present data and commercial but on the section of the section o
AP Test Prob8 anza-sonica-as-on / Substantial m	Search organisation Terms (starts with *) (b) (starts with *) (starts with	RMS: Gener
Form Country specific detai MSCs Trail etes	Search in OHS Search in CTIS ID Name Address City postCode country phone email actions	V DHA 2 SHE 0 COLD 0 SORE
Part I Trial sites Part II IR Evaluation Organisation	x Cancel √Add blid site Site street Site post Site First	+ AM str

Step 2

If the user does not find the site in the OMS (red error message displayed) or the organisations displayed are not the ones the user is looking for, the user should then search for the site in CTIS by selecting the second radio button "Search in CTIS".

Cinical trials - Notices & alerts	Clinical study report	Select trial site X Internation and the set of the set
AP Test Prob8 2022-50040-59	w/ Substantial m	Search organisation tene tarts with * Dr tarts with * Corey Tene Tene
Form MSCs Part I	Country specific detail Trial sites	Search in OMS O Search in CTIS + these expensations d Care Search argundention ID Name Address City postCode country phone email actions
Part II -rs Evaluation	Trial sites	X Cancel VAAd total site # Add site

Step 3

If the user does not find the site in CTIS (red error message displayed) or the organisations displayed are not the ones the user is looking for, the user can opt to create the site in CTIS by clicking the button "New Organisation", which will now appear enabled.

Clinical trials Notic	es & alerts 📳 🛛 Clinical s	tudy reports - Annual safety reportion - BET - Hore administration	Ĩ
0 Picase	note that, in accordance with Reg atom. It is the responsibility of ea	Select trial site 8	acting personal data and commercially confidential late in CDS.
P Test Prob8 202	2-50943-19-00/ Subst	Search organisation antial m tere (acts with v) to (acts with v) (curry	RMS: Green
		Parce Parce + New organization d Clear Sourch organization	✓ Chill 2 See 0 Chill & Solet
	Form Country sp	scilic detail ID Name Address City postCode country phone email actions	5
	MSCs Trial site		×
	Part I Irial site	e	
	-Fil	KCancel Add total size	+ Add Or
Eval	uation Organisa adapted 10	ion Site struct Site post Site First Organisation name Site location address Site City code country Title name	Lest name Deportment Phone Email Actions

Step 4

The user completes the displayed form.

IMPORTANT: Users are advised to enter the city and post-code, although these fields are not highlighted as mandatory, to ensure notifications that include sites registered in CTIS pass the technical validation. Moreover, in the case of investigational sites/third party vendors, this is relevant information for inspections.

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			84		wat	101								
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	Transial and other arrangements	-												\$ ·
	Congliance with satisful requirements on Sala Protoc					I NORTH								8
	Compliance with our of Bulligical samples				_	CROF	-							¥.
	Al decements													3

Step 5

The user then clicks submit and a pop-up confirmation window appears.

Please note that organisation IDs for organisations registered in CTIS will start with ORL. Users may wish to take note of this "Organisation ID" for future reference, although they are always able to search using the Organisation name.

Step 6

The user should confirm and click the "Add trial site" button.

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ham HSG Det 1	Gautry gands deals (Not 3 - Press) Not the	3	-1-							1
Part 21 Int Evaluation	Teldaha			-						

Step 7

The trial site is displayed. In this particular case, for trials sites, the user can edit the additional pending information by using the pencil.

HSCs	Trial sites													
Part1 Part11	Trial sites													
-R	Organisation 33	Organization name	Strington	Die street address	Shedg	Sile pot cole	Site cavity	7de	First Name	Latrare	Department	has	bal	1
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Important notes

1. The user is given ample options to search (i.e., first in OMS, then in CTIS), with a view to prevent duplication and ensure better quality of data.

2. Once the user has registered an Organisation in CTIS, it will remain in DRAFT status. The draft Organisation will be visible only within the scope of the draft CTA or draft notification, i.e. it will not appear when other sponsors search in CTIS.

3. Once the CTA or notification, which contains this Organisation registered in CTIS in DRAFT status, is submitted, the locally registered site in CTIS is changed from DRAFT status to ACTIVE status. This implies that the site is now searchable by other users, including users from different organisations such as other sponsors. This also implies that the local site is no longer editable. If the user now wishes to change or remove the site from the Clinical Trial application or Notification, the user will have to raise a modification or update the notification, respectively.

For further information on this topic, please see the <u>step-by-step guide</u> in EMA training Module 3.