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SCIENCE MEDICINES HEALTH

# EMA Role in the Implementation of new legislation: Clinical Trial Regulation

Annual PCWP/HCPWP meeting with Eligible Organisations
20 November 2019

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Head of Committees and Inspections Department

# The Clinical Trial (CT) Regulation: what is new?

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## Before May 2004

Different processes and requirements for clinical trial authorisations in each Member States…

… resulted in delays and complications detrimental to effective conduct of clinical trials in the EU.

## Directive 2001/20/EC (CT Directive)

First step to harmonise processes and requirements for clinical trial authorisations.

Implementation 1 May 2004.

Concerns expressed soon after its implementation.

## Regulation (EU) No. 536/2014 (CT Regulation)

Published on 27 May 2014.

Application 6 months after confirmation published in the OJ of full functionality of EU portal and EU database

Transitional arrangements.

# The Clinical Trial Regulation: what is new?

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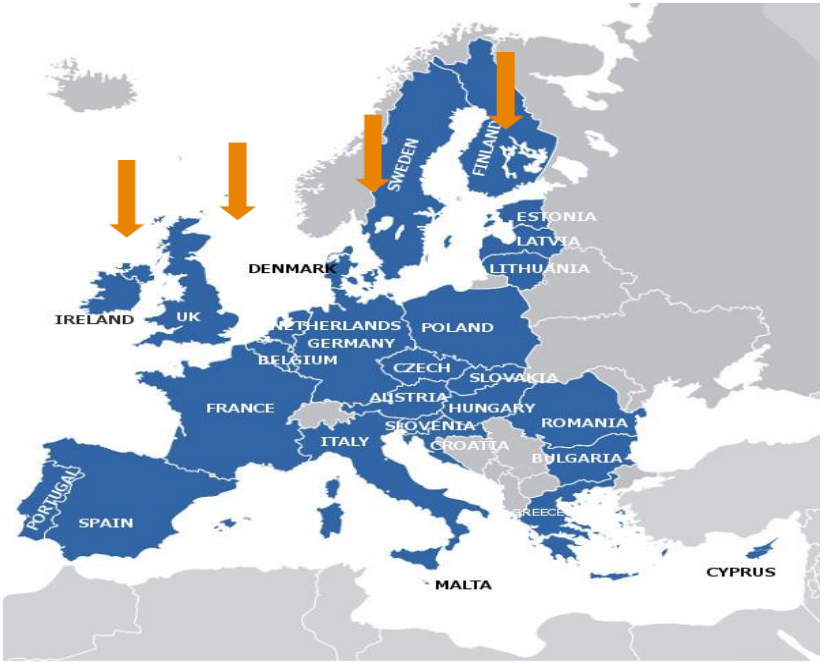
## CT Directive versus CT Regulation

### Implemented in national laws




### Directly applicable

Objectives of new CTR

- To protect the rights, safety, dignity and well-being of subjects and the reliability and robustness of the data generated in the CT;
- To foster innovation and simplify the clinical trial application process, in particular for multistate trials;
- To increase transparency, keeping the balance between protecting public health and fostering the innovation capacity of European medical research while recognising the legitimate economic interests of the sponsors.
- **Overall objective: Make EU attractive for R&D.**

# Scope of Regulation (EU) No. 536/2014

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- **Scope:**
  - **Interventional clinical trials with medicinal products for human use**
  - **NEW** category of low-intervention clinical trials with adapted requirements.
    - The investigational medicinal products (IMP) are authorised and used according to the terms of MA;
    - If the IMP is not used in accordance with the terms of the MA, that use is supported by published scientific evidence on S&E;
    - Minimal additional risk or burden to the safety of the subjects compared to normal clinical practice.

- **Not covered:**
  - Non-interventional trials;
  - Trials without medicinal products (e.g. devices, surgery, etc).

# Key changes introduced by the CT Regulation

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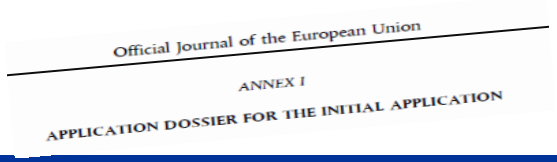
- **Single e-submission to all MSCs** via an EU portal (accessible to MS NCAs and Ethics Committees);
- **Harmonised dossier** (Annex I to the Regulation);
- **Coordinated assessment** between Reporting MS and MS Concerned;
- One **single decision** per Member State Concerned;
- **Tacit decision** for the MS single decision
- Introducing a **risk adapted approach** by applying less stringent rules to those trials conducted with medicines which are already authorised and which pose *only minimal risk compared to normal clinical practice;*


Official Journal of the European Union

ANNEX I

APPLICATION DOSSIER FOR THE INITIAL APPLICATION

# Key changes introduced by the CT Regulation

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- **Reinforcing supervision of clinical trials** by introducing Union Controls in Member States to ensure that the Regulation is properly supervised and enforced;
- Provisions concerning **clinical trials conducted outside the EU** but referred to in a clinical trial application within the EU, which will have to comply with regulatory **requirements** that are at least **equivalent to those applicable in the EU.**
- New provisions for **Informed Consent**
- **Increasing transparency** as regards clinical trials and their outcomes;

# Summary of key changes from CT Directive to CT Regulation

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| As-is (Directive 2001/20) – EudraCT | To be (CT Regulation) - The EU portal and database |
|---|---|
| • **Multiple submissions for one trial** (1 submission per each MSC*) /**no harmonized dossier** (e-submission limited to structured data and paper based submission) | • **Single e-submission to all MSCs/harmonized dossier** for one trial & e-submission of structured data and documents by MSCs |
| • Double submission within a Member State Concerned (MSC): **to National Competent Authorities (NCAs) and to Ethics Committees** | |
| • **Individual assessment by each MSC** with no IT collaboration tool available | • **Joint assessment** for Part I facilitated by collaboration tools |
| • **No single MSC decision (NCA & ECs)** | • **Single MSC decision** |
| • Burden to NCAs in uploading information in the system | • Distribution of the burden among users |
| • **Limited EudraCT data availability** to the public : structured data from the application (CTA) and summary of results | • **View all CT related information** |
| • MSC* = member state concerned | |

# EMA role: The EU portal and database

# Regulation (EU) No. 536/2014 - Art 80 EU Portal

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*"The Agency shall, in collaboration with the Member States and the Commission, set up and maintain a **portal at Union level** as a **single entry point for the submission of data and information relating to clinical trials** in accordance with this Regulation. The EU (European Union) Portal shall be **technically advanced** and **user friendly** so as to avoid unnecessary work. Data and information submitted through the EU portal shall be stored in the EU Database."*

# Regulation (EU) No. 536/2014 - Art 81 EU Database

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*"The Agency shall, in collaboration with the Member States and the Commission, **set up and maintain a EU database** at Union level. The Agency shall be considered to be the controller of the EU database and shall be responsible for avoiding unnecessary duplication between the EU database and the EudraCT and Eudravigilance databases."*

# Implementation of the CT Regulation: EMA role

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**CTIS SYSTEM**

**EU PORTAL AND DATABASE**

(Art. 80 to 84)

- **Single EU entry point** for clinical trial applications (**e-dossier**)
- Provides **workspace** with **collaboration** tools and capabilities for **coordinated assessment** between Member State Concerned
- One single decision per Member State Concerned
- Enables **supervision at EU level**, including inspections
- Provides **publicly available** information

**SAFETY REPORTING**

(Art. 40 to 44)

- **Upgrade of EudraVigilance** clinical trial module for the electronic **reporting of SUSARs**
- Delivers an Annual safety reports (ASRs) repository

**EUDRACT LEGACY**

(Art. 98)

- Delivers transition between the current and new systems

# Collaborative working

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## The EMA is working collaboratively

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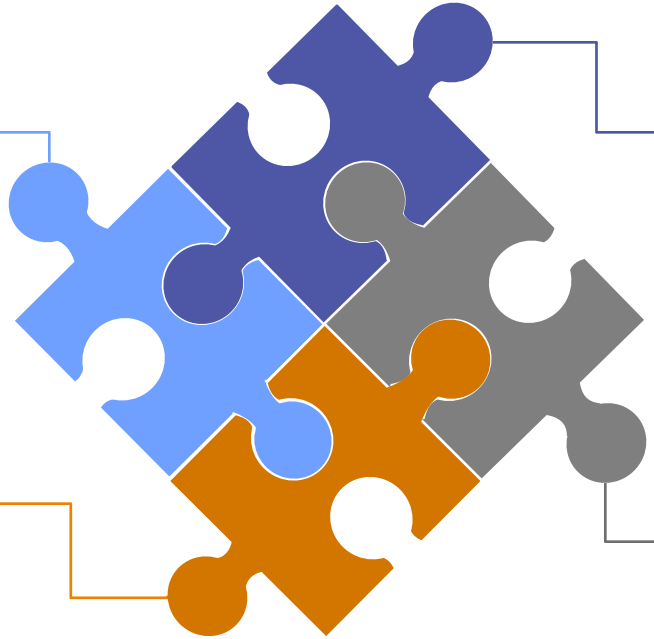
**EUROPEAN MEDICINES AGENCY**

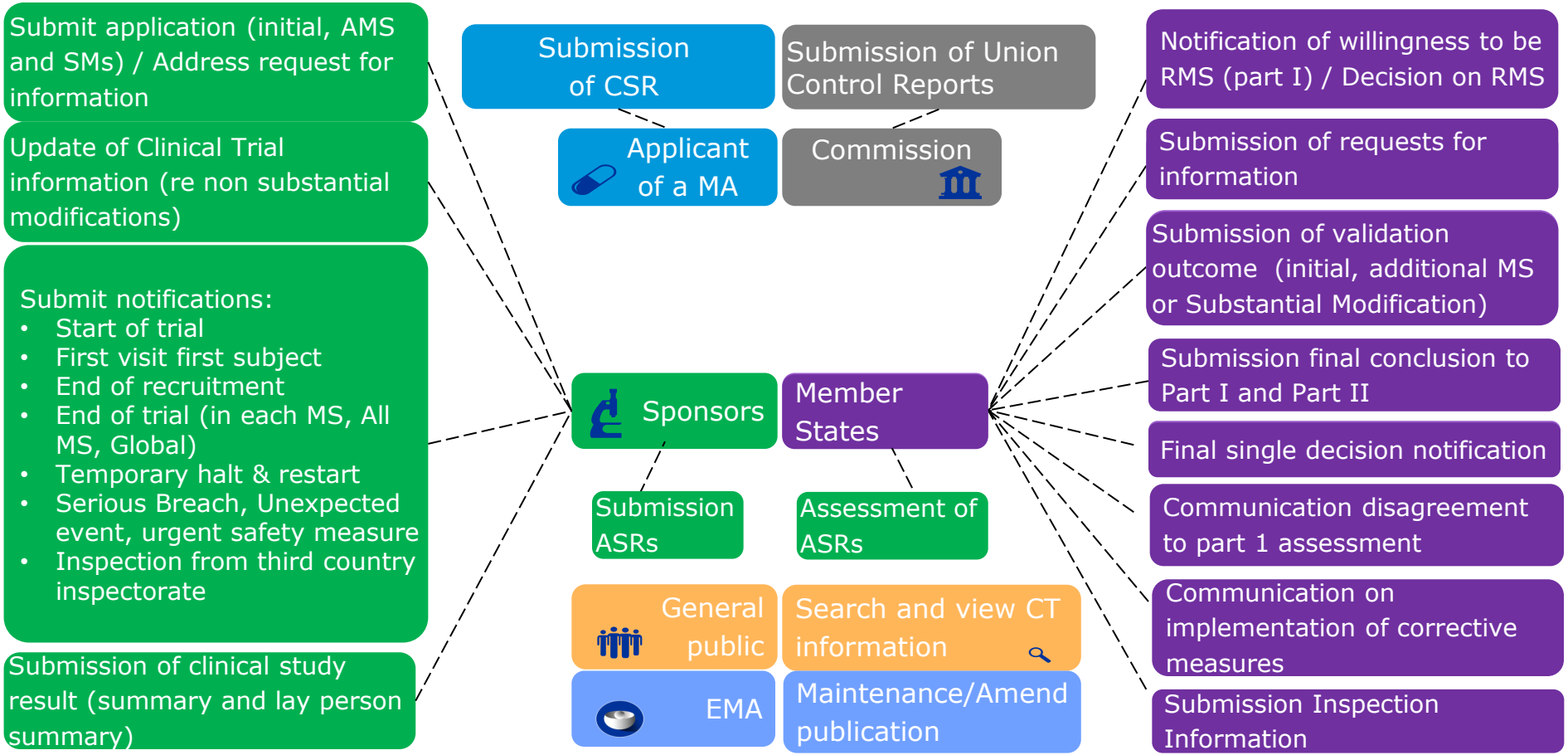


**MEMBER STATES & ETHICS COMMITEES**

**STAKEHOLDERS**
- Sponsors
- CROs
- HCPs
- Patient Representatives

## systems developed to implement the regulation

# CTIS- Actors and activities in the CTIS system



# EU portal and database – high level system overview

## Public website

### Entry site

- Display news, announcements and scheduled downtimes
- View publicly available statistics on clinical trials registered in the EU Database
- Access in all official languages of the European Union

### Public search

- Search for keywords and filter results
- Find public clinical trials via the same portal as pro active publications, medicinal products and articles

### Public clinical trial data

- Access detailed clinical trial information
- Download trial information and documents
- View and download predefined reports

# CT Regulation and Transparency

# Objectives of the public disclosure of clinical trial information



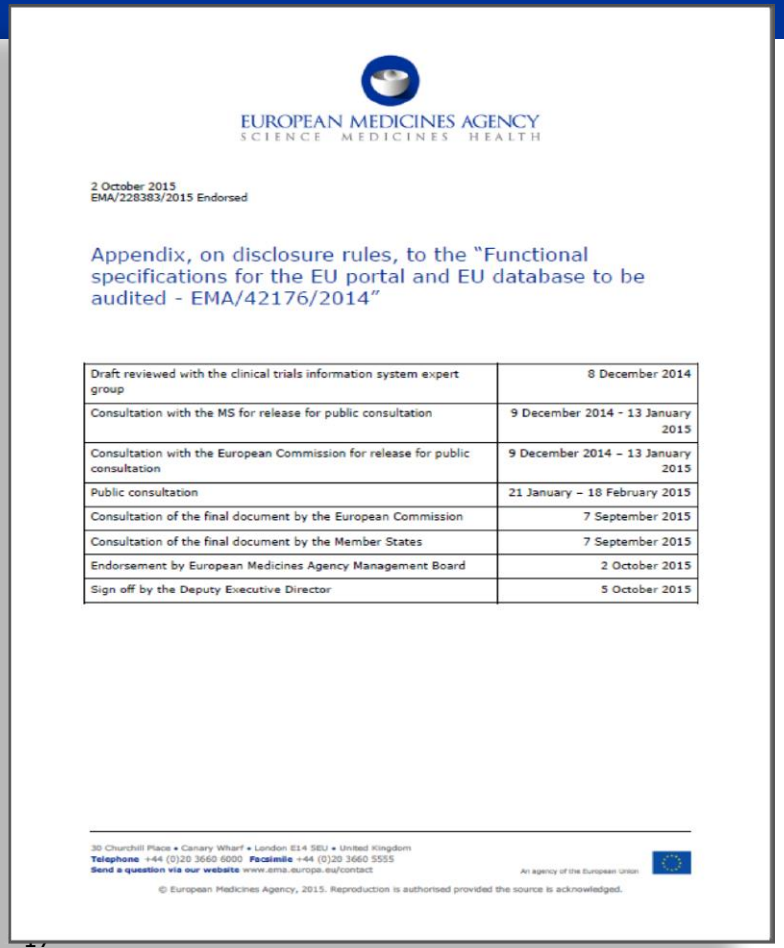
- Have all clinical trials been publicly registered?
- Is there a trial in which I could participate?
- What was the outcome of the trial I did participate in?
- What trials were the basis of the marketing authorisation, what were their results?
- What is known about the medicine I am taking/prescribing?
- Can we review the data used to support the marketing authorisation?
- Has the trial we are designing already been conducted? Were there problems with similar trials?
- Strike the right balance to inform the public, protect public health and foster the innovation capacity of European medical research

# CT Regulation: transparency legal requirements

## Article 81(4) of Regulation (EU) No. 536/2014

EU database publically accessible by default, with exceptions justified on any of the following grounds:

- Protection of personal data;
- Protection of commercially confidential information in particular taking into account the MA status of the medicinal product, unless there is an overriding public interest in disclosure;
- Protecting confidential communication between MS in relation to the preparation of the assessment report;
- Ensuring effective supervision of the conduct of a clinical trial MSs;



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2 October 2015
EMA/228383/2015 Endorsed

Appendix, on disclosure rules, to the "Functional specifications for the EU portal and EU database to be audited - EMA/42176/2014"

| | |
|---|---|
| Draft reviewed with the clinical trials information system expert group | 8 December 2014 |
| Consultation with the MS for release for public consultation | 9 December 2014 - 13 January 2015 |
| Consultation with the European Commission for release for public consultation | 9 December 2014 – 13 January 2015 |
| Public consultation | 21 January – 18 February 2015 |
| Consultation of the final document by the European Commission | 7 September 2015 |
| Consultation of the final document by the Member States | 7 September 2015 |
| Endorsement by European Medicines Agency Management Board | 2 October 2015 |
| Sign off by the Deputy Executive Director | 5 October 2015 |

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- Appendix, on disclosure rules, to the "Functional specifications for the EU portal and EU database to be audited - EMA/42176/2014"

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/10/WC500195084.pdf

# Publication of data with CT regulation

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- Only applications on which a decision has been reached will be made public;
- All data and documents in the system will be made public with few exceptions;
- Summary of results for laypersons
- The default is always to make public at the first opportunity;
- Sponsors have options to defer the timing of publication of specific data/documents (use of deferrals will be monitored);
- Need to strike the balance between access to information and protecting the interest of sponsors

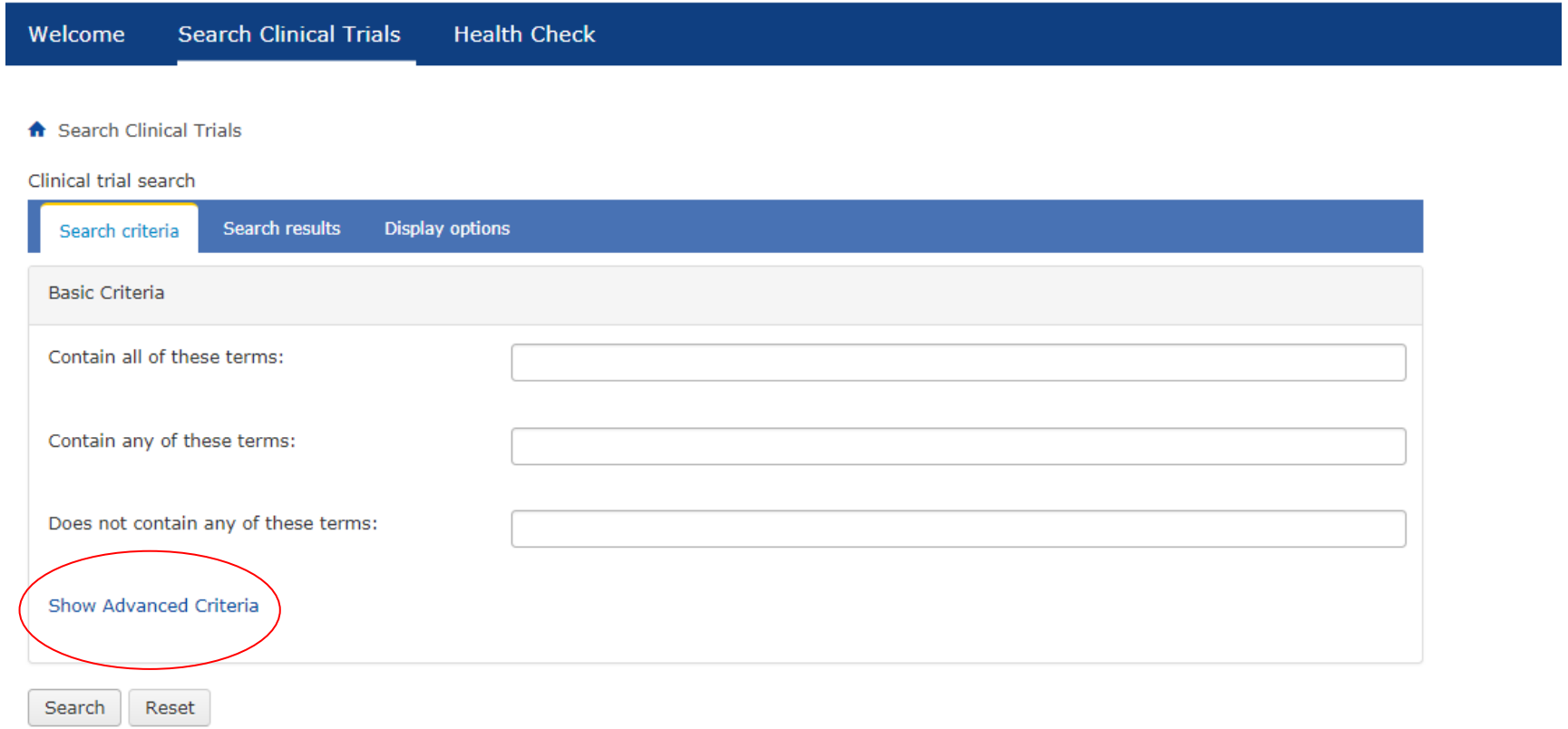
# What will be published?*

- Clinical trial protocol details
- Product details (including IMPD S&E, IB/SmPC)
- Sponsor contact details in the EU
- Principal investigator details, including clinical investigator sites address
- Statement on the suitability of the facility
- Clinical trial summary of results
- Clinical study reports for trials provided as part of a marketing authorisation applications
- Notifications of start of trial/ start of recruitment/ temporary halt/end of trial
- Notifications of serious breaches/ unexpected events/urgent safety measures
- Member State Assessment reports
- Member State inspection reports

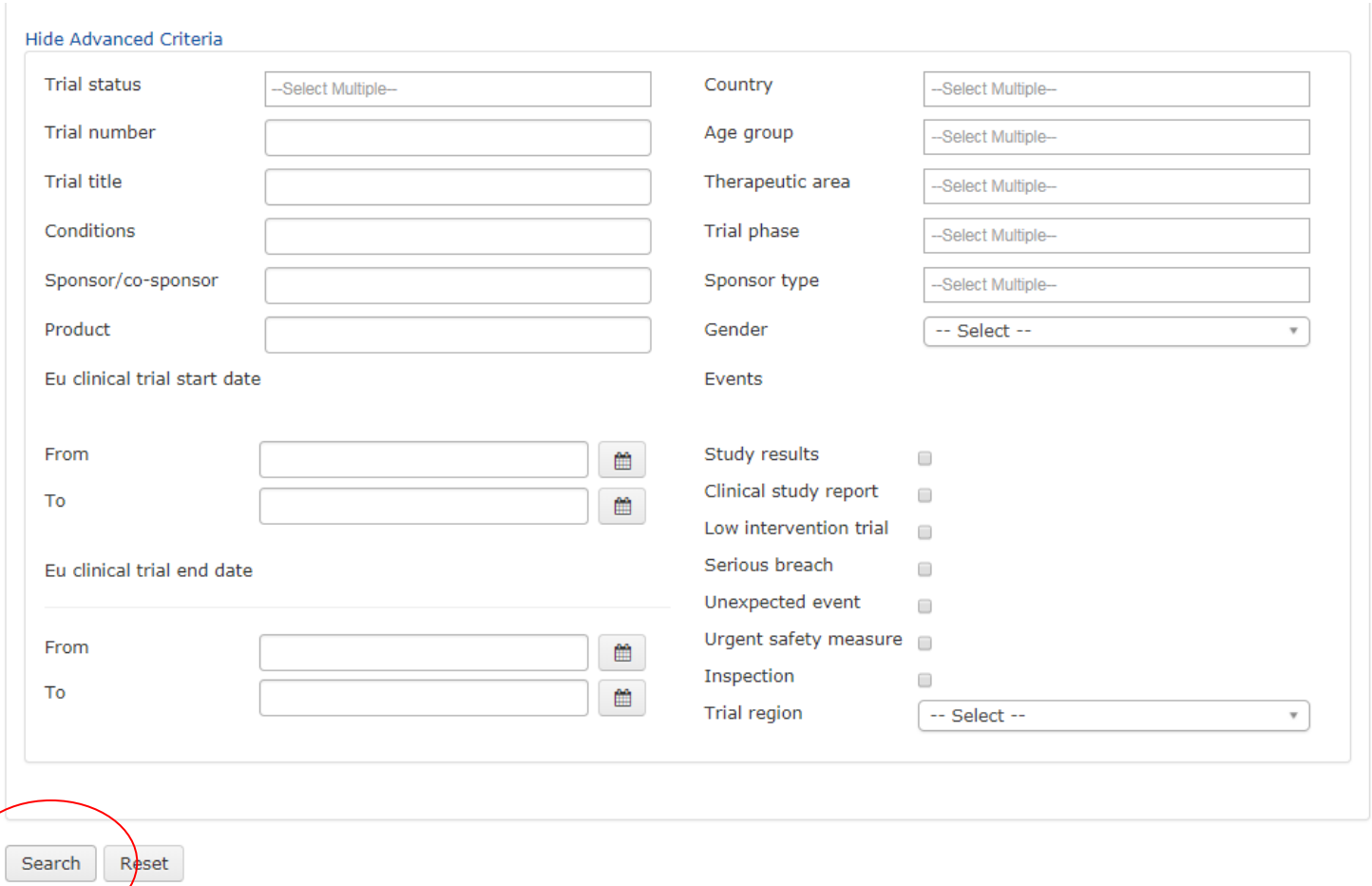
***This is not an exhaustive list***

# EU Database: Public view

# Public website – Basic search



# Public website – Advanced search



# Public website– Search results view (*Dummy data*)

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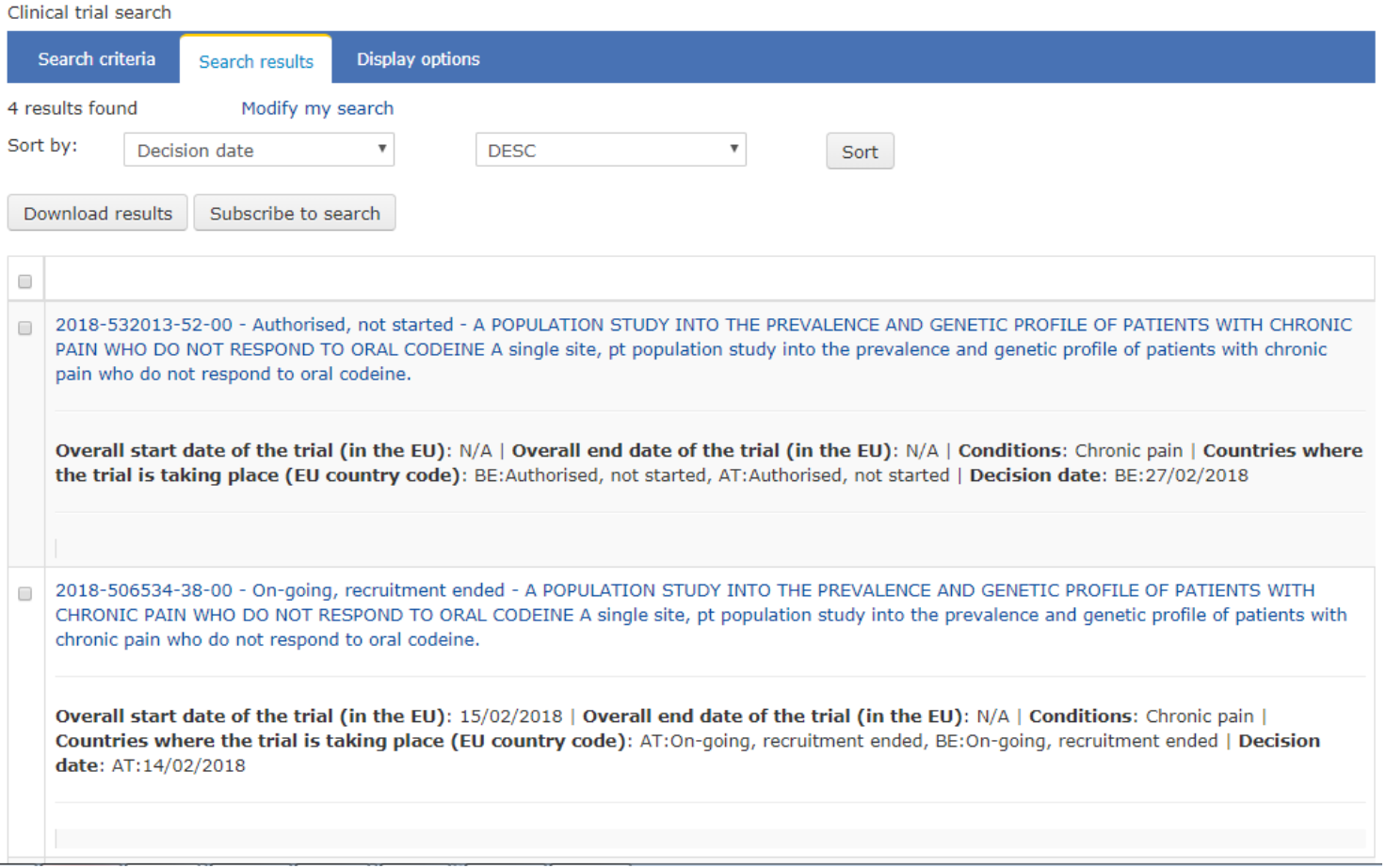

# Public website – Modify display options for search results

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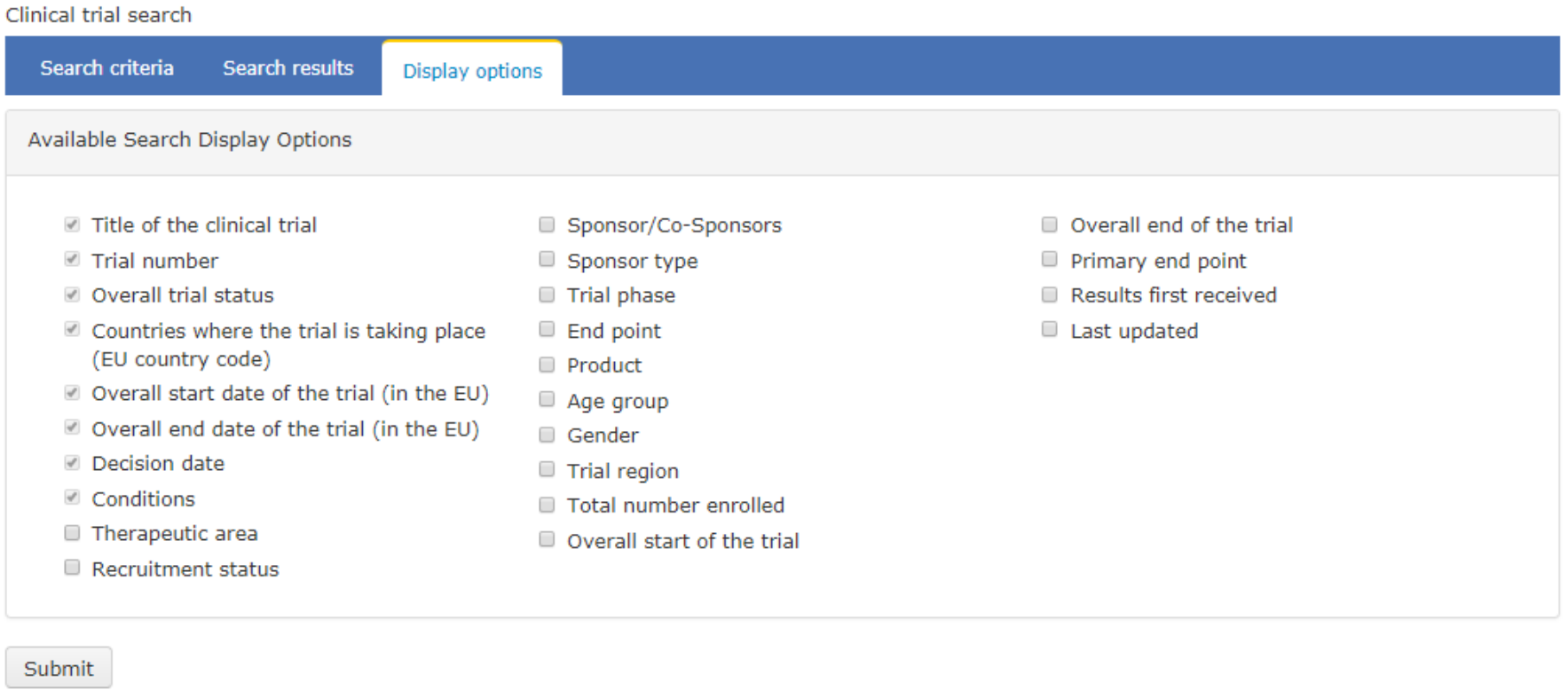

# Public website – Single trial view Summary (*Dummy data*)

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A POPULATION STUDY INTO THE PREVALENCE AND GENETIC PROFILE OF PATIENTS WITH CHRONIC PAIN WHO DO NOT RESPOND TO ORAL CODEINE A single site, pt population study into the prevalence and genetic profile of patients with chronic pain who do not respond to oral codeine.

EUCT number: 2018-532013-52-00

Download CT

Summary | Full trial information | Events | Trial results | Corrective measures | Inspection Record

## Trial information

Conditions(s)

Sponsor

Therapeutic area ] - Genetic Phenomena [G05]

First submitted 23/02/2018

Last update

## Trial status

Start of trial | End of trial | Global end of trial

| Member state | Trial status | Last update | Start of trial | Start of recruitment | End of recruitment | End of trial |
|---|---|---|---|---|---|---|
| Belgium | Authorised | | | | | |
| Austria | Authorised | | | | | |

Request removal of public information

# Public website – Single trial view (Full trial information)

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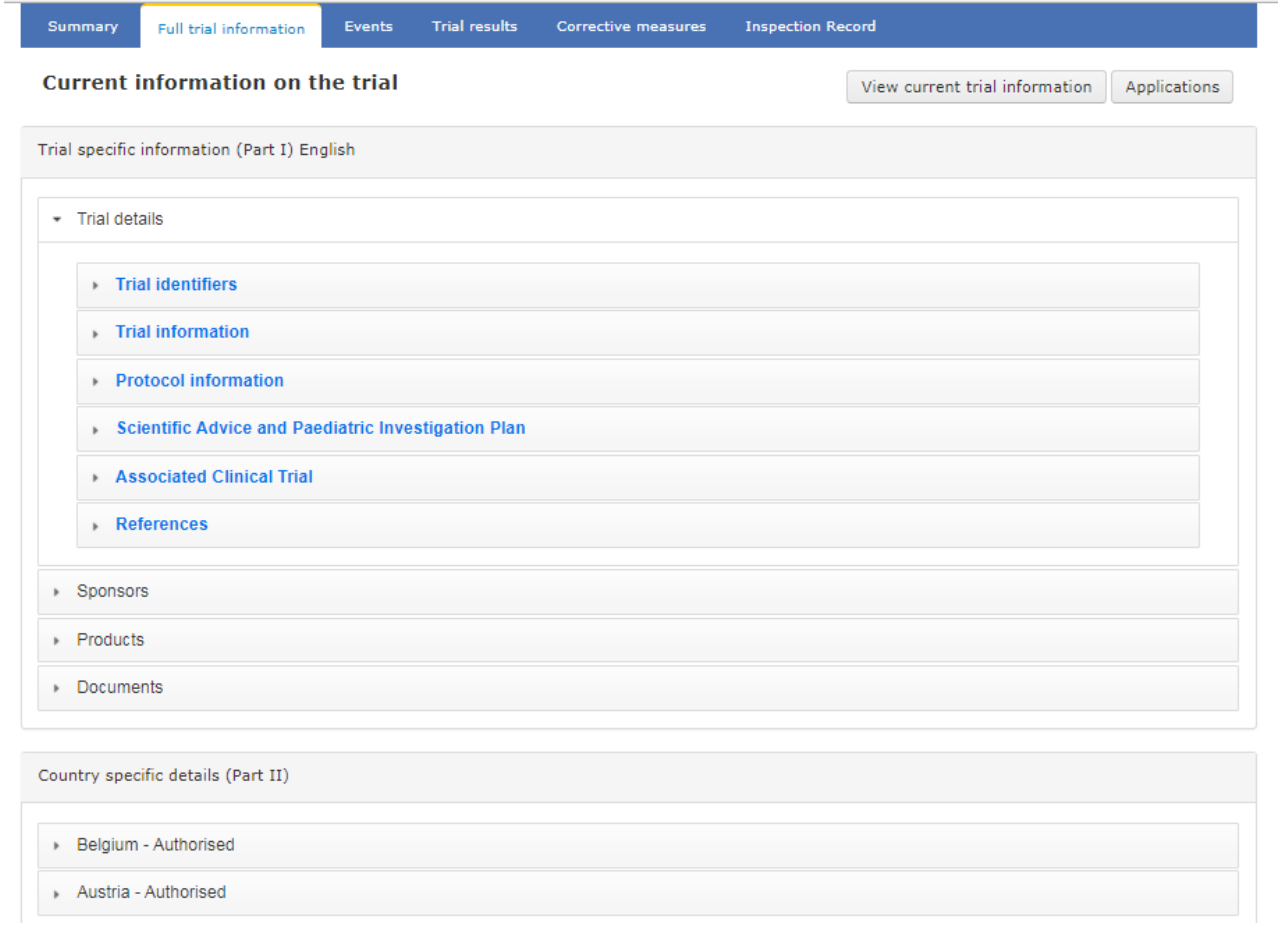

# Public website – Events (Notifications)

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Download CT

Summary | Full trial information | Events | Trial results | Corrective measures | Inspection Record

Notifications

- Serious Breach (None)
- Unexpected Event (1)

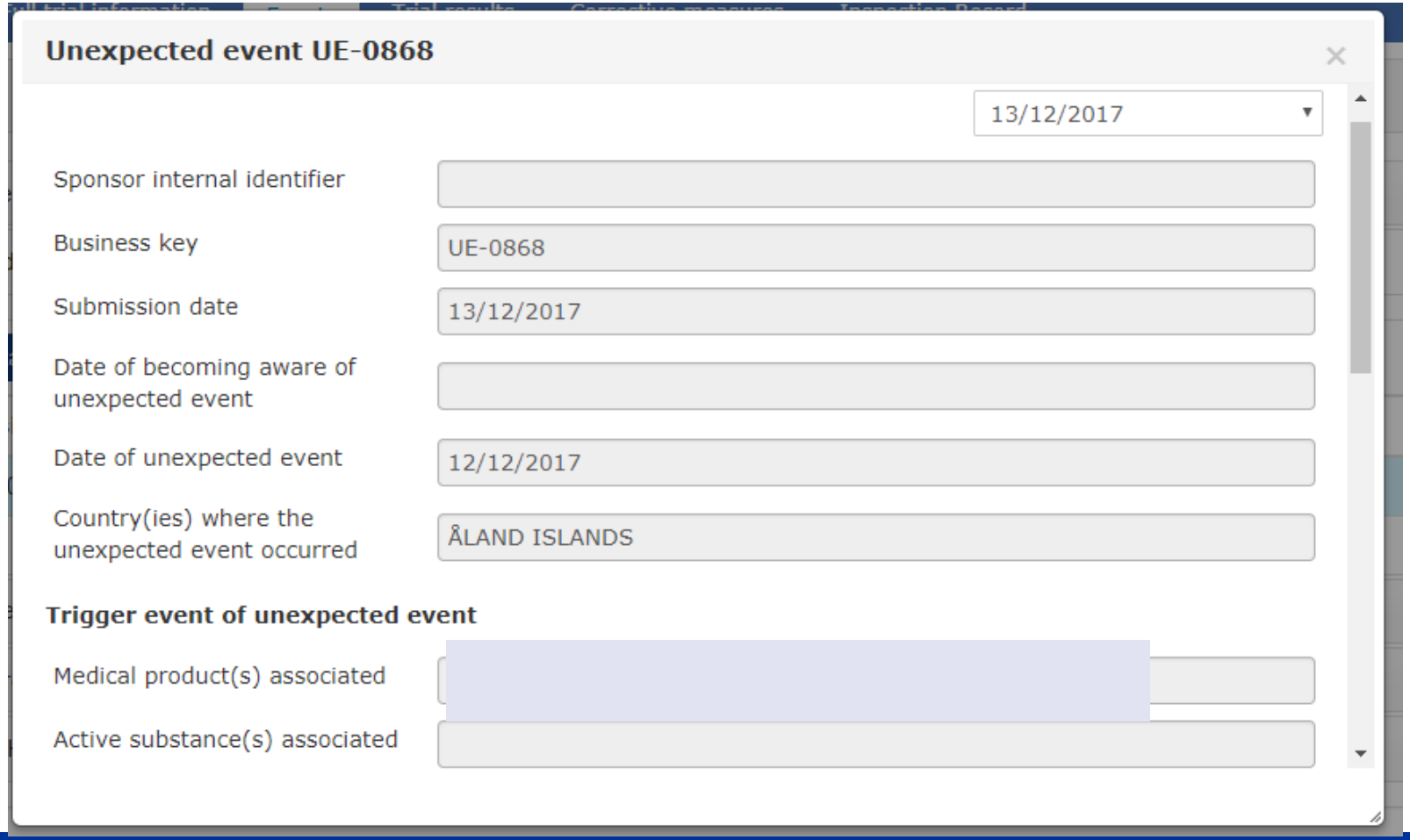
View Details

| | Business key | MSCs | Internal sponsor ID | Last modified | Submission date |
|---|---|---|---|---|---|
| ○ | UE-0868 | BELGIUM, AUSTRIA | | | 13/12/2017 |

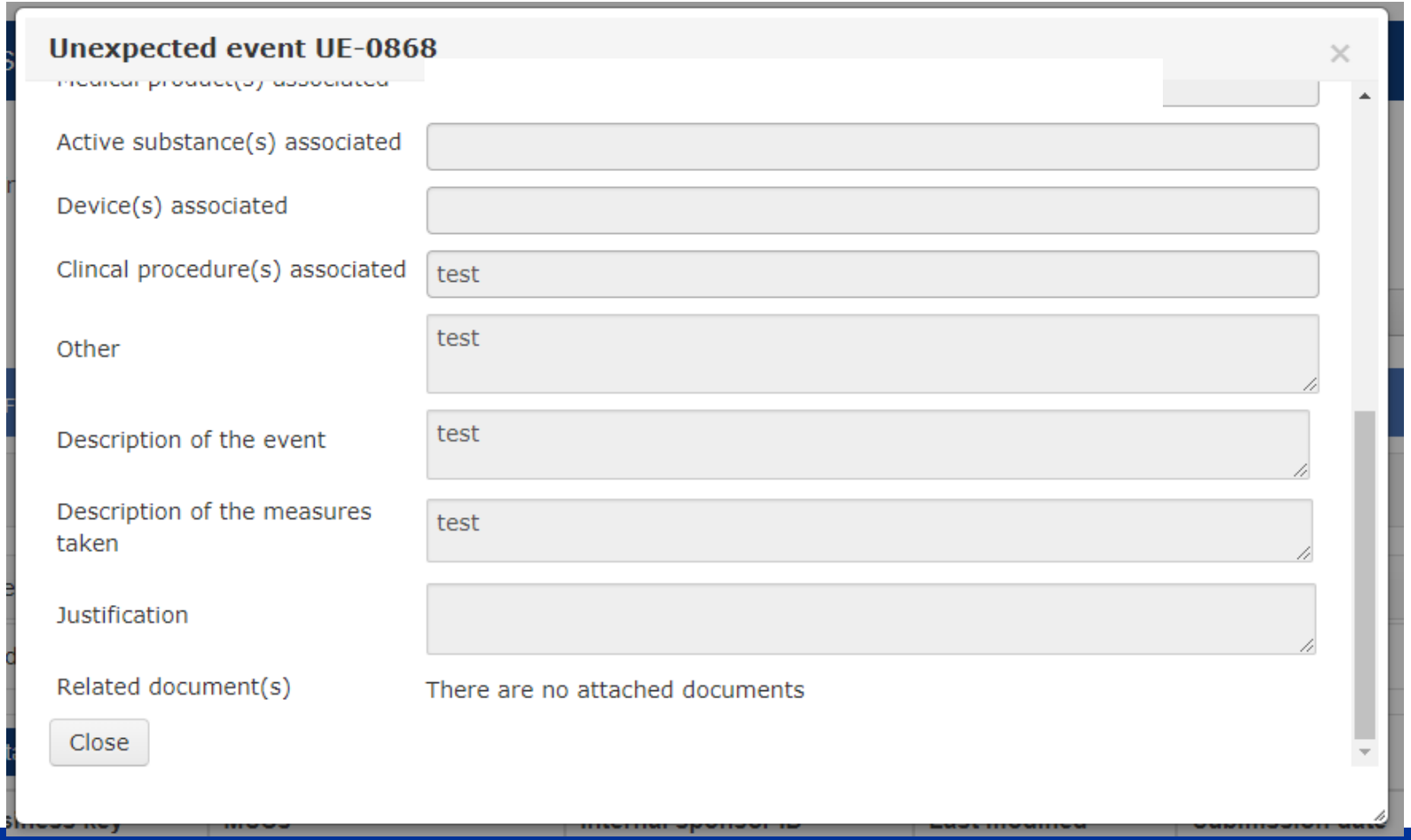
- Urgent Safety Measure (1)
- Inspection report from country outside of the EAA (None)
- Temporary Halt (7)

Request removal of public information

# Public website – Unexpected event detailed view



# Public website – Unexpected event detailed view



# Public website – Trial Results (*Dummy data*)

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EUCT number: 2017-571366-86-00

Download CT

Summary | Full trial information | Events | Trial results | Corrective measures | Inspection Record

Trial results

▾ Summary results

View

| | Version | Publication date |
|---|---|---|
| ○ | 1.4 current | 1/1/2012 |
| ○ | 1.3 | 1/1/2013 |

▸ Layperson summary results

▸ Clinical study reports

Request removal of public information

# Public website – Inspection record (*Dummy data*)

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View Clinical Trial

EUCT number: 2017-571366-86-00

Download CT

Summary | Full trial information | Events | Trial results | Corrective measures | Inspection Record

Inspection record

▾ Inspection record 1/1/2006 - Greece

View

| | Version | Publication date |
|---|---|---|
| ○ | 1.1 | 1/9/2014 |
| ○ | 1.2 current | 1/6/2015 |

▸ Inspection record 1/1/2015 - France

Request removal of public information

# Public website – Download trial information (*Dummy data*)

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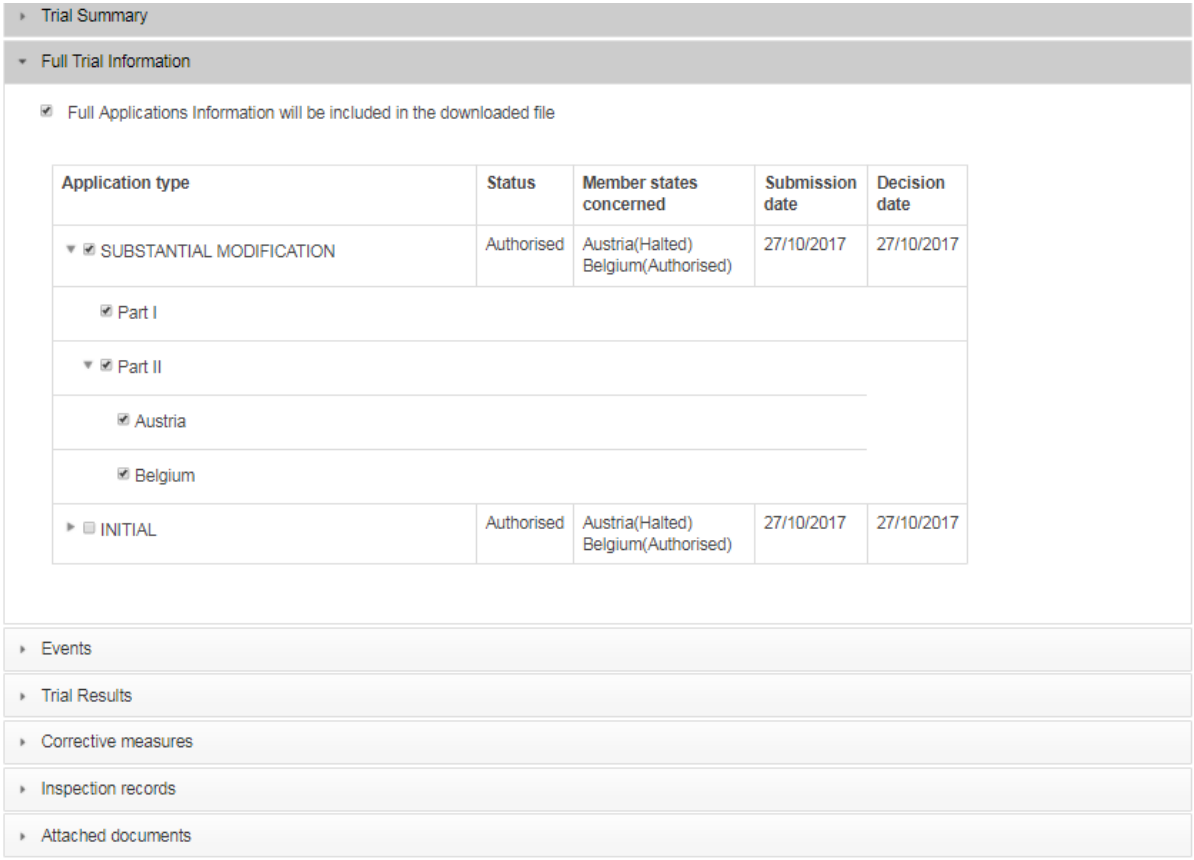

- Trial Summary
- Full Trial Information

Full Applications Information will be included in the downloaded file

| Application type | Status | Member states concerned | Submission date | Decision date |
|---|---|---|---|---|
| SUBSTANTIAL MODIFICATION | Authorised | Austria(Halted) Belgium(Authorised) | 27/10/2017 | 27/10/2017 |
| Part I | | | | |
| Part II | | | | |
| Austria | | | | |
| Belgium | | | | |
| INITIAL | Authorised | Austria(Halted) Belgium(Authorised) | 27/10/2017 | 27/10/2017 |

- Events
- Trial Results
- Corrective measures
- Inspection records
- Attached documents

Download clinical trial | Cancel

# EU portal and database - online training approach

The online learning will be delivered using the following channels:

**User manual** which will provide detailed instructions on all aspects of the system for all users.

**Short demo videos (5 – 10 minutes)** which are tailored to a specific task or sub-task which can be completed on the system, categorised by user group and split according to the business process to which they relate

**Quick guides** which are a tailored and slimed down version of manuals which walk a user through a specific action or process

**In-system information** training provided within the EU portal and database itself via built in help sections. These will provide the user with instant access to the relevant sections of the user manual for the task they are completing within the system

**Dedicated training webinars** which will be targeted at specific stakeholder groups, will be based around a specific set of processes and act as a question and answer forum

# Conclusions

# Conclusions

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**Single electronic submission**
*trial application, modification, registration and results reporting*

**TRANSPARENCY**

***Generate trust***
***Build confidence***
***Empower***

**EMA**
*Maintenance and update of IT systems*

**Collaboration between MS**

**One single decision per MS**

**Streamlined, coordinated, proportionate and transparent**


For more information:

https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trial-regulation

# Thank you for your attention

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