CTR:
Utilizzo del Portale Europeo

Guida pratica per promotori no profit

10 Settembre 2024

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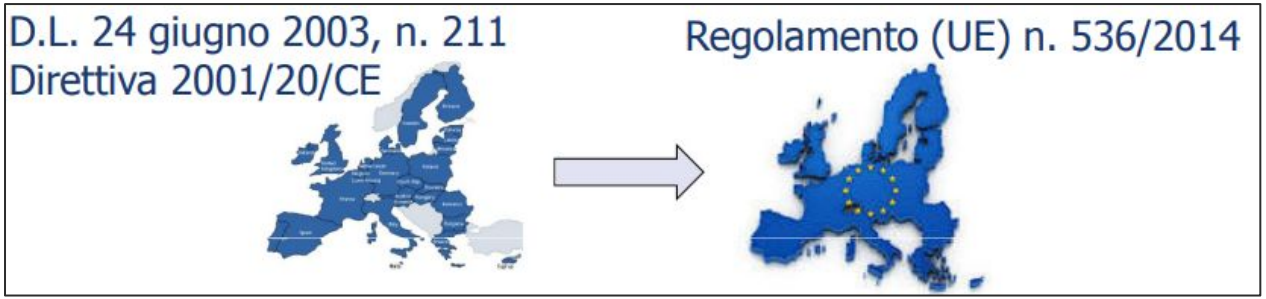
Clinical trial regulation 536/2014

The EU CTR is a new EU legislation designed to simplify and harmonize clinical trials, replacing European Clinical Trial Directive (CTD) with new rules for the submission and conduct of the trials in the european economic area (EEA) countries.

AIM: Europe more attractive and competitive in clinical research

SCOPE: all interventional studies with at least 1 IMP

IN FORCE: 31/01/2022



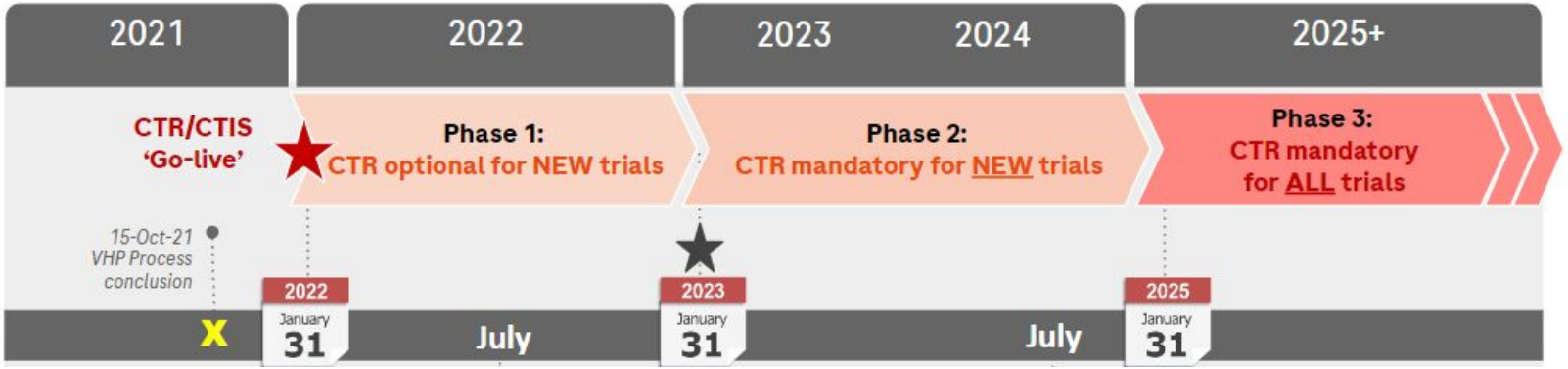
Clinical Trial Directive (CTD): law that defines the common goals for all the European countries. Each country can decide how to proceed.

Clinical Trial Regulation (CTR): binding legislative act that needs to be applied as it is in all the european economic area (EEA)

- Directly applicable without necessity to be receipt
- Harmonization within Member states
- Less national autonomy

Clinical trial regulation 536/2014
Implementation phases: Timelines

EMA CTR Phases



New trials: to be submitted under CTR from Jan 2023

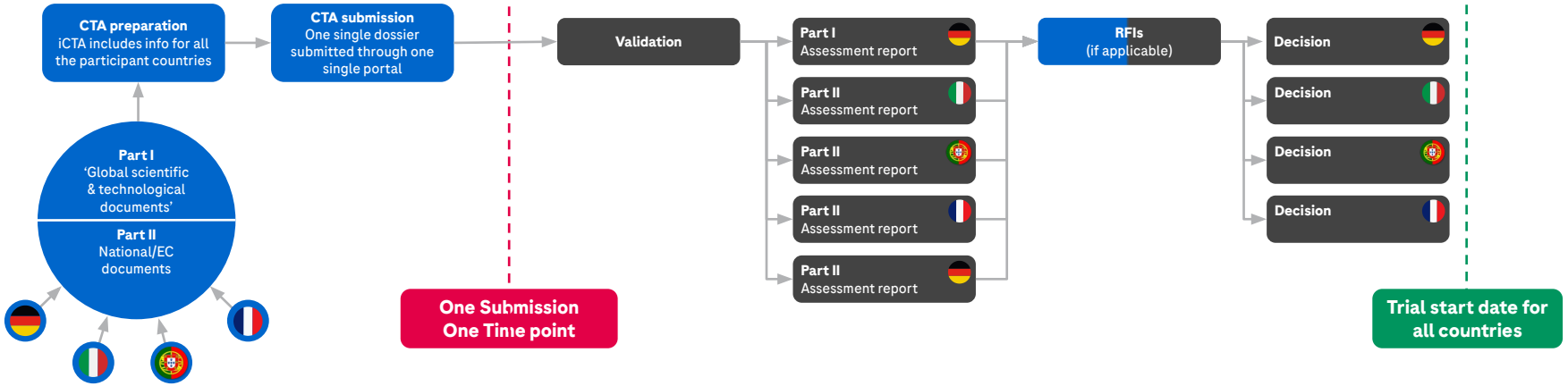
Ongoing trials: to switch to CTR by Oct 24, in order to be sure to obtain approval by 31st Jan 25

Initial CTA Submission under CTR

No differences between HA and EC submission. Parte I (common) and Parte II (county specific) submitted together

Only one portal , "Clinical Trial Information System" or "EU Portal"

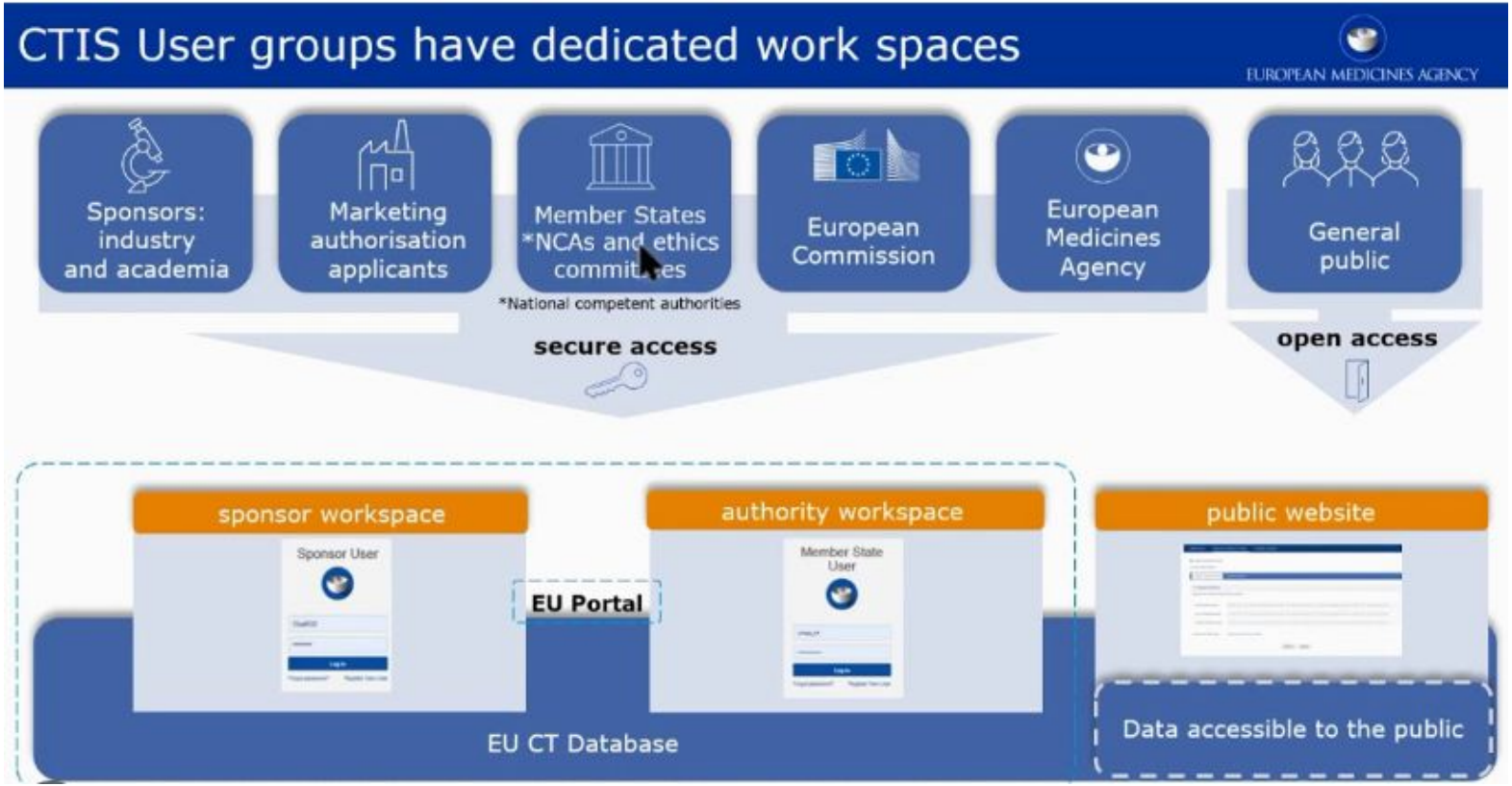
No changes are allowed to the iCTA during the assessment period.



= Sponsor

= European Medicines Agency

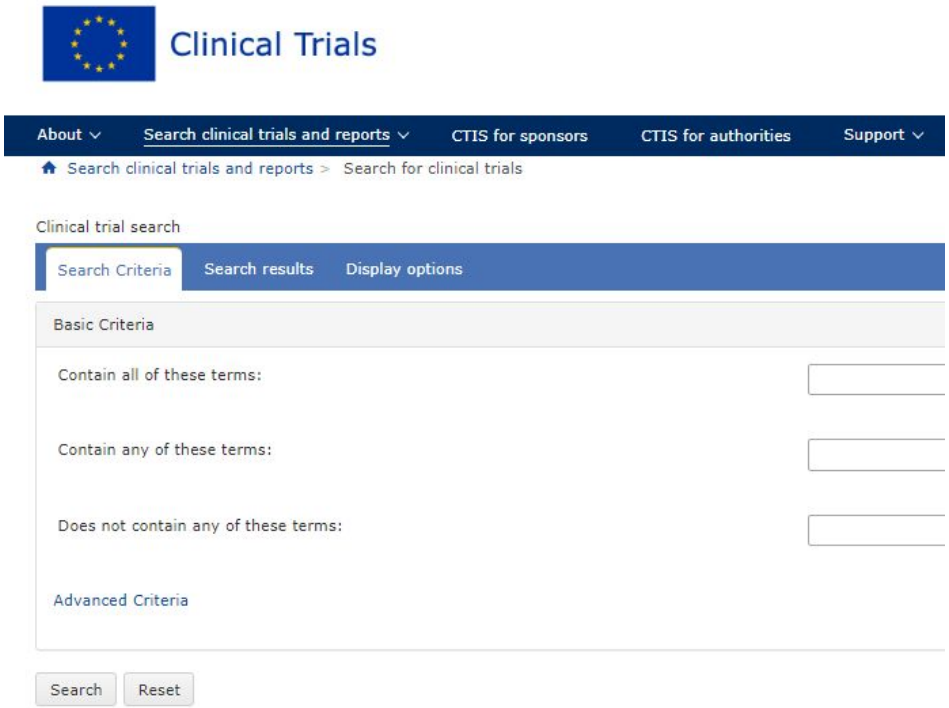
CTIS Portal



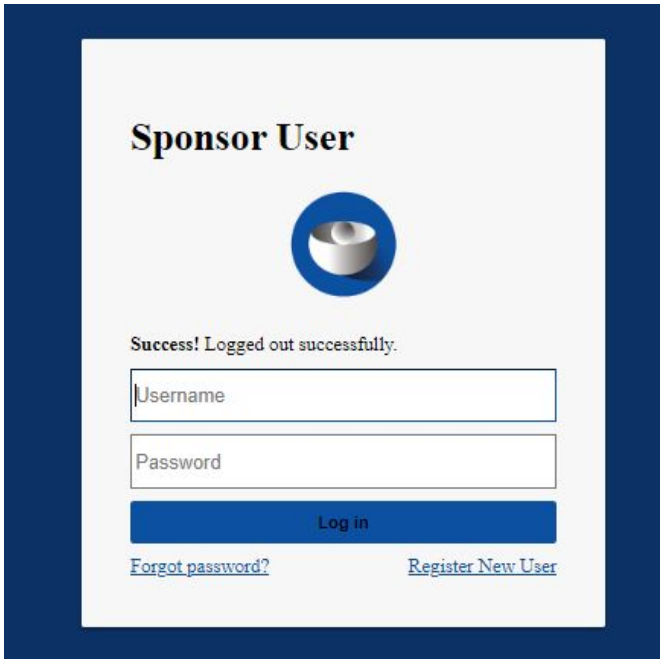
https://euclinicaltrials.eu

CTIS Portal

Public area

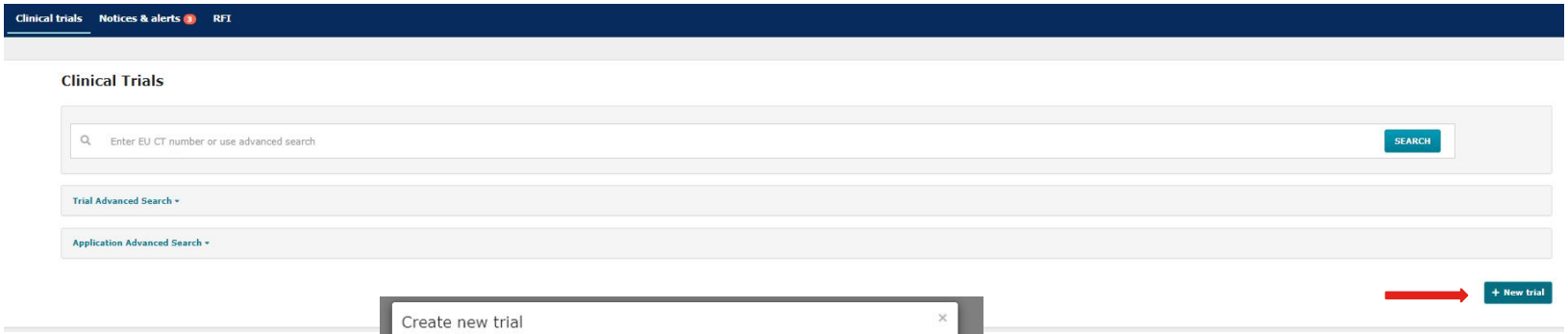


Sponsor

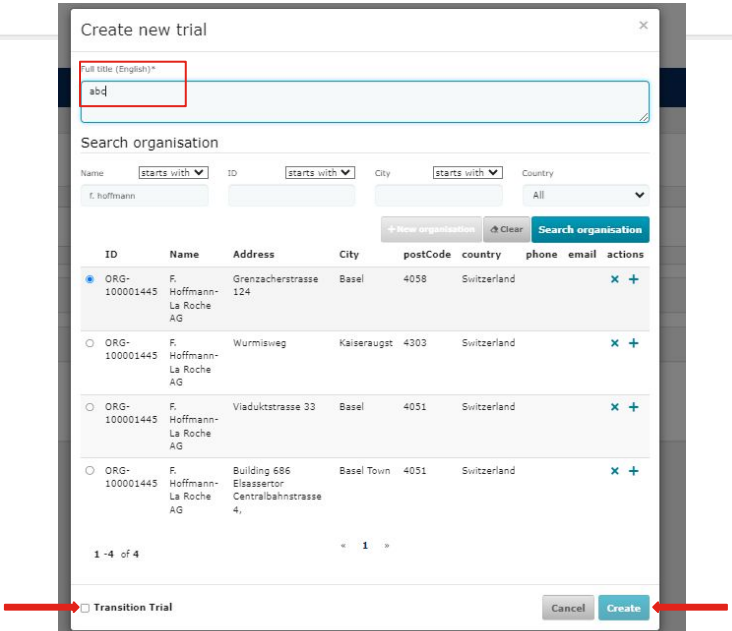


https://euclinicaltrials.eu

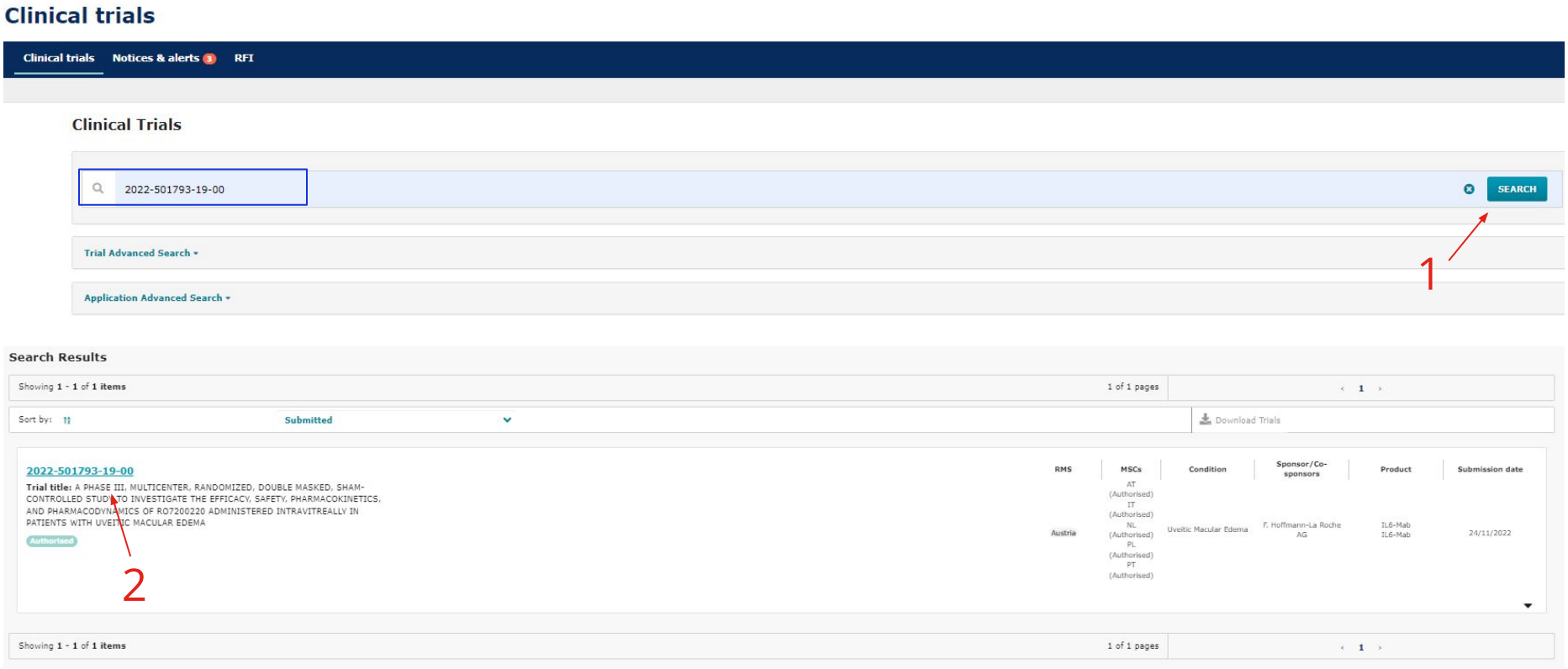
Create EU CT Number



1. Add the full title
2. Search the organization name
3. Select the right one
4. Tick on Transition if it is a switch application or not tick if it is a new trial
5. Click on create



CTIS overview- how to search a study:



CTIS overview- how to search a study:

TRIAL INFORMATION

Sponsor	F. Hoffmann-La Roche AG	**Member states concerned**	DE · ES · FR · IT · PL
Trial phase	Therapeutic confirmatory (Phase III)	**Medical conditions**	Choroidal neovascularization secondary to pathologic myopia
Therapeutic area	Diseases [C] - Eye Diseases [C11]	**Low intervention study**	No
Medical device	No	**Population type**	Patients (Women of child bearing potential using contraception)
		Start of trial	09/04/2024
		Transitioned Trial	No

IMP

Expand all

▼ FARICIMAB

MSC TRIAL STATUS

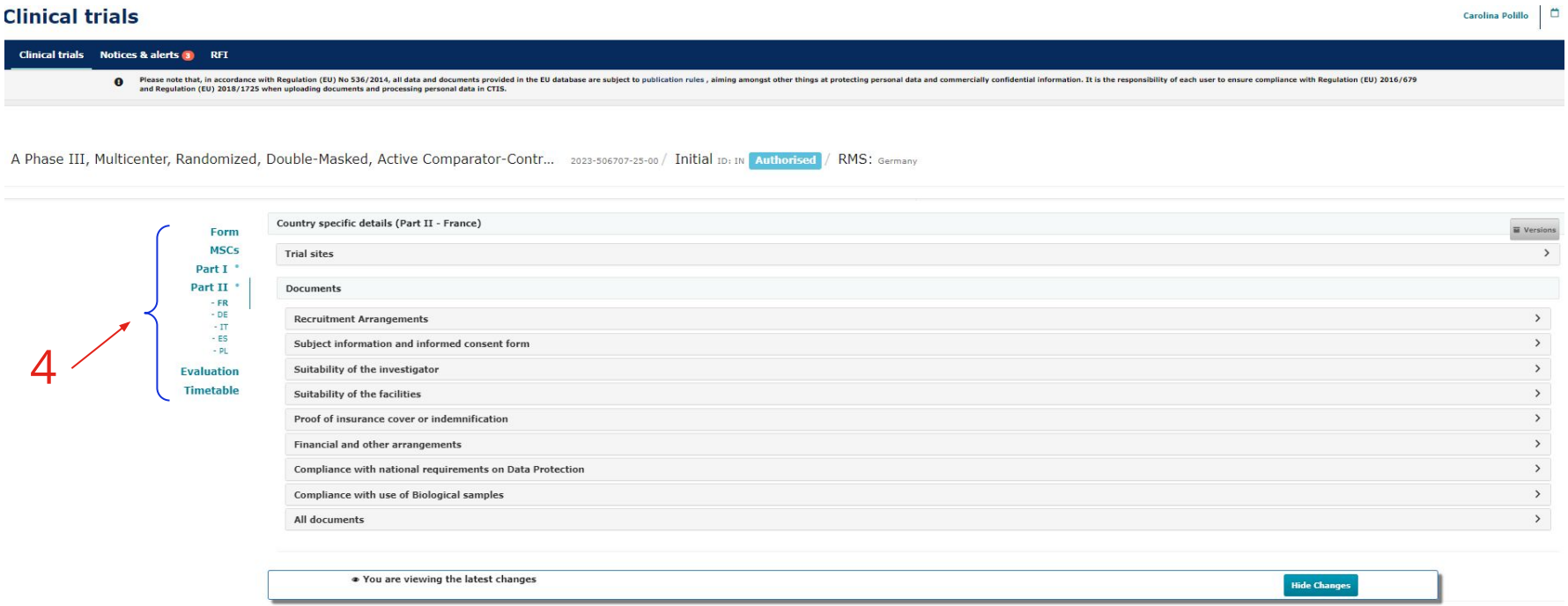
Member State	MSC Trial Status	First decision date	Start of trial	End of trial	Recruitment start date
DE	Authorised	02/04/2024	15/04/2024		29/04/2024
ES	Authorised	27/03/2024	30/05/2024		04/06/2024
FR	Authorised	26/03/2024	30/04/2024		20/06/2024
IT	Authorised	27/03/2024	09/05/2024		26/06/2024
PL	Authorised	02/04/2024	09/04/2024		11/04/2024

APPLICATION AND NON-SUBSTANTIAL MODIFICATION

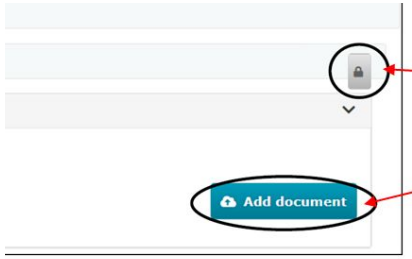
Type	ID	Parts	MSCs	Submission date	Decision date	Reason	Scope	Link	
Substantial modification	SM-1	Part I & Part II Part I & Part II Part I & Part II Part I & Part II Part I & Part II	ES(Authorised) FR(Authorised) DE(Authorised) IT(Authorised) PL(Authorised)	23/04/2024	31/07/2024	+	+		+ INFO
Non-substantial modification	NSM-1	Part II	PL(Authorised)	09/04/2024	09/04/2024	-	-	-	
Initial	IN	Part I & Part II Part I & Part II Part I & Part II Part I & Part II Part I & Part II	FR(Authorised) DE(Authorised) IT(Authorised) PL(Authorised) ES(Authorised)	17/11/2023	26/03/2024	-	-	-	+ INFO

3

CTIS overview- how to search a study:



CTIS overview- how to upload documents:



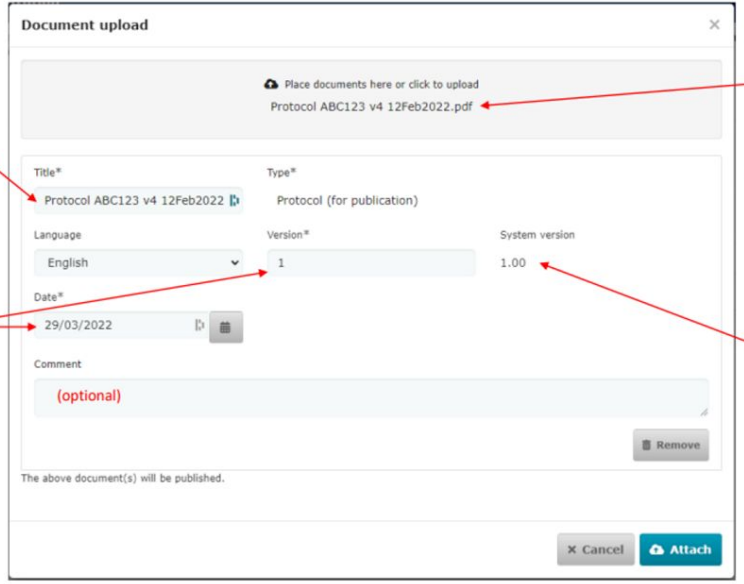
1. Before starting upload of the document, it is necessary to lock the section
2. Then click on add document
3. Unlock the section and save

Uploading documents in CTIS

The **Title** of the document in CTIS. The filename as it was uploaded is pre-filled here, this should be changed to match the requirements for document coding and titles [redacted] Always remove version and date from the Title, [redacted]

Change the default version (1) and default date (today) to the actual date and version of the document (in this example: version 4, date 12/02/2022).

Please note: the version field is free text: e.g. a zero of N/A can be filled in for documents that do not have a version number.



The **filename** of the uploaded file. The uploaded files can have any name, except for some forbidden characters:

The filename provided is not valid. No special characters (/ , . ; |) allowed.

The CTIS System version of a document, always starting at 1.00 for the first version of a document uploaded into CTIS, and increasing when using the Update functionality. Cannot be edited. System Version therefore does not necessarily match the true version.

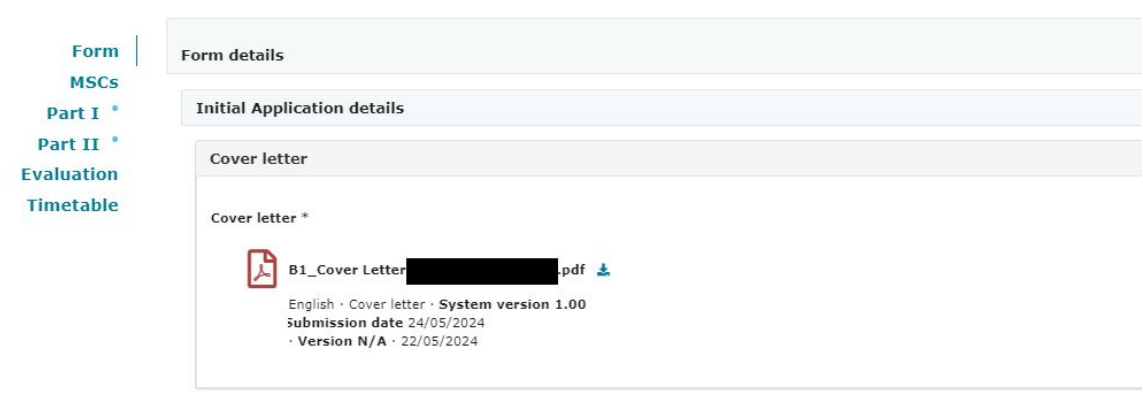
Initial Clinical Trial Application (CTA)

Initial CTA: PART I

PART I / FORM SECTION:

Cover Letter	A template is available on the HMA website (v4 March 2024) → you can find it in this webpage https://www.hma.eu/about-hma/working-groups/clinical-trials-coordination-group.html, under the section "GUIDANCE - Transitional Trials". This template is for multinational trials but can be modified for single-country trials.
Proof of Payment	To be added as per local requirements (mandatory for Italy)
Compliance with Regulation (EU) 2016/679	A template is available on the EMA website → https://health.ec.europa.eu/document/download/dcbff0c5-b4e8-479b-88a5-f308b006d126_en?filename=compliance_reg2016_679_template_en.pdf
Trial Category	You will need to select in which category your study is falling into, and justify your choice. Also refer to the EMA "Revised CTIS transparency rules and historical trials: quick guide for users"

PART I / FORM SECTION, example:



PART I / FORM SECTION, example:

Compliance with regulation

Compliance with Regulation (EU) 2016/679

Compliance with Regulation (EU) 2016/679 *

r1_compliance with regulation 2016-679

English · Compliance with Regulation (EU) 2016/679 · **System version 1.00**
Submission date 08/08/2024
· **Version N/A** · 27/04/2023

Trial category

Justification of trial category

Trial category *

Category 2

Justification for trial category *

This is a Phase III study - is a confirmatory/registrational trial and the development program for the molecule is ongoing

Category	Trial type
Category 1 Pharmaceutical development clinical trials	Phase I clinical trials in healthy volunteers or patients Phase 0 trial in healthy volunteers or patients Bioequivalence and bioavailability trials Similarity trials for biosimilars Equivalence trials for combination or topical products
Category 2 Therapeutic exploratory & confirmatory clinical trials	Phase I and phase II integrated clinical trials Phase II clinical trials Phase II and phase III integrated clinical trials Phase III clinical trials
Category 3 Therapeutic use clinical trials	Phase III and phase IV integrated clinical trials Phase IV clinical trial and low interventional trials

NOTE:

based on the category of your trial, doc/data will be made public at different timepoints

Revised EMA transparency Guidance → GO LIVE & full implementation on 18 June 2024

Applicable for ALL submissions from 18 June 2024

- **New CTA submissions:** structured data and documents publication according to new rules
- **Historic submissions (ongoing):**

  - Only structured data will be made public from 18 June 2024.

  - Document publication triggered **by following 1st submissions from 18th June 2024:**

    - Substantial Modifications (part I and/or part II)
    - Non-Substantial Modification part II
    - Additional Member State (triggering publication of part II docs only)

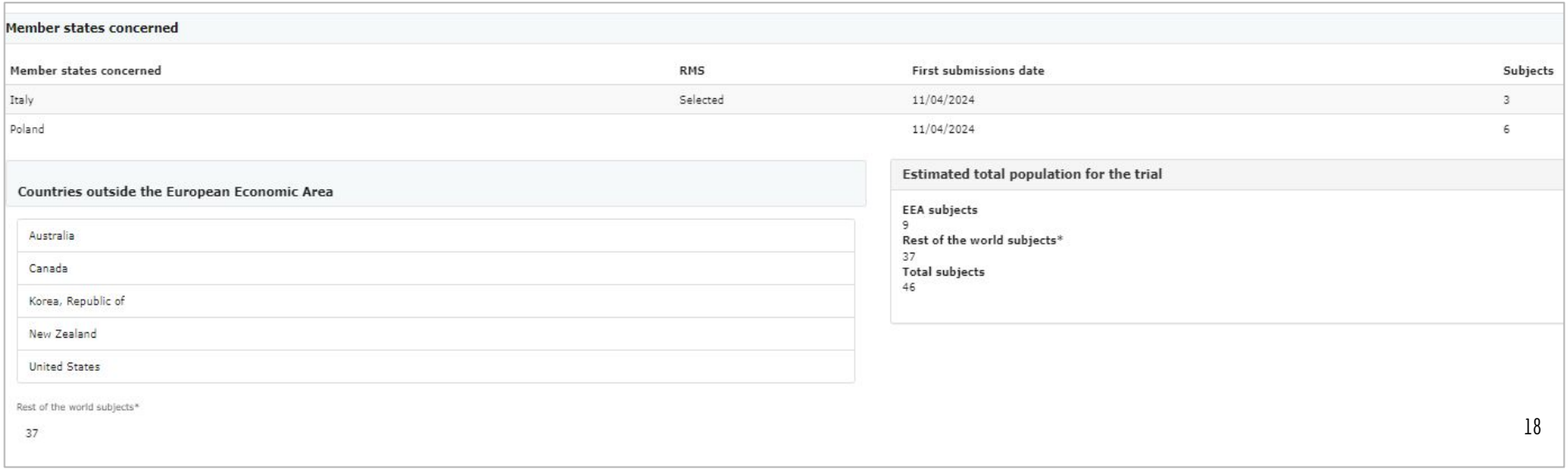
  Only with THESE SUBMISSIONS (no matter of scope) Sponsors can update redacted document prior to publication.

Also refer to the QUICK USER GUIDE released by EMA.

PART I / Member States Concerned (MSC) Section:

All mandatory structured application data	- Member state(s) concerned - Reporting member state proposed - Number of Patient planned in each participating EEA Countries - List of non-EEA countries, if applicable - Total number of patients in the trial

EXAMPLE FOR MULTI-COUNTRY STUDY:



Member states concerned

Member states concerned	RMS	First submissions date	Subjects
Italy	Selected	11/04/2024	3
Poland		11/04/2024	6

Countries outside the European Economic Area

- Australia
- Canada
- Korea, Republic of
- New Zealand
- United States

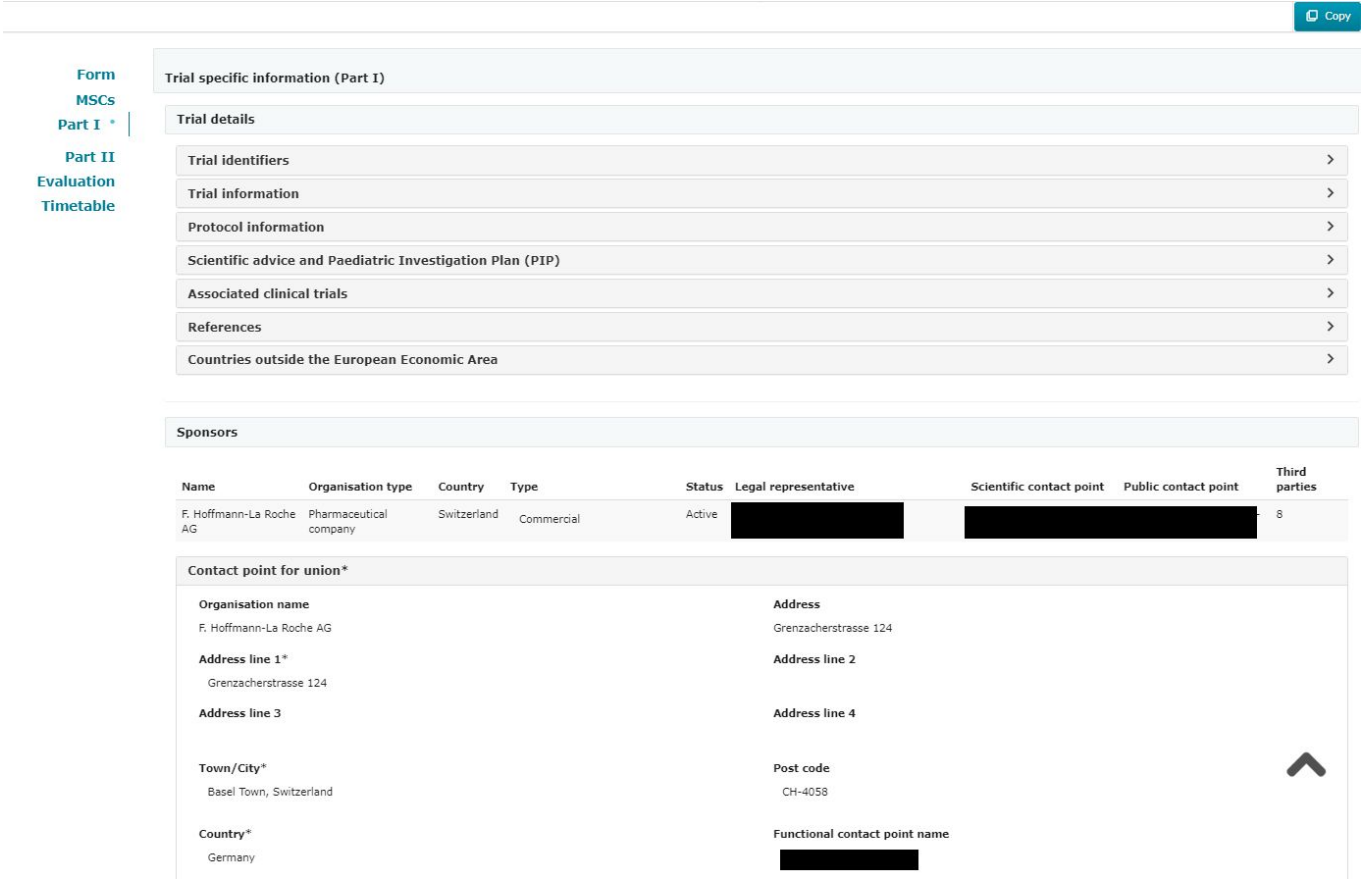
Rest of the world subjects*

37

Estimated total population for the trial

EEA subjects
9
Rest of the world subjects*
37
Total subjects
46

PART I / CTIS DATA & DOCUMENTS, overview:



Copy

Form
MSCs
Part I *
Part II
Evaluation
Timetable

Trial specific information (Part I)

Trial details

- Trial identifiers
- Trial information
- Protocol information
- Scientific advice and Paediatric Investigation Plan (PIP)
- Associated clinical trials
- References
- Countries outside the European Economic Area

Sponsors

Name	Organisation type	Country	Type	Status	Legal representative	Scientific contact point	Public contact point	Third parties
F. Hoffmann-La Roche AG	Pharmaceutical company	Switzerland	Commercial	Active	[redacted]	[redacted]		8

Contact point for union*

Organisation name
F. Hoffmann-La Roche AG

Address
Grenzacherstrasse 124

Address line 1*
Grenzacherstrasse 124

Address line 2

Address line 3

Address line 4

Town/City*
Basel Town, Switzerland

Post code
CH-4058

Country*
Germany

Functional contact point name
[redacted]

PART I / CTIS DATA & DOCUMENTS:

All mandatory structured application data	- EU CT Data - example: Protocol Number, Title, I/E criteria, endpoints, MedDRA term, etc.. - Sponsor Information & 3rd Parties - IMPs information
Protocol	Redacted & not redacted
Lay CTD	Synopsis in lay language (to be redacted if needed)
Patient facing material	Relevant to endpoints and provided to patients after ICF signature (to be redacted if needed)
IDMC Charter	If applicable
Scientific Advice / PIP number	If applicable
IMPs & Quality Documents	- QIMPD(s) - QIMPD(s) Safety and Efficacy - GMP Relevant documents - Label(s) - Reference Safety Information

PART I / CTIS DATA & DOCUMENTS, in details:

Trial specific information (Part I)

Trial details

Trial identifiers

Full title (English) *

A Phase III, Randomized, Double-Blind, Placebo-Controlled Study of Atezolizumab Plus Carboplatin and Etoposide with or Without Tiragolumab (Anti-Tigit Antibody) in Patients with Untreated Extensive-Stage Small Cell Lung Cancer

Full title Languages	Translation
Full title (Greek)	+
Full title (Polish)	+

Public title (English) *

A Study of Atezolizumab plus Carboplatin and Etoposide with or Without Tiragolumab (Anti-Tigit Antibody) in Patients with Untreated Extensive-Stage Small Cell Lung Cancer

Public title Languages	Translation
Public title (Polish)	+
Public title (Greek)	+

Some countries needs to translate all CTIS Data Fields; this is N/A for ITA

Protocol code

GO41767

Secondary identifying numbers

WHO universal trial number (UTN)	ClinicalTrials.gov identifier (NCT number)	ISRCTN number
UXXXX-XXXX-XXXX	NCTXXXXXXXX	ISRCTNXXXXXXXX

Additional registries

Registry name	Registry identifier

If your trial is a Low Interventional Trial, tick this and upload the Justification Document

MSCs
Part I *
Part II *
Evaluation
Timetable

Trial information

Trial category

☐ Low intervention trial

Attachment of justification of low interventional clinical trial

No document available

Trial phase*

Therapeutic confirmatory (Phase III)

Medical condition *

Medical condition (English)	Medical condition (Languages)	Is the medical condition considered to be a rare disease
Small cell lung cancer (SCLC)	Greek · Polish ·	No

Therapeutic area

Diseases [C] - Neoplasms [C04]

Medical condition MedDRA information

Version	Level	Classification code	Term name	System organ class
21.1	PT	10041068	Small cell lung cancer extensive stage	100000004864
21.1	PT	10041067	Small cell lung cancer	100000004864

Main objective

Trial scope *

[redacted]

Other scope description *

[redacted]

Main objective (English) *

[redacted]

Main objective Languages	Translation
Main objective (Greek)	+
Main objective (Polish)	+

Secondary objective

New ID	Secondary objective (English)	Secondary objective (Languages)
1	[redacted]	Greek · Polish ·
2	[redacted]	Greek · Polish ·

Eligibility criteria

Principal inclusion criteria *

New ID	Principal inclusion criteria (English)	Principal inclusion criteria (Languages)
1	[redacted]	Greek · Polish ·
2	[redacted]	Greek · Polish ·

Add the 5-6 most important & critical I/E criteria

Principal exclusion criteria *

New ID	Principal exclusion criteria (English)	Principal exclusion criteria (Languages)
1	[redacted]	Greek · Polish ·
2	[redacted]	Greek · Polish ·

End points

Primary end points*

New ID	Primary end points (English)	Primary end points (Languages)
1	[redacted]	Croatian · Slovak ·

Secondary end points

New ID	Secondary end points (English)	Secondary end points (Languages)
1	[redacted]	Croatian · Slovak ·
2	[redacted]	Croatian · Slovak ·
3	[redacted]	Croatian · Slovak ·

Trial duration *

Estimated recruitment start date in EEA	Estimated end of trial date in EEA	Estimated global end date of the trial
04/02/2022	28/12/2026	30/12/2026

Source of monetary support or material support

Organisation name
F. Hoffmann-La Roche AG

I
ion
ble

Individual Participant Data (IPD) Sharing Statement

Plan to share IPD*

Undecided

Plan description

N/A

This is a new field, which is in CTIS since May 2024, and is a Mandatory field = PLAN TO SHARE IDP (individual participant data).
Users need to select a response from a drop-down list of pre-defined values (Yes/No/Undefined), to meet the requirements of the International Committee of Medical Journals Editors.
The second field, 'Plan description', is optional. It allows users to describe the plan in detail, in free text, using up to 1000 characters (how Individual Participant Data and other supporting materials will be made available to other researchers).

Population of trial subjects

Age range *

18-64 years

Age range secondary identifier

Are subjects male?

Are subjects female?

Clinical trial group *

Patients

Vulnerable population

Recruitment population group *

Women of child bearing potential using contraception

Part II
Evaluation
Timetable

Trial information

Protocol information

Clinical trial protocol

Protocol *

d1_protocol-[redacted]-redacted

English · Protocol (for publication) · **System version 1.00**
Submission date 08/08/2024
· **Version 7** · 11/12/2023

d1_protocol-[redacted]

English · Protocol (not for publication) · **System version 1.00**
Submission date 08/08/2024
· **Version 7** · 11/12/2023

d1_protocol[redacted]-redacted gr

Greek · Protocol (for publication) · **System version 1.00**
Submission date 08/08/2024
· **Version 7** · 11/12/2023

d1_protocol-[redacted]gr

Greek · Protocol (not for publication) · **System version 1.00**
Submission date 08/08/2024
· **Version 7** · 11/12/2023

D4_Patient facing documents_EQ-5D-5L_SE-SE.pdf

Swedish (Sweden) · Protocol (for publication) · **System version 1.00**
Submission date 09/05/2024
· **Version 1.2** · 01/01/2009

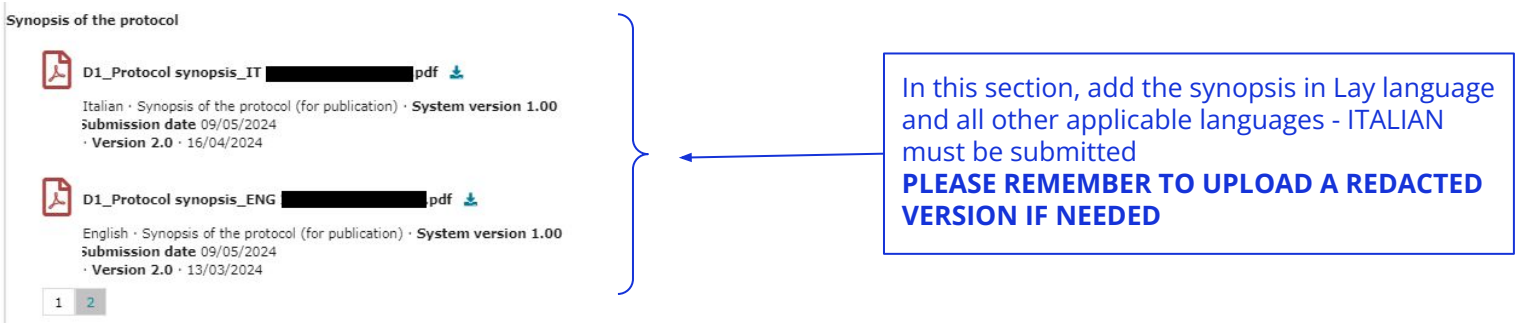
D4_Patient facing documents_EQ-5D-5L_EN.pdf

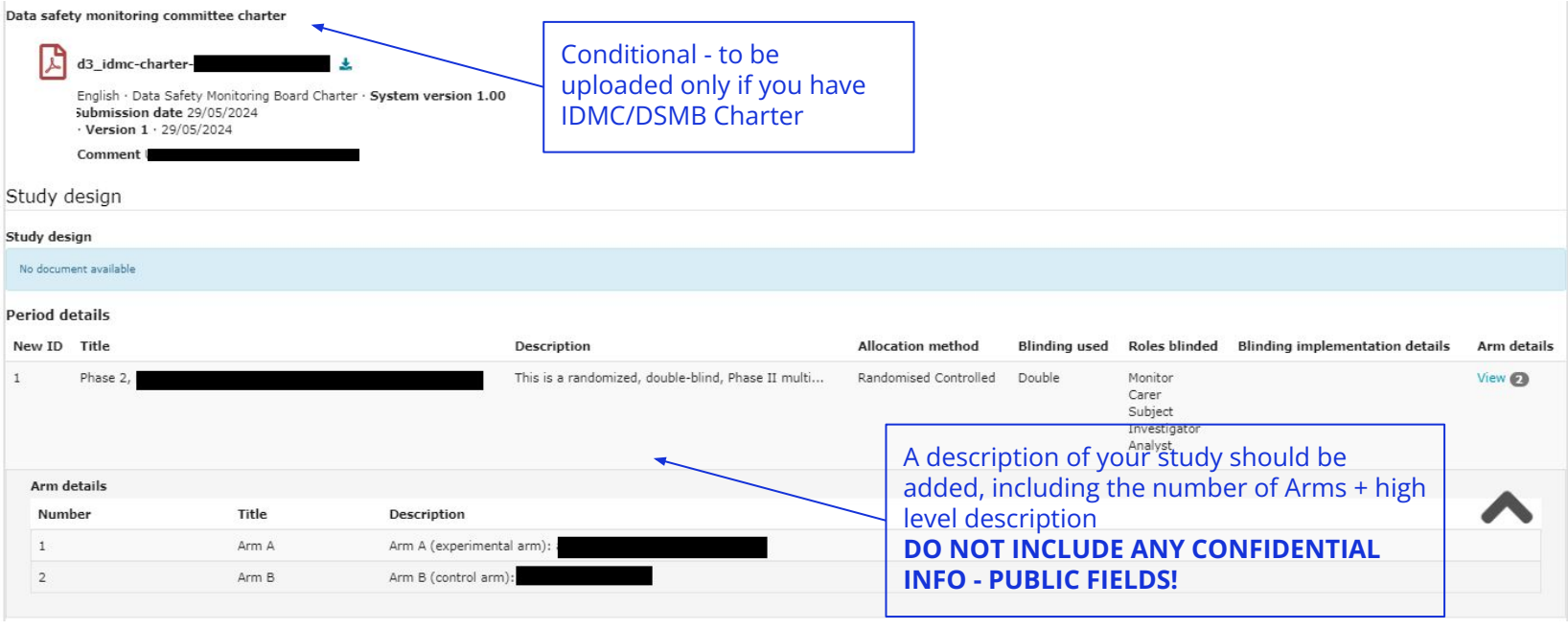
English · Protocol (for publication) · **System version 1.00**
Submission date 09/05/2024
· **Version 1.2** · 01/01/2009

REMEMBER: Upload the redacted version first, and then the non redacted under the redacted version, as "Not for publication" by using the **+** icon, to avoid CCI and PPD to become publicly available.

NOTE: in case you have a multi-country trial with Greece, remember they must submit the translated protocol

In this section upload the Patient Facing material relevant to primary/secondary endpoints and provided to patients **after** ICF signature - in ENG (if not already present in the protocol) + all applicable languages according to the Q&A doc (currently v6.9 - HERE). THIS IS APPLICABLE FOR ITA.
PLEASE REMEMBER TO UPLOAD A REDACTED VERSION IF NEEDED


Synopsis of the protocol
D1_Protocol synopsis_IT [redacted] pdf
Italian · Synopsis of the protocol (for publication) · System version 1.00
Submission date 09/05/2024
· Version 2.0 · 16/04/2024
D1_Protocol synopsis_ENG [redacted] pdf
English · Synopsis of the protocol (for publication) · System version 1.00
Submission date 09/05/2024
· Version 2.0 · 13/03/2024
1 2
In this section, add the synopsis in Lay language and all other applicable languages - ITALIAN must be submitted
PLEASE REMEMBER TO UPLOAD A REDACTED VERSION IF NEEDED


Data safety monitoring committee charter
d3_idmc-charter-[redacted]
English · Data Safety Monitoring Board Charter · System version 1.00
Submission date 29/05/2024
· Version 1 · 29/05/2024
Comment [redacted]
Conditional - to be uploaded only if you have IDMC/DSMB Charter
Study design
Study design
No document available
Period details
New ID
Title
Description
Allocation method
Blinding used
Roles blinded
Blinding implementation details
Arm details
1
Phase 2, [redacted]
This is a randomized, double-blind, Phase II multi...
Randomised Controlled
Double
Monitor
Carer
Subject
Investigator
Analyst
View 2
Arm details
Number
Title
Description
1
Arm A
Arm A (experimental arm): [redacted]
2
Arm B
Arm B (control arm): [redacted]
A description of your study should be added, including the number of Arms + high level description
DO NOT INCLUDE ANY CONFIDENTIAL INFO - PUBLIC FIELDS!

Part I *

Part II *

Evaluation Timetable

Scientific advice and Paediatric Investigation Plan (PIP)

Scientific advice

Paediatric investigation plan

Associated clinical trials

References

Online references

Optional/Conditional fields

Countries outside the European Economic Area

Argentina

Australia

Brazil

Canada

Korea, Republic of

Mexico

Taiwan

United Kingdom

United States

This is automatically completed after you complete the MSC Page in CTIS

Rest of the world subjects*

173

Countries outside the European Economic Area

Sponsors

Name	Organisation type	Country	Type	Status	Legal representative	Scientific contact point	Public contact point	Third parties
F. Hoffmann-La Roche AG	Pharmaceutical company	Switzerland	Commercial	Active	[redacted]	[redacted]	Trial Information System - TISL	8

Contact point for union*

Organisation name
F. Hoffmann-La Roche AG

Address
Grenzacherstrasse 124

Address line 1*
Grenzacherstrasse 124

Address line 2

Address line 3

Address line 4

Town/City*
Basel Town, Switzerland

Post code
CH-4058

Country*
Germany

Functional contact point name
Clinical Trial Accountable

Contact

First name * [redacted]

Last name * [redacted]

Phone * [redacted]

Email * [redacted]

By clicking on this line, extra sub-sections will appear:

- Legal representative (needed **only** if the sponsor is outside of the EEA)
- Scientific/public contact point (mandatory) & Contact point for Union (mandatory)
- Third parties

PART I / CTIS DATA & DOCUMENTS, vendor example

Remember to not use personal info (names, emails..) as these fields will be publicly available

Third parties

ID	Name	Country	Address	Town/City	Post code	Phone	Email	Duties
444470	Labcorp Central Laboratory Services SARL	Switzerland	Rue Moise-Marcinhes 7	Meyrin	1217	+4118882682623	ctasubmissions@labcorp.com	Other - General Laboratory
444467	IQVIA Limited	United Kingdom	3 Forbury Place, 23 Forbury Road	Reading	RG1 3JH	+441184506016	eu_clinical_trials_information@iqvia.com	Other - Global CRO
444462	Almac Clinical Technologies LLC	United States	25 Fretz Road	Souderton	18964-2610	+12156608500	info@almacgroup.com	Other - Randomization
444473	Parexel International (IRL) Limited	Ireland	70 Sir John Rogerson's Quay	Dublin 2	D02 R296	+35314739500	info@parexel.com	Data management
444464	CellCarta	Belgium	Sint-Bavostraat 78	Antwerp	2610	+3235020500	info@cellcarta.com	Other - Speciality Laboratory
444472	Labcorp Early Development Laboratories Inc.	United States	3301 Kinsman Boulevard	Madison	53704-2523	+16082105493	madison.SA@covance.com	Other - Speciality Laboratory
444469	Labcorp Central Laboratory Services LP	United States	8211 Scicor Drive	Indianapolis	46214-2942	+13172711200	ctasubmissions@labcorp.com	Other - General Laboratory
444466	Cellcarta Naperville LLC	United States	1841 Centre Point Circle Suite 100	Naperville	60563-4973	+16304736655	info@cellcarta.com	Other - Speciality Laboratory

PART I / CTIS DATA & DOCUMENTS, IMP Section

IMPs must be added one by one, by using the ADD button and selecting the correct option:

- **TEST** IMP
- **COMPARATOR** IMP
- **PLACEBO**
- **AUXILIARY** IMP = Auxiliary Medicinal Product (AxMP) used within the marketing authorisation only need to be listed in the Cover Letter and not in CTIS. All other AxMPs (unauthorized or authorized but modified AxMP) must be listed in CTIS as well.

Role: Test **Name: Tecentriq 1 200 mg concentrate for solution for infusion**

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	Type	Excluded MSC
PRD5434943	EU/1/17/1220/001	Authorised	Tecentriq 1 200 mg concentrate for solution for infusion	Solution for infusion	Atezolizumab 1200mg / 20ml	RO5541267/F03-01	Atezolizumab	SUB178312	-	L01FF05	5	-	-	Product	

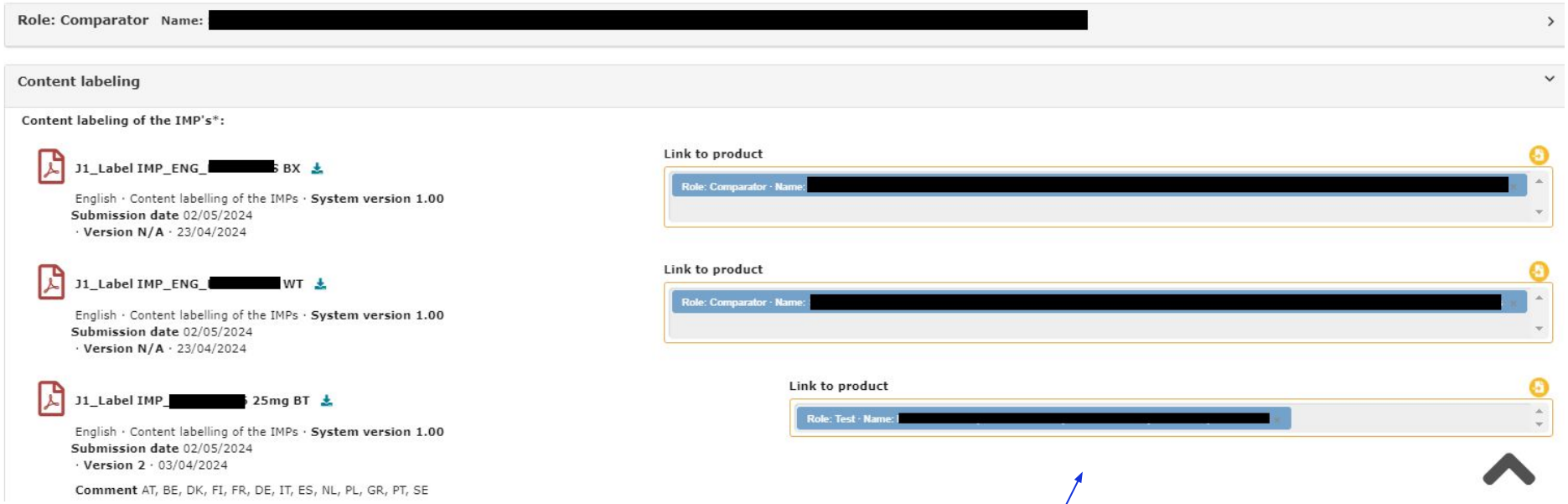
Details for Product with EU MP number: PRD5434943

- **Medicinal product details** — Automatically populated
- **Product characteristics** — To be completed manually
- **Dosage and administration details** — To be completed manually
- **Information about the modification of the Medicinal Product** — To be completed manually (this will appear for authorized IMPs only)
- **Product Classification** — Automatically populated
- **Product authorisation details** — Automatically populated (this will appear for authorized IMPs only)
- **Orphan Designation** — Automatically populated for authorized, to be populated manually for non authorized
- **Active substance** — Automatically populated
- **Advanced Therapy Medicinal Product** — To be completed only if needed
- **Device associated with medicinal product** — To be completed only if needed

- **Investigator brochure for the medicinal product**
- **Compliance with (GMP) for the Medicinal Product**
- **IMPD Quality**
- **IMPD - Safety and Efficacy**

To be completed will all applicable documents: s-QIMPD/full-QIMPDs, SmPC/IB, IMPD_S-E...

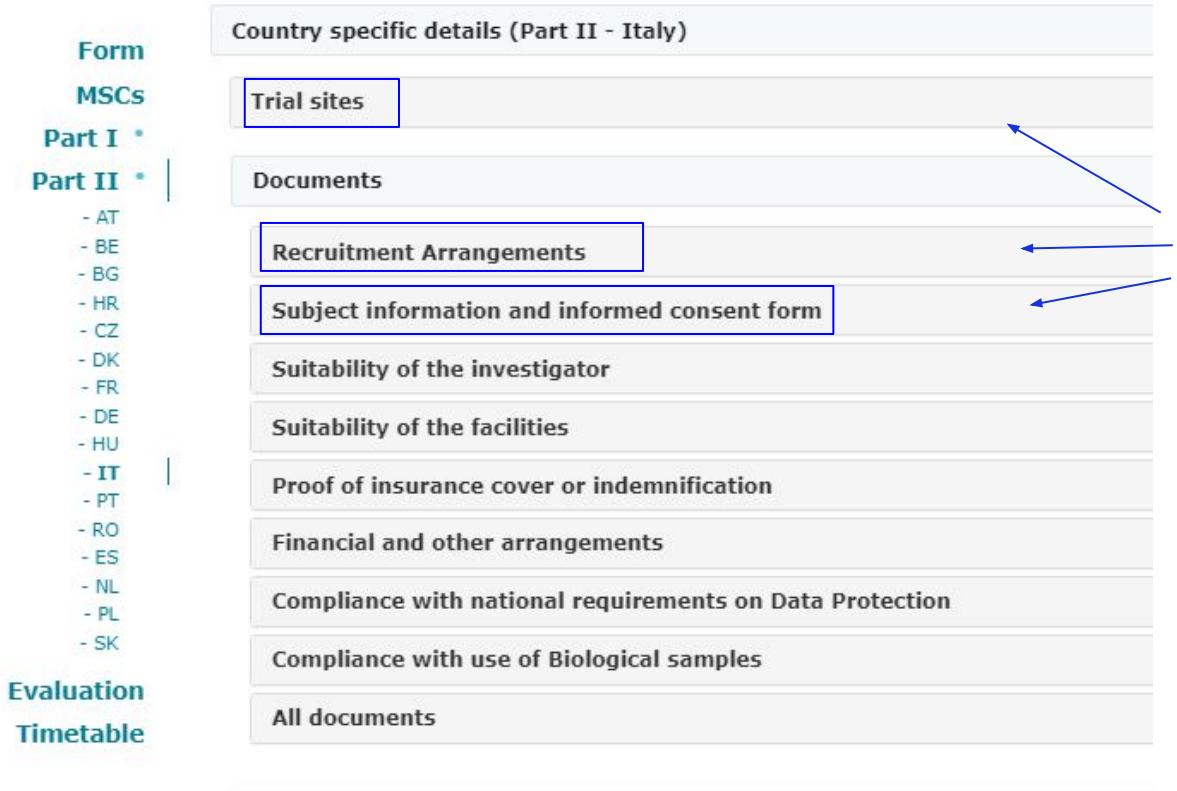
PART I / CTIS DATA & DOCUMENTS, Labels



Each label must be linked to a specific product by selecting the product from the drop down menu

Initial CTA: PART II

PART II / DOCUMENTS, overview:



Language requirements for Part 2:
Art. 26 of Regulation (EU) 536/2014 states that "The language of the application dossier, or parts thereof, shall be determined by the Member State concerned. Member States shall, when applying the first subparagraph, consider the possibility of accepting a language of common understanding in the medical field in documentation not intended for subjects", therefore the presentation of Part II documents in English is acceptable, except for those intended for patients.

PUBLIC SECTIONS

Don't forget to redact **PPD** (personal data) and **CCI** (Commercially Confidential Information)

PART II / TRIAL SITES:

All sites participating to the trial:	- On Part II - the sites are uploaded from Organization Management System (OMS) / CTIS or created in CTIS - and First, Last name, department, phone and email are completed manually. - Check with your sites which phone and email address can be used, knowing that this will be made publically available

EXAMPLE FOR MULTI-SITES STUDY- CTIS VIEW:

Remember to not use personal info (names, emails..) as these fields will be publicly available

Trial sites

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
484354	Azienda Ospedaliera Universitaria Citta Della Salute E Della Scienza Di Torino	Via Cherasco 15	Via Cherasco 15	Turin	10126	Italy	Prof.	[redacted]		Oculistica	[redacted]	
484320	Fondazione Policlinico Universitario Agostino Gemelli IRCCS	Largo Francesco Vito 1	Largo Francesco Vito 1	Rome	00168	Italy	Prof.	[redacted]		Oftalmologia	[redacted]	
484350	Azienda Ospedaliera Policlinico Universitario Tor Vergata	Viale Oxford 81	Viale Oxford 81	Rome	00133	Italy	Prof.	[redacted]		UNIT Patologie Retiniche	[redacted]	

It is important to check if your site(s) is/are available in Organization Management System-OMS. There are 2 options:

1. Via OMS directly
2. Or drop-down list and search function in CTIS

<u>If your site is not available in OMS</u>, you must:

- Ask your site to register themselves in OMS - please see OMS guide
- You can create it in CTIS directly

PART II / TRIAL SITES, example - OMS view:

EXAMPLE FOR MULTI-LOCATIONS SITE
- Search in OMS directly https://spor.ema.europa.eu/omswi/#/searchOrganisations :

⏮ ◂◂ Page 1 of 2 ▸▸ ⏭ Showing 20 of 22 results

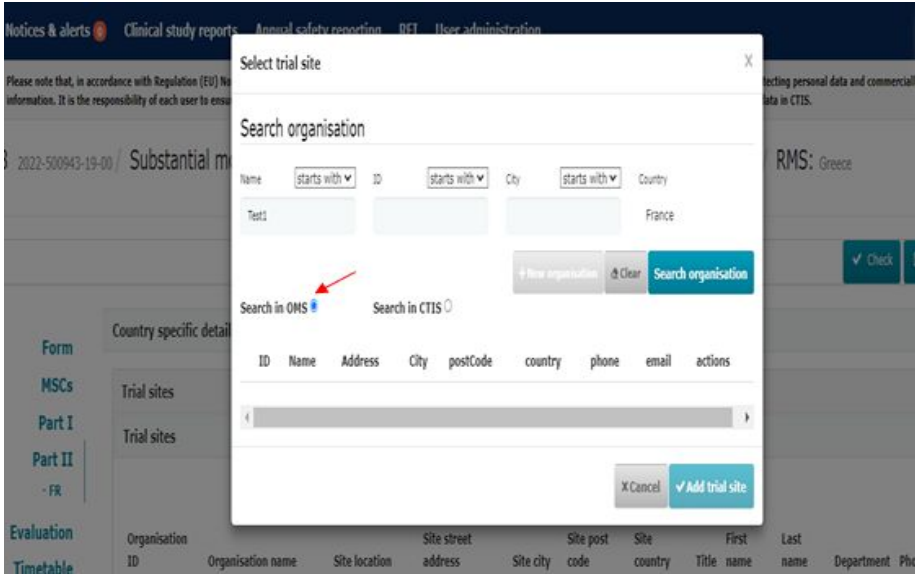
Organisation ID	Organisation Name ▲	Country	Location ID	City	Address	Postcode	Location status	Modified	Actions
ORG-100010457	Azienda Ospedaliera Universitaria Citta Della Salute E Della Scienza Di Torino	Italy	LOC-100053045	Turin	Via Gianfranco Zuretti 29	10126	ACTIVE	2023-05-05T08:25:03	+ ✎ 🔍
ORG-100010457	Azienda Ospedaliera Universitaria Citta Della Salute E Della Scienza Di Torino	Italy	LOC-100053046	Turin	Piazza Polonia 94	10126	ACTIVE	2023-05-05T08:25:02	+ ✎ 🔍
ORG-100010457	Azienda Ospedaliera Universitaria Citta Della Salute E Della Scienza Di Torino	Italy	LOC-100015993	Turin	Corso Bramante 88	10126	ACTIVE	2023-12-08T15:37:21	+ ✎ 🔍
ORG-100010457	Azienda Ospedaliera Universitaria Citta Della Salute E Della Scienza Di Torino	Italy	LOC-100074965	Turin	Via Cherasco 15	10126	ACTIVE	2023-05-16T09:36:43	+ ✎ 🔍
ORG-100010457	Azienda Ospedaliera Universitaria Citta Della Salute E Della Scienza Di Torino	Italy	LOC-100079215	Turin	Corso Spezia 60	10126	ACTIVE	2023-05-05T14:13:19	+ ✎ 🔍

A list of sites with the same ORG ID appears, and the user must choose the correct one, based on the site's address/location ID.

→ Check with the sites which is the right one.

PART II / TRIAL SITES, example - CTIS:

Step 1 – The user must first search OMS, as the “Search in OMS” radio button is ticked by default. If already searched in OMS and checked with site, user will select the right site from the list (*please note: if you already did the pre-work in OMS or if you already asked for confirmation to the site or if only 1 site appears*).



Trial sites

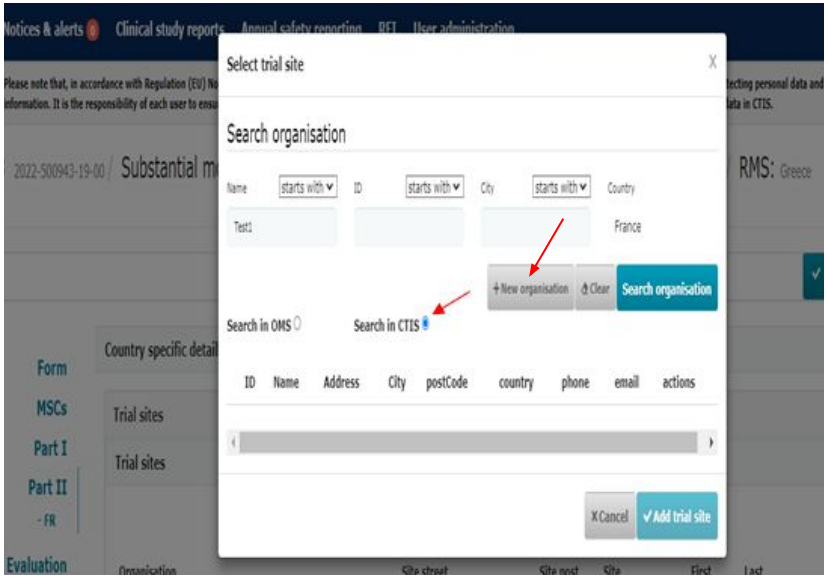
Trial sites

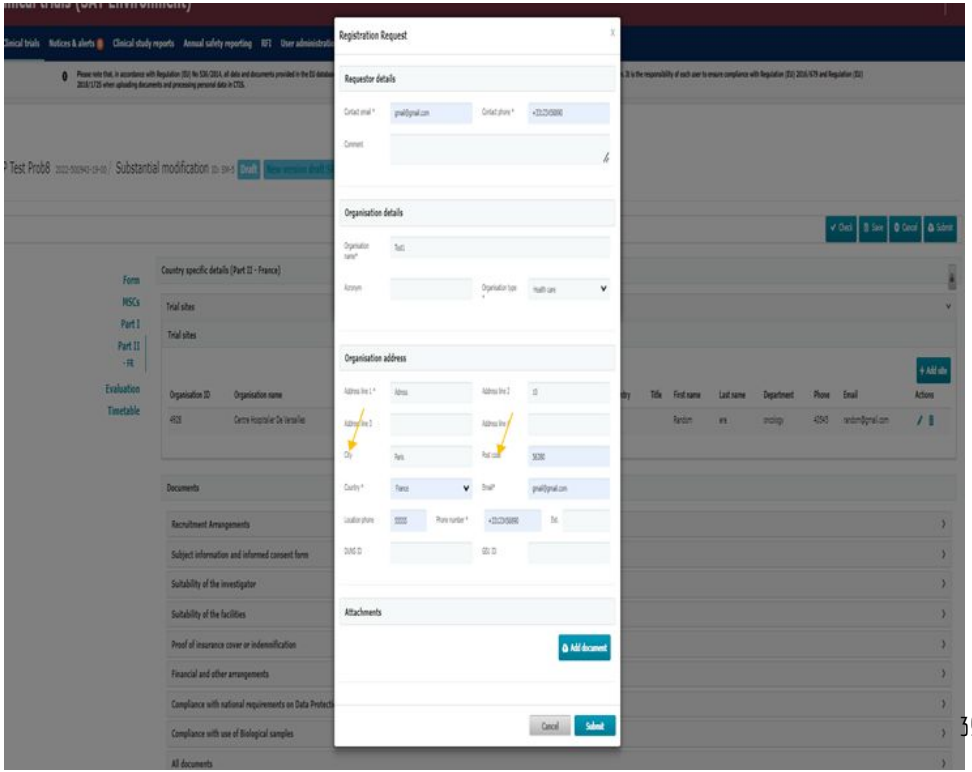
Organisation ID	Organisation name	Site location	Site street address	Site city	Site post code	Site country	Title	First name	Last name	Department	Phone	Email
484354	Azienda Ospedaliera Universitaria Citta Della Salute E Della Scienza Di Torino	Via Cherasco 15	Via Cherasco 15	Turin	10126	Italy	Prof.	[redacted]		Oculistica	[redacted]	

PART II / TRIAL SITES, example:

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”.

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

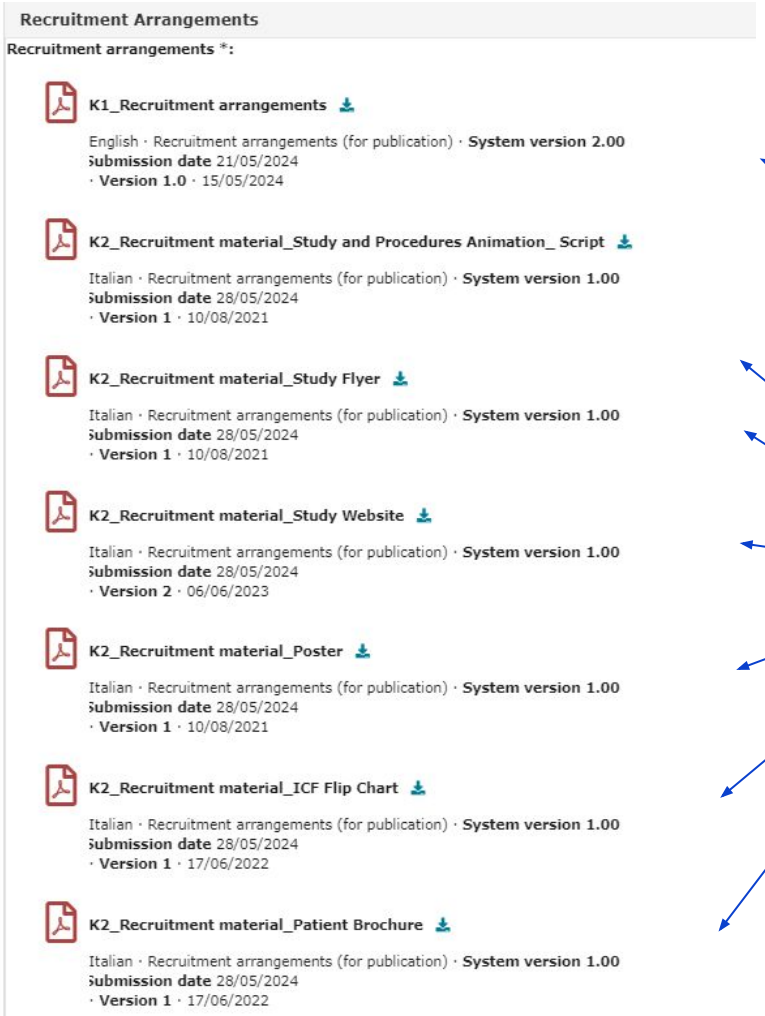




PART II / DOCUMENTS:

Recruitment arrangement	This section refers exclusively to recruitment material (copies of the advertising material, including any printed materials, and audio or visual recordings), no other documentation shall be submitted under this section (*CTR wording)* A new document is required by CTR in this section: "Recruitment and Informed consent procedure" -> EMA template This section will be public and available to the public once the study is approved. NB.: documents redaction may be needed
Subject Information	This section refers exclusively to all information given to the subjects together with the informed consent form ***before*** their decision to participate or abstain from participation in the clinical trial (*CTR wording)* No other documentation shall be submitted under this section (several ICF can be uploaded: e.g. 1 main ICF; 1 optional biopsy ICF…), knowing that only 1 country specific version of each ICF can be uploaded. This section will be public and available to the public once the study is approved. NB.: documents redaction may be needed
Suitability of Investigator	This section contains 2 parts: Investigator's CV and suitability of the Investigators. EMA templates are available For Italy (only for Principal Investigator): use EMA CV template and Declaration of Interest (DoI) template published by CCNCE
Suitability of the facilities	This document is signed by the legal representative of the site, EMA template must be used. In Italy: General director or delegate must sign the document
Proof of insurance cover or indemnification	There are no EMA CTR requirements for the insurance - except national requirements For Italy: it is required the upload of the insurance certificate as required per DM 14 July 2009
Financial and other arrangements	A brief description of the financing of the clinical trial and Information on financial transactions and compensation paid to subjects and investigator/site, any other agreement between the sponsor and the site For For Italy: Patient reimbursement and indemnity template published by CCNCE
Compliance with national requirements on data Protection	This is an optional section but there is the EMA template that can be used. For Italy, this section stays empty
Compliance with use of Biological samples	It is not mandatory document, but there is the EMA template that can be used. For In Italy it is mandatory.

PART 2 / DOCUMENTS, example:



PUBLIC SECTION

Don't forget to redact **PPD** (personal data) and **CCI** (Commercially Confidential Information)

Recruitment and Informed consent procedure

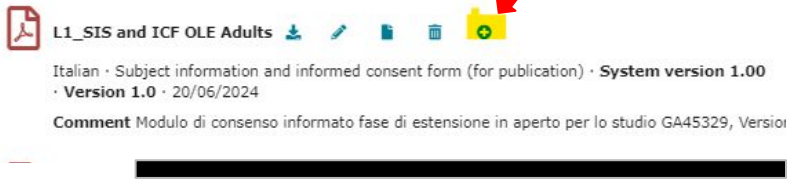
Recruitment materials

Also for Part 2, pay attention to the naming convention! This MUST be followed for all docs you are uploading in CTIS.
Also, pay attention to the version and date, as well as the language. EC will carefully assess this and might raise Validation Qs if the info is not consistent with what they have in their files

PART 2 / DOCUMENTS, example:

PUBLIC SECTION

REMEMBER: Upload the redacted version first, and then the non redacted under the redacted version, as "Not for publication", to avoid CCI and PPD to become publicly available.



Subject information and informed consent form

Subject information and informed consent form *:

L1_SIS and ICF OLE Adults

Italian · Subject information and informed consent form (for publication) · **System version 1.00**
Submission date 18/07/2024
· **Version 1.0** · 20/06/2024

Comment Modulo di consenso informato fase di estensione in aperto per lo studio GA45329, Versione 1.0, 20 giugno 2024

L1_SIS and ICF 16-17-years

Italian · Subject information and informed consent form (not for publication) · **System version 1.00**
Submission date 18/07/2024
· **Version 1.0** · 20/06/2024

Comment Assenso per lo studio GA45329, età 16-17 anni, versione 1.0, 20 giugno 2024

← Informed consent **NOT** redacted

L1_SIS and ICF 16-17-years_REDACTED

Italian · Subject information and informed consent form (for publication) · **System version 1.00**
Submission date 18/07/2024
· **Version 1.0** · 20/06/2024

Comment Assenso per lo studio GA45329, età 16-17 anni, versione 1.0, 20 giugno 2024

← Informed consent **REDACTED**

L1_SIS and ICF Main Adults_REDACTED

Italian · Subject information and informed consent form (for publication) · **System version 1.00**
Submission date 18/07/2024
· **Version 1.0** · 27/06/2024

Comment Modulo di consenso informato principale per lo studio GA45329, Versione 1.0, 27 giugno 2024

← Informed consent **REDACTED**

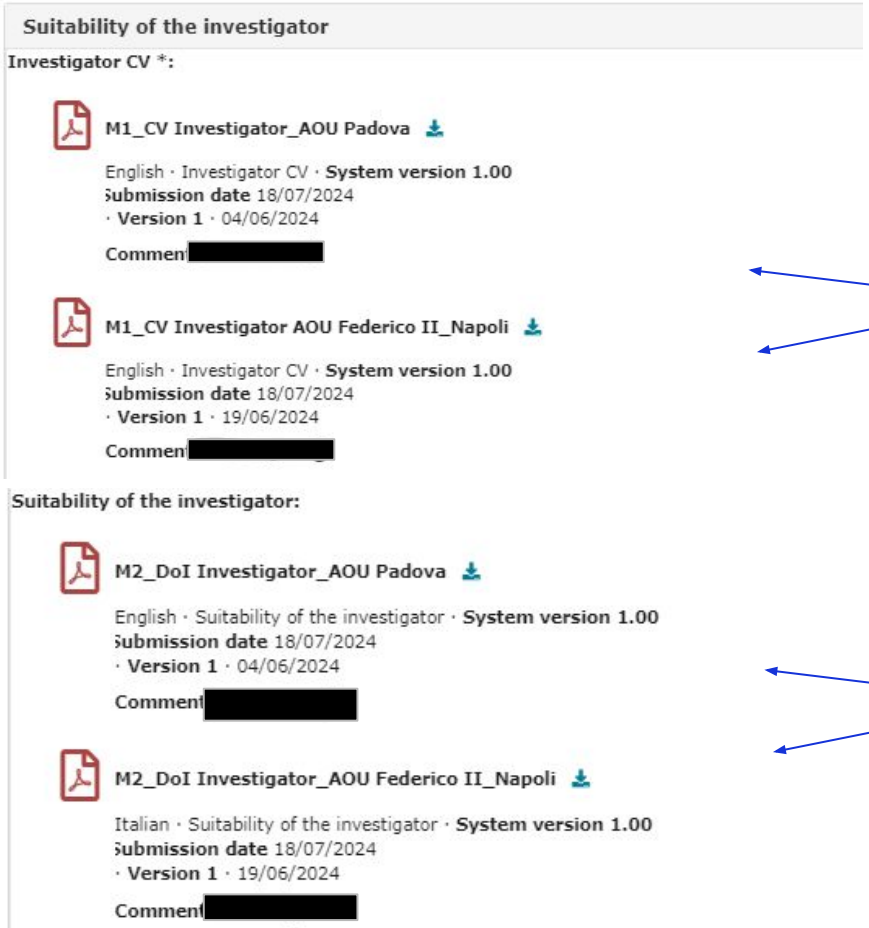
L1_SIS and ICF Main Adults

Italian · Subject information and informed consent form (not for publication) · **System version 1.00**
Submission date 18/07/2024
· **Version 1.0** · 27/06/2024

Comment Modulo di consenso informato principale per lo studio GA45329, Versione 1.0, 27 giugno 2024

← Informed consent **NOT** redacted

PART 2 / DOCUMENTS, example:

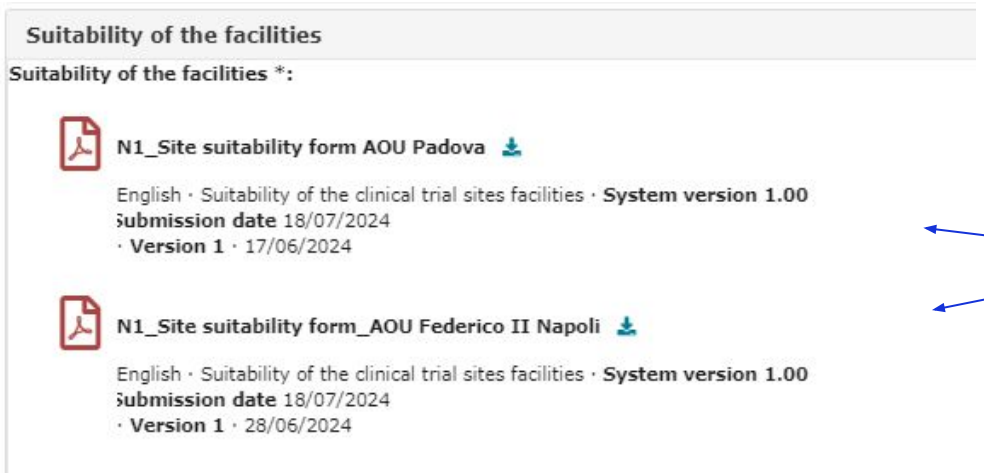


Principal Investigator's CVs

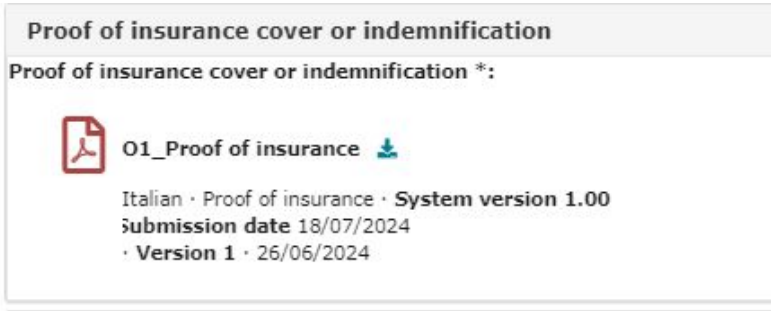
Suitability of the
Principal investigator: DoIs

Suggestion: don't use PI name in the document name, but add it in the comment, in order to avoid issue in case of PI's change!

PART 2 / DOCUMENTS, example:



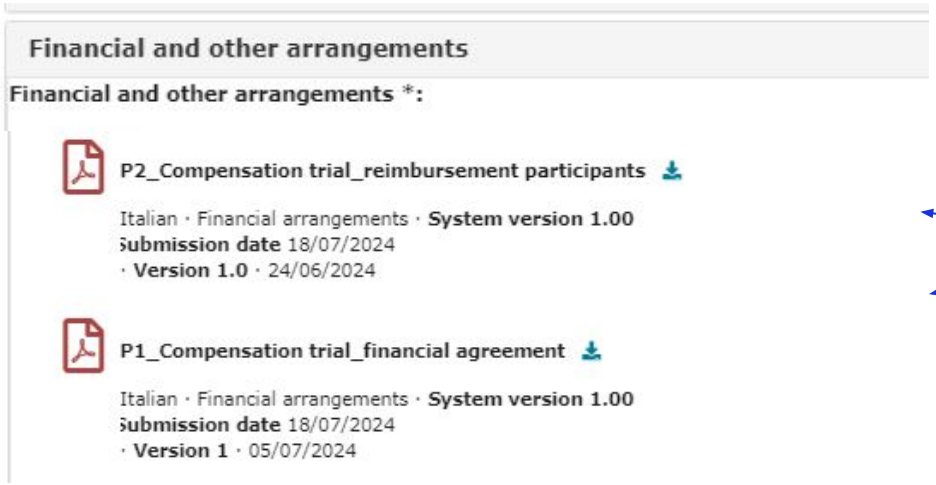
Suitability of the sites:
Site suitability form (SSF)



Certificate of insurance

Suggestion: SSF and Insurance sections are not public, so no need to redact signature.

PART 2 / DOCUMENTS, example:



- Trial compensation for participants
- Financial arrangements

Compliance with the applicable rules for the collection, storage and future use of biological samples of the subject.

Initial CTA: after submission

What happens after you submit the application?

STEP 1 = **Validation**

- During this step, HA/EC are doing an administrative check of the documents and the CTIS entries;
- 10d are the standard timelines for this step, if you do not receive Validation Questions.
- For this step, receiving questions is quite common → most of them are related to inconsistencies in the dates present in CTIS/Cover Letter/missing documents in the hands of the authorities.

STEP 2 = **Assessment**

- During this step, HA/EC are checking the content of the documents;.
- If RFIs are received, you will have a max of 12 calendar days to answer

STEP 3 = **Country decisions**

- Each participating country has to provide a final decision max 5 days from completion of step 2

What happens after you submit the application?

Application Details

EU CT number: [redacted]

Submission Date: 24/02/2022

MSCs	Validation	Assessment Part I	Assessment Part II	Decision
BELGIUM			Not acceptable (30/05/2022)	Not authorised (16/06/2022)
FRANCE			Acceptable (03/05/2022)	Authorised (17/06/2022)
GERMANY RMS	Valid (22/03/2022)	Acceptable (14/06/2022)	Acceptable (07/06/2022)	Authorised (20/06/2022)
HUNGARY			Acceptable (03/06/2022)	Authorised (17/06/2022)
ITALY			Acceptable (19/05/2022)	Authorised (17/06/2022)
PORTUGAL			Lapsed (18/05/2022)	--
SPAIN			Acceptable (30/05/2022)	Authorised (20/06/2022)
POLAND			Acceptable (31/05/2022)	Authorised (21/06/2022)

Tacit → NB. It can be tacit

ASSESSMENT PART I acceptable +
ASSESSMENT PART II acceptable +
Positive MS Decision\Tacit consent =
Study Authorised

What happens after your application is approved?

After authorisation of the trial in CTIS the sponsor should **notify:**

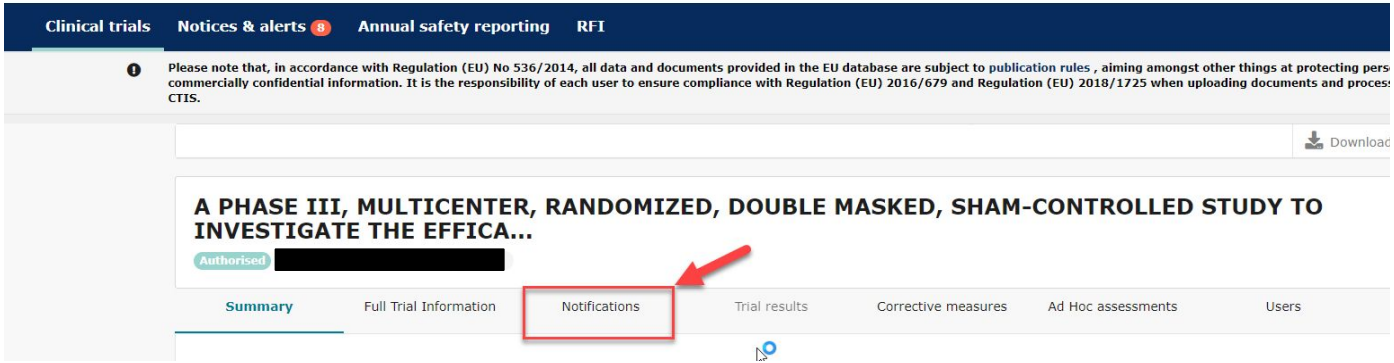
- **the day of start of the trial** = First Site activation date in that country
- **the start of enrollment** = First patient screened/ ICF signed

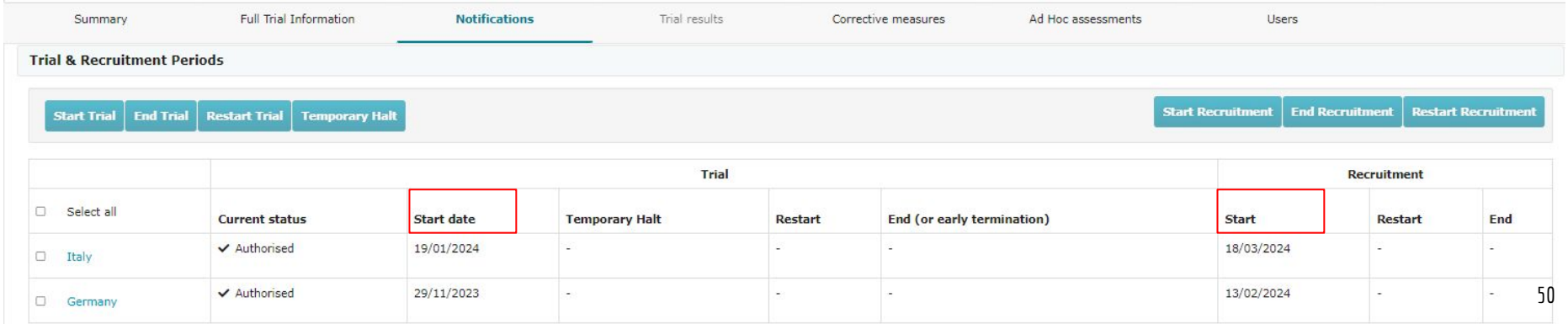
NOTE: If no patients will been screened in a country within the 2 years after the application authorisation, a prolongation of the CTR approval needs to be requested via a Substantial Modification for Part II.

NB: the approval needs to be received before the expiry of this 2 year timeframe.

What happens after your application is approved?

Clinical trials





Select all	Trial					Recruitment		
	Current status	Start date	Temporary Halt	Restart	End (or early termination)	Start	Restart	End
Italy	✔ Authorised	19/01/2024	-	-	-	18/03/2024	-	-
Germany	✔ Authorised	29/11/2023	-	-	-	13/02/2024	-	-

Questions & Answers

SWITCH CTD → CTR

Switching Ongoing Studies from CTD to CTR

Studies in scope for the switch to CTR

All ongoing CTD studies with at least one Investigational Medicinal Product (IMP) and:

- With EoT after 30 Jan 2025
- Requiring inclusion of new EEA MS after 31 Jan 2023

Ongoing clinical trials currently governed by the CTD and falling into one or both of the categories above will need to transition to the CTR regulatory framework.

→ If such clinical trials have not transitioned to the CTR by that date (30 JAN 25), they will be considered not in conformity with CTR, and Sponsors could be subject to corrective measures and penalties.

NON-INTERVENTIONAL CLINICAL TRIALS ARE NOT IN SCOPE FOR CTR

Switching Ongoing Studies from CTD to CTR

The transition of clinical trials from the CTD to CTR is an administrative process and would typically include a full Part I and Part II dossier and can take up 106 days to be approved.

BUT:

EMA has agreed to follow an expedited evaluation procedure, focusing on the validation a minimum application dossier, restricted to documents already authorised under the CTD.

The timeline for the expedited procedure is estimated to be around 22 days:

- 10 days (validation phase without RFI)
- 7 days (assessment phase without RFI)
- 5 days (decision)

NOTE: The expedited procedure remains open until **16 October 2024** only.

EMA recommends that the expedited procedure is strictly followed to ensure a simple and efficient transition.

What type of documents are required for an expedited transition?

It is recommended that the expedited procedure is strictly followed to ensure a simple and efficient transition:

- Only the minimum documents should be provided.
- Document templates do not need to be aligned with CTR (e.g. protocol). This can be done with the first modification after the CTR switch.
- Documents submitted should be the same as those already submitted and approved via the CTD. If this is not the case, you might receive validation questions, which will increase the approval timelines —> 22d approval timelines will NOT be kept.

TRANSITION PROCESS, what in scope:

Only clinical trials **authorised under the CTD** with at least one active site in the EEA on **30 January 2025** need to be transitioned.

Trials that have **ended locally in all EEA MSs**, in line with the CTD, will not need to be transitioned, even in the case where the global end of trial has not been reached yet.

TRANSITION:

SITES:

ALL sites, except the ones that have performed the last visit of the last subject (or at a later point in time as defined in the protocol), before or at the moment of transition submission

COUNTRIES:

ALL countries with at least 1 site needing transition at time of transition application based on the explanation above

PART I / FORM SECTION:

Cover Letter	Clearly stating: - Name of EC that have previously given approval under CTD to the trial (It is expected that the ethics committee which carried out the initial assessment remains responsible for the assessment) - The documentation being submitted, confirming previous review and approval A template is available on the HMA website (v4 March 2024) → you can find it in this webpage https://www.hma.eu/about-hma/working-groups/clinical-trials-coordination-group.html, under the section "GUIDANCE - Transitional Trials". This template is for multinational trials but can be modified for single-country trials.
Application data	Add EUDRACT number
Proof of Payment for the switch	N/A for Italy for Switches
Compliance with Regulation (EU) 2016/679	A template is available on the EMA website → https://health.ec.europa.eu/document/download/dcbff0c5-b4e8-479b-88a5-f308b006d126_en?filename=compliance_reg2016_679_template_en.pdf
Trial Category	You will need to select in which category your study is falling into, and justify your choice. Also refer to the EMA "Revised CTIS transparency rules and historical trials: quick guide for users"

Form
MSCs
Part I *
Part II
aluation
metable

Form details

Initial Application details

Cover letter

Cover letter *

B1_Cover Letter [redacted].pdf

English · Cover letter · **System version 1.00**
Submission date 11/04/2024
· **Version N/A** · 11/04/2024

Transition Trial

Transition Trial

EUDRA CT number * [redacted]

VHP number

Proof of payment of fee

Italy

Proof of Payment

No document available

Poland

Proof of Payment

No document available

Compliance with regulation

Compliance with Regulation (EU) 2016/679

Compliance with Regulation (EU) 2016/679 *

R1_Compliance with Regulation 2016-679

English · Compliance with Regulation (EU) 2016/679 · **System version 1.00**
Submission date 11/04/2024
· **Version NA** · 27/04/2023

Trial category

Justification of trial category

Trial category *

Category 2

Justification for trial category *

Deferral is selected because this is a confirmatory/registrational trial and the development program for the molecule is ongoing

EudraCT of the study

No Payment is needed for Italy for the switch- you can leave this blank

Same as for Initial CTA - a category must be selected

Category	Trial type
Category 1 Pharmaceutical development clinical trials	Phase I clinical trials in healthy volunteers or patients Phase 0 trial in healthy volunteers or patients Bioequivalence and bioavailability trials Similarity trials for biosimilars Equivalence trials for combination or topical products
Category 2 Therapeutic exploratory & confirmatory clinical trials	Phase I and phase II integrated clinical trials Phase II clinical trials Phase II and phase III integrated clinical trials Phase III clinical trials
Category 3 Therapeutic use clinical trials	Phase III and phase IV integrated clinical trials Phase IV clinical trial and low interventional trials

PART I / Member States Concerned (MSC) Section:

All mandatory structured application data	- Member state(s) concerned - Reporting member state proposed - Number of Patient planned in each participating EEA Countries - List of non-EEA countries, if applicable - Total number of patients in the trial

EXAMPLE FOR MULTI-COUNTRY STUDY:

Member states concerned

Member states concerned		First submissions date	Subjects
Italy	Selected	11/04/2024	3
Poland		11/04/2024	6

Countries outside the European Economic Area

Australia
Canada
Korea, Republic of
New Zealand
United States

Rest of the world subjects*

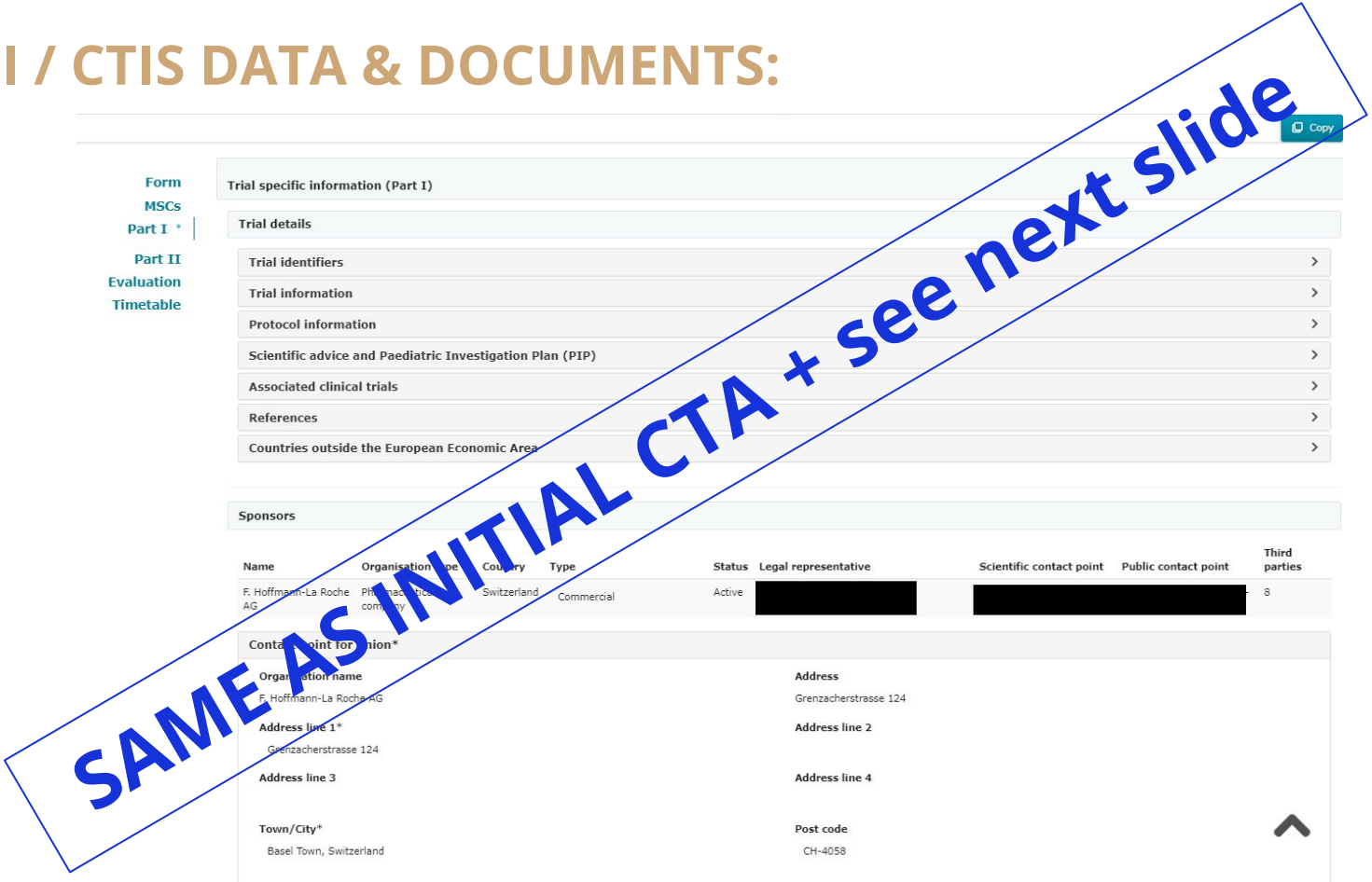
37

Estimated total population for the trial

EEA subjects
9
Rest of the world subjects*
37
Total subjects
46

SAME AS INITIAL CTA

PART I / CTIS DATA & DOCUMENTS:



SAME AS INITIAL CTA + see next slide

PART I / CTIS DATA & DOCUMENTS:

All mandatory structured application data	- 3rd Parties & Sponsor Information - EU CT Data - example: Protocol Number, Title, I/E criteria, endpoints, MedDRA term, etc.. - IMPs information
Protocol	Redacted & not redacted
Lay CTD	Not to be provided with Expedited Review (add a placeholder instead)
Patient facing material	Not to be provided with Expedited Review (add a placeholder instead)
IDMC Charter	Not to be provided with Expedited Review only if this document was not approved under CTD - In case it was, it can be provided and needs to be mentioned in the Cover letter
Scientific Advice / PIP number	Not to be provided with Expedited Review if this document was not approved under CTD - In case it was, it can be provided and needs to be mentioned in the Cover letter
IMPs & Quality Documents	- QIMPD(s) - GMP Relevant documents - Investigator's Brochure or SmPCs (for each IMP) - QIMPD(s) Safety and Efficacy (only if approved under CTD; if not - add a placeholder) - Labels - Not to be provided with Expedited Review (add a placeholder instead)

PART I / CTIS DATA & DOCUMENTS:

All other documents are NOT needed for the switch, but will need to be submitted at the first Part 1 Substantial Modification.

Examples:

- Lay CTD in ENG and local language: add a blank placeholder
- Patient Facing Material: add a blank placeholder
- QIMPD Safety and Efficacy (if NOT approved under CTD): add a blank placeholder
- Labels: add a blank placeholder

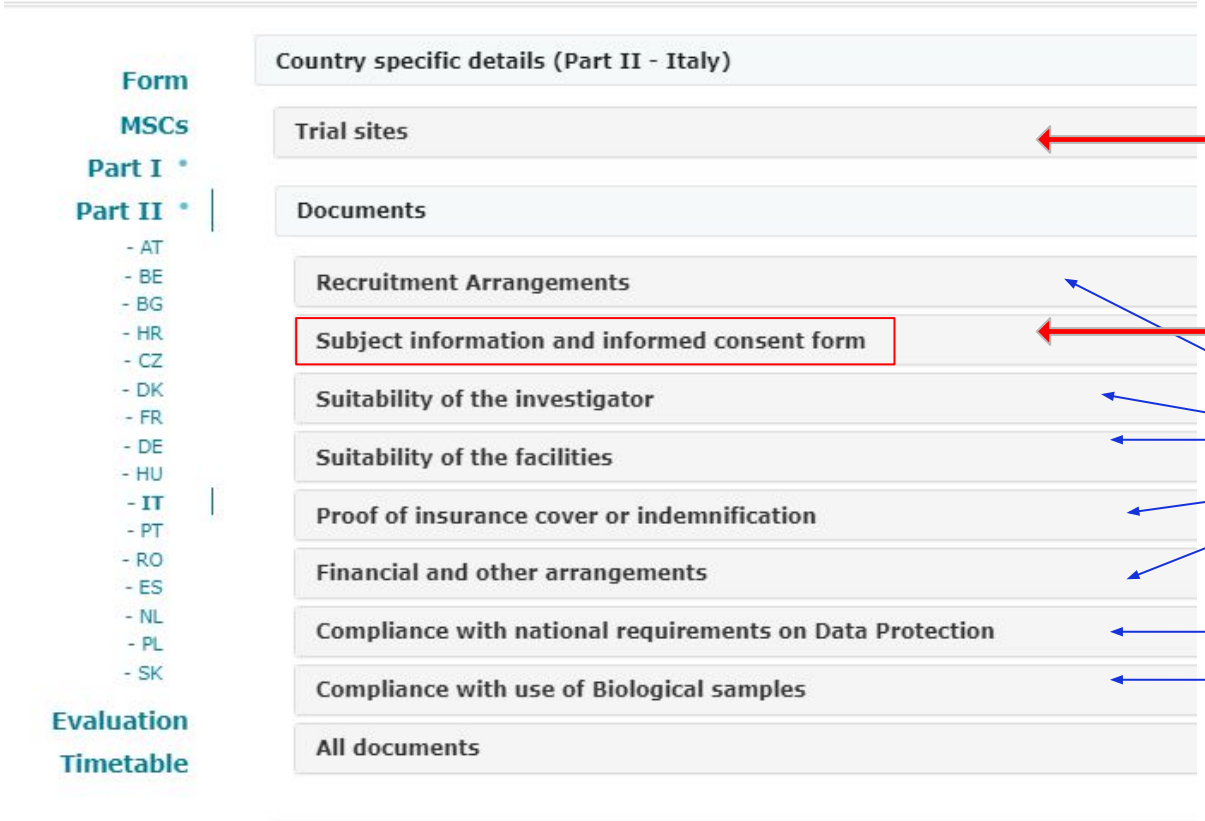
TIP:

- If your study is considered a Low Interventional Trial under CTR, you have to submit the "*Justification for a Low-Interventional Trial*" only if you have submitted a similar doc under CTD; if not, leave this section blank and update it during the first Substantial Modification.

PART II / DOCUMENTS - switch application:

Recruitment arrangement	A placeholder will be uploaded (blank doc)
Proof of insurance cover or indemnification	A placeholder will be uploaded (blank doc)
Financial and other arrangements	A placeholder will be uploaded (blank doc)
Suitability of the facilities	A placeholder will be uploaded (blank doc)
Compliance with national requirements on data Protection	For Italy, this section stays empty (this is an optional section)
Compliance with use of Biological samples	This section stays empty, as the CTR specific Biological sample handling form has not been approved under CTD (this is an optional section)
Subject Information	All latest approved versions (several ICF can be uploaded: e.g. 1 main ICF; 1 optional biopsy ICF…), knowing that only 1 country specific version of each ICF can be uploaded.
Suitability of Investigator	A placeholder will be uploaded (blank doc)

PART II / DOCUMENTS, overview:



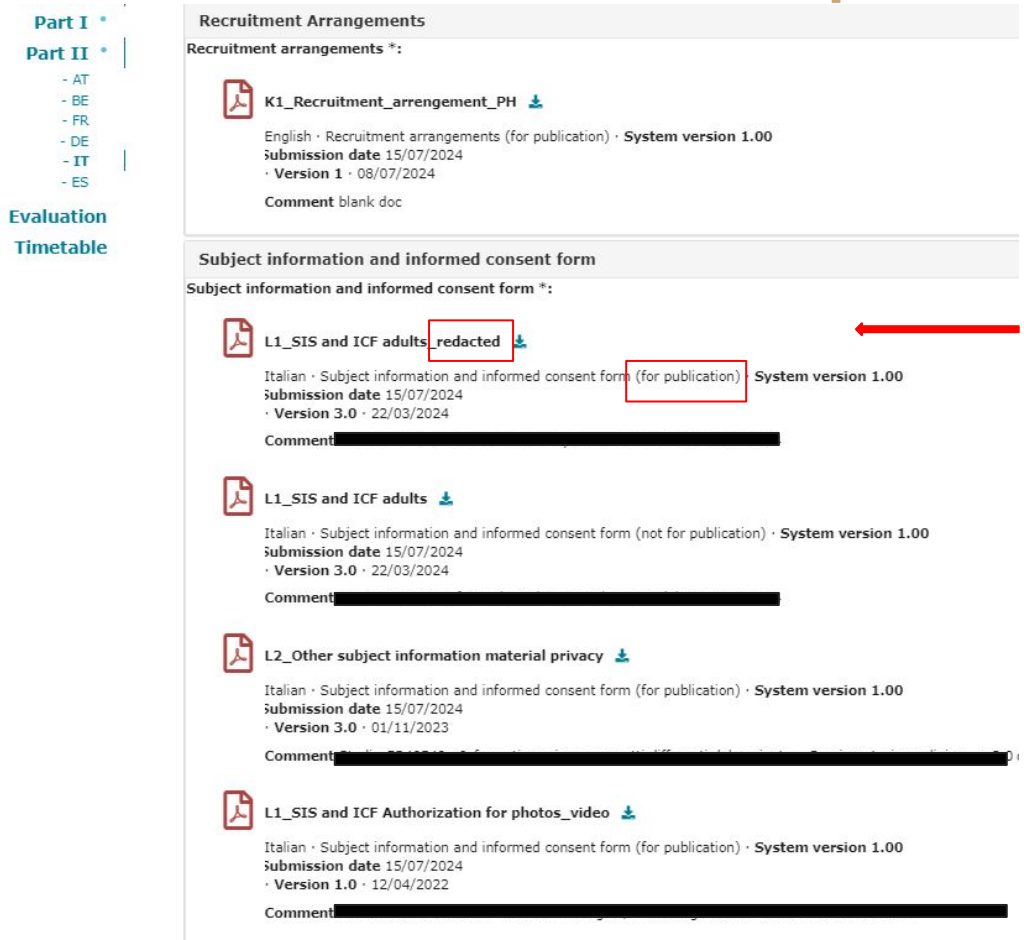
ALL sites, except the one that have performed the last visit of the last subject, (or at a later point in time as defined in the protocol); before or at the moment of transition submission

All latest approved versions under CTD by CEC

Blank document

Empty sections

PART II / DOCUMENTS, example:



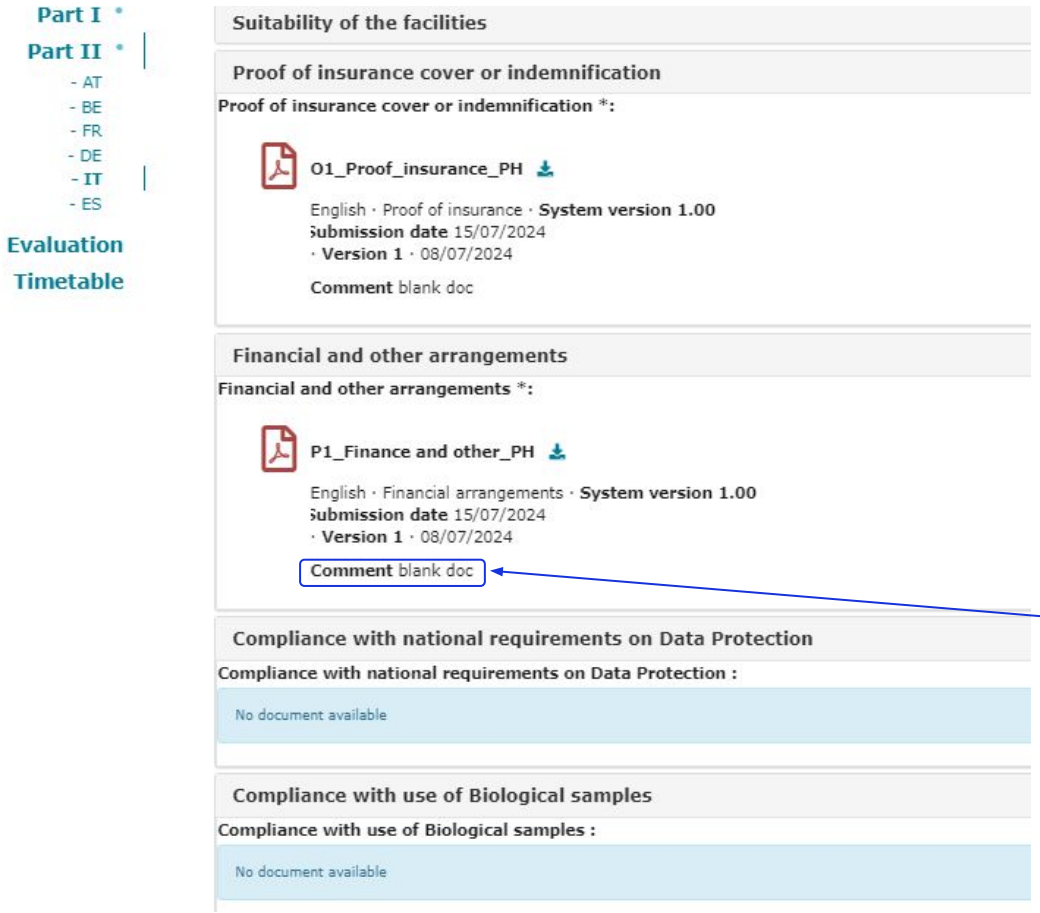
Blank document

Don't forget to redact **PPD** (personal data) and **CCI** (Commercially Confidential Information) if needed

Latest versions of approved ICFs

PART II / DOCUMENTS, example:

PART II / DOCUMENTS, example:



Blank document

You can leave a comment to let the HA/EC know that the uploaded doc is a placeholder

Empty sections

Approval of the transition submission

In General - as soon as the **1st country** has issued an authorisation (Final decision) the STUDY is governed by CTR:

→ All study specific notifications are handled in accordance to CTR.

After authorisation of the transitioned trial in CTIS

- the sponsor should notify **the day of start of the trial** (First Site activation date in the country) of that country under the Directive (CTD start date before the CTR authorisation date is technically possible in CTIS), indicating the date of start **for every MSC** in CTIS.
- The sponsor should notify the **Start of recruitment / End of recruitment for every MSC.**

NOTE: If no patients will been screened in a country within the 2 years after the switch authorisation, a prolongation of the CTR approval needs to be requested via a Substantial Modification for Part II.

NB: the approval needs to be received before the expiry of this 2 year timeframe.

1st Substantial Modification after Switch CTD-CTR

1st SUBSTANTIAL MODIFICATION after switch:

- The sponsor should bring documents related to the clinical trial in line with the CTR requirements at the first Substantial Modification (part I and/or part II).
    - IF the 1st SM ONLY applies to part I documents, a Part I ONLY SM will be created/ compiled and submitted.
    - IF the 1st SM ONLY applies to a MS, a Part II MSC SM ONLY will be created/ compiled and submitted.
    - IF the 1st SM applies to Part I and ALL Part II MSC, a SM for the whole application will be created - the SM submission (Part I and/ or Part II).
- **Placeholders, uploaded under the switch application, need to be replaced with CTR required documents,** with the **exception of the site suitability statement** which does not need to be retrospectively created.
- At the 1st SM, the ICFs must be updated with all CTR requirements (e.g. EU CT number on the title page of the ICF and a text indicating that a description of the trial will be available on the EU website) - TOGETHER with the ICF updates for the SM, if you have any.
- The protocol will also need to be updated, in order to contain all CTR required wordings - UNLESS you have closed recruitment & your patients are in F/up only (and not receiving active treatment).
- Recruitment and informed consent procedure is not required if enrollment is closed
- A new MSC can be submitted once all the Part 1 updated documentation has been approved in CTIS during this first SM.

NOTE: new transparency rules apply also to the SM-1 (if the switch application occurred before the 18th of June), so PPD and CCI need to be redacted in documents uploaded in public sections.

PART I for 1st SM / DOCUMENTS & DATA:

Cover Letter **Modification Description Letter**	To be added for each SM; in the CL, add a list of documents you are uploading in each section and specify if the doc is a NEW one, UPDATED due to the SM or UPLOADED a part of the first SM after the switch.
Proof of Payment	To be added for each SM
Compliance with Regulation & Trial Category	Should not change throughout the study
All mandatory structured application data	Update any data field if needed because of your modification
Protocol	If applicable (Redacted & not redacted)
Lay CTD	**To be added in the first SM**
Patient facing material	**To be added in the first SM**
Reference Safety Information	Investigator's Brochure or SmPCs (for each IMP) - if applicable
IDMC Charter	**If applicable and not submitted during Expedited Review, to be added in the first SM**
Scientific Advice / PIP number	**If applicable and not submitted during Expedited Review, to be added in the first SM**
IMPs & Quality Documents	- QIMPD(s) & GMP Relevant documents - if applicable - **QIMPD(s) Safety and Efficacy - to be added in the first SM (if not added in the switch)** - **Labels - to be added in the first SM**

PART II for 1st SM / DOCUMENTS:

Recruitment arrangement	Placeholder need to be replaced with CTR required documents at the first substantial modification application after the authorisation of the transition application, with the exception of the site suitability statement which does not need to be retrospectively created. NB. If recruitment is closed for the trial, the document: “Recruitment and Informed consent procedure” is not required.
Proof of insurance cover or indemnification	
Financial and other arrangements	
Suitability of the facilities	
Suitability of Investigator	
Compliance with national requirements on data Protection	Optional section - needs to be completed if needed per local regulation
Compliance with use of Biological samples	Optional section - needs to be completed if needed per local regulation
Subject Information	At the 1st Modification, post CTR switch authorisation, the EU CT number on the title page of the ICF and a text indicating that a description of the trial will be available on the EU website need to be added in the ICF (if not already there).

Modifications under CTR

Changes to an ongoing clinical trial under CTR

Please refer to EMA Q&A 6.9 - July 2024 Annex IV for further clarification.

Substantial modification (art 2.2.13) Regulation (EU) No 536/2014 Questions & Answers Draft February 2021 37	Modifications to a trial are regarded as 'substantial' when they are likely to have a significant impact on: the safety or rights of the subjects and/or the reliability and robustness of the data generated in the clinical trial.	approval required
Non-substantial change relevant to the supervision of the trial (art 81.9)	New concept under the CTR, which aims to update certain, specified information in the CTIS without the need for an SM application, when this information is necessary for oversight but does not have a substantial impact on patients safety and rights and/or data robustness. Art 81.9 changes can be submitted only if the change does not trigger additional changes, which are expected to be submitted as an SM application. The combination of different art 81.9 changes can accumulate into a change that needs to be submitted as an SM. Importantly, 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).	submission required - can be performed between 2 submissions and approval is automatically issued
Non-substantial modification	A 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.	Notification required together with a SM

Types of modification under CTR

Modifications

Substantial Modifications (SM)

Approval Required

Submission of SM not permitted during review period = Limited SMs per year

Non-Substantial Modifications

No notification is needed, the modification can immediately be implemented

The non-SM has to be submitted with the the next SM related to the relevant part + track this NSM in the Cover letter

Non-substantial change relevant to supervision of trial - (art 81.9) - CALLED NSM in CTIS!

Submission Required, can be performed between 2 submissions

An immediate approval is provided

Different post approval submission scenarios

Table 7.4.2.1. Allowed submissions whilst ongoing evaluation of a CTA.

	Submission of an SM to Part I and Part II	Submission of an SM to Part I	Submission of an SM to Part II	Submission of a non-SM	Submission of an application for additional MSC
Initial application	Not until a decision is issued by all MSCs	Not until a decision is issued by all MSCs	Not until a decision is issued by all MSCs	Not until a decision is issued by all MSCs	Not until a decision is issued by all MSCs
Evaluating Part I & Part II SM application	No	No	No	No	No
Evaluating Part I only SM application	No	No	No	No	No
Evaluating Part II only SM application	No	No	Only to MS who did not receive the Part II SM	No	yes
Evaluating add additional member state	No	No	Only to MS not evaluating the application to add an additional MSC	No	Only to MS that is not an MSC or evaluating an assessment to become an MSC

Links and references

Useful links

- Guidance for the Transition of clinical trials from the Clinical Trials Directive to the Clinical Trials Regulation
- CTCG best practice guide naming of documents, version 2.01 , 9 March 2023
- 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
- HMA website (please check under KEY DOCUMENT LIST in order to find template and useful info)
- CTIS training modules
- Revised CTIS transparency rules, historical trials and interim period: quick guide for users
- https://www.ema.europa.eu/en/documents/other/clinical-trial-information-system-ctis-sponsor-handbook_en.pdf
- EMA templates: https://health.ec.europa.eu/medicinalproducts/eudralex/eudralex-volume-10_en

Italian References

- DM 1 feb 2022 - Individuazione dei CEN (3 CE nazionali: pediatrico, per ATMPs, per studi di enti pubblici)
- DM 26 gen 2023 - Individuazione dei 40 CET (Comitati Etici Territoriali) *entra in vigore il 7 giugno 2023*
- DM 27 gen 2023 - Gestione degli studi nella fase transitoria Direttiva-CTR (studi interventistici con farmaco)
- DM 30 gen 2023 - Determinazione della tariffa unica (AIFA e CE)
- DM 30 gen 2023 - Criteri per la composizione e il funzionamento dei CET

- AIFA FAQ CTR_dic 2022
- AIFA chiarimenti DM attuativi_24 mar 2023
- Guida alla predisposizione dei documenti di cui all'art.7 paragrafo 1 del Regolamento (UE) n. 536/2014 approvata dal Centro di coordinamento CE, versione del 12 mag 2023 n°4
- AIFA FAQ CTR e transizione v1_mag 2023
- AIFA Indicazioni_Operative_CTIS_v1_mag_2023
- AIFA_FAQ integrazione a cambio CEC-CET del 07 giu e 28 giu 2023

Useful Links:

https://www.aifa.gov.it/centro-coordinamento-comitati-etici

https://www.aifa.gov.it/regolamento-europeo-sperimentazioni-cliniche

Questions & Answers

GRAZIE PER L'ATTENZIONE