



Federal Institute
for Drugs
and Medical Devices



CT authorisation in the EU: present and future

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- Clinical Trials in the EU
- Clinical Trials – under Regulation (EU) No. 536/2014
- Transition period from Directive to Regulation
- Clinical Trials Portal & Database programme
- Current & future challenges for the NCAs
- Conclusions

Clinical Trials in the EU – what has changed over time?



...Before May 2004

National rules, different processes/requirements for authorisation in each EU Member States

...resulted in delays and complications

...Directive 2001/20/EC

(since 1 May 2004)

First step to harmonise processes and requirements for clinical trial authorisations

Introduction of e-application form

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

(published May 2014)

Full harmonisation and combined assessment of multinational trials (after full functionality of the EU portal and EU database)

e-submission



The Clinical Trial Regulation: what is new?

Directive

versus

Regulation

Implemented in national laws

- First step towards EU harmonisation in a non-harmonised field, but due to implementation in national laws **room for national specialities** (timelines etc.)
- Lack of harmonisation between Member States hampers multi-state trials
- Establishment of first databases for the national competent authorities (NCA) and the public (EudraCT database and EU clinical trial register)
- Introduction of parallel - but independent - assessment by NCA and ethics committee(s) (EC) in each member state

Directly applicable

Objectives of new CT Regulation

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

The Clinical Trial Regulation: what is in scope?

In scope

- **Interventional** clinical trials with medicinal products for human use
- **Low-intervention** clinical trials:
 - Authorised products (IMP)
 - If IMP not used in accordance with the terms of the Marketing Authorisation, use supported by published scientific evidence on Safety & Efficacy
 - Minimal additional risk or burden to the safety of the subjects compared to normal clinical practice.

Not in scope

- **Non-interventional** trials (observational studies);
- Trials without medicinal products (e.g. devices, surgery, etc).

Key changes from Directive to Regulation (1)

- To stay with fundamental GCP principles but to implement a **more risk based approach** to reduce unnecessary bureaucratic burden (less stringent rules to trials conducted with medicines which are already authorised)
- **Simplifying safety reporting requirements**
- **Reinforcing supervision of clinical trials** with Union controls in Member States and third countries, inspection and coordinated supervision
- Provisions concerning **clinical trials conducted outside the EU** and 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**
- Further define the concept of co-sponsorship
- Clarification to some provisions for informed consent
- Establishment of an EU portal and EU database
- Archiving of the Trial master File – 25 years

Key changes from Directive to Regulation (2)

As-is (Directive 2001/20) – EudraCT

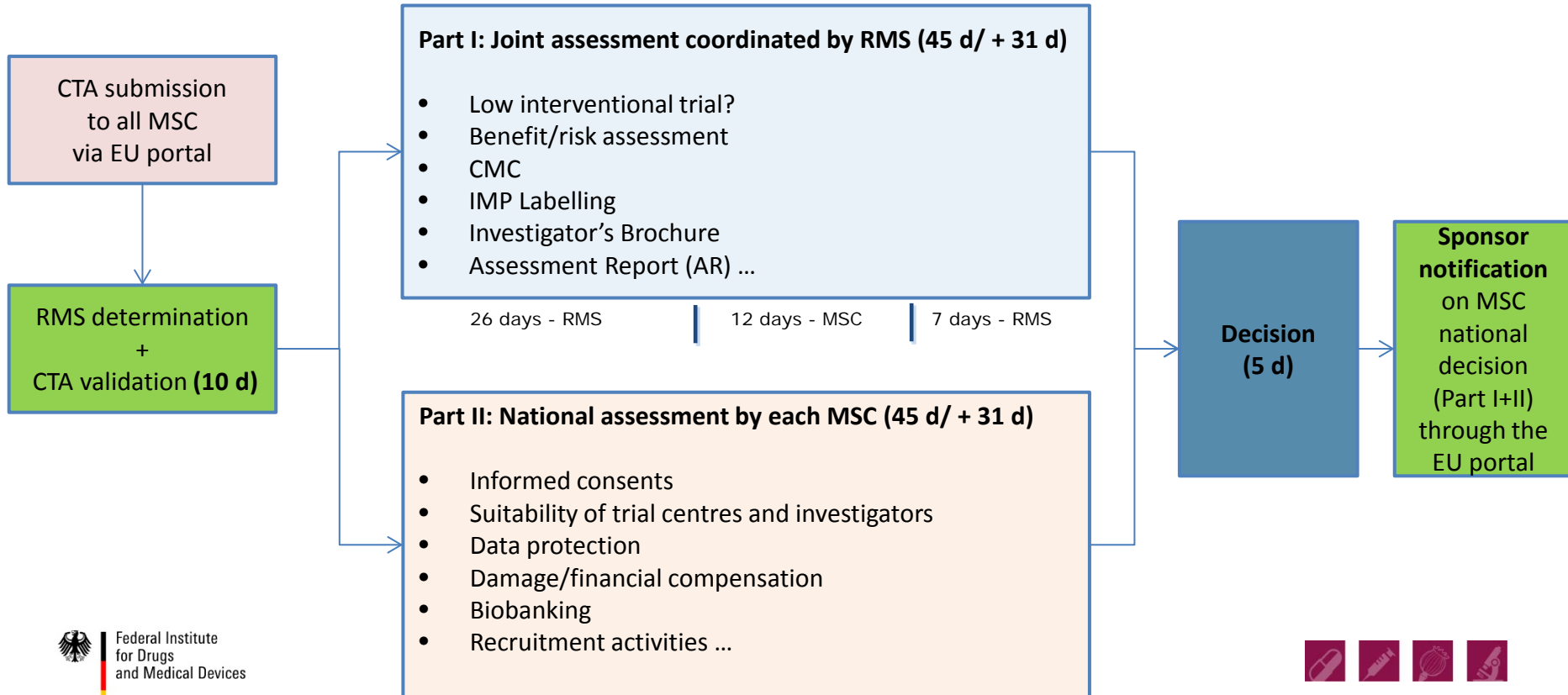
- Multiple submissions for one trial (1 submission per each MSC*) /no harmonized dossier (e-submission limited to structured data and paper based submission)
- Double submission within a MSC: to NCA **and** to Ethics Committees
- Individual assessment by each MSC with no IT collaboration tool available
- No single MSC decision (NCA & ECs)
- Burden to NCAs in uploading information in the system
- Limited EudraCT data availability to the public: structured data from the application (CTA) and summary of results

To be (CT Regulation) – The EU portal and database

- Single e-submission to all MSCs/**harmonized dossier for one trial & e-submission** of structured data and documents by MSCs
- Segmentation of the CTA dossier into **two parts**
- **Joint assessment** of Part I facilitated by collaboration tools
- **Single** MSC decision
- Distribution of the burden among users
- **View** all CT related information

MSC* = member state concerned

CTA Authorisation process with the new Regulation (1)

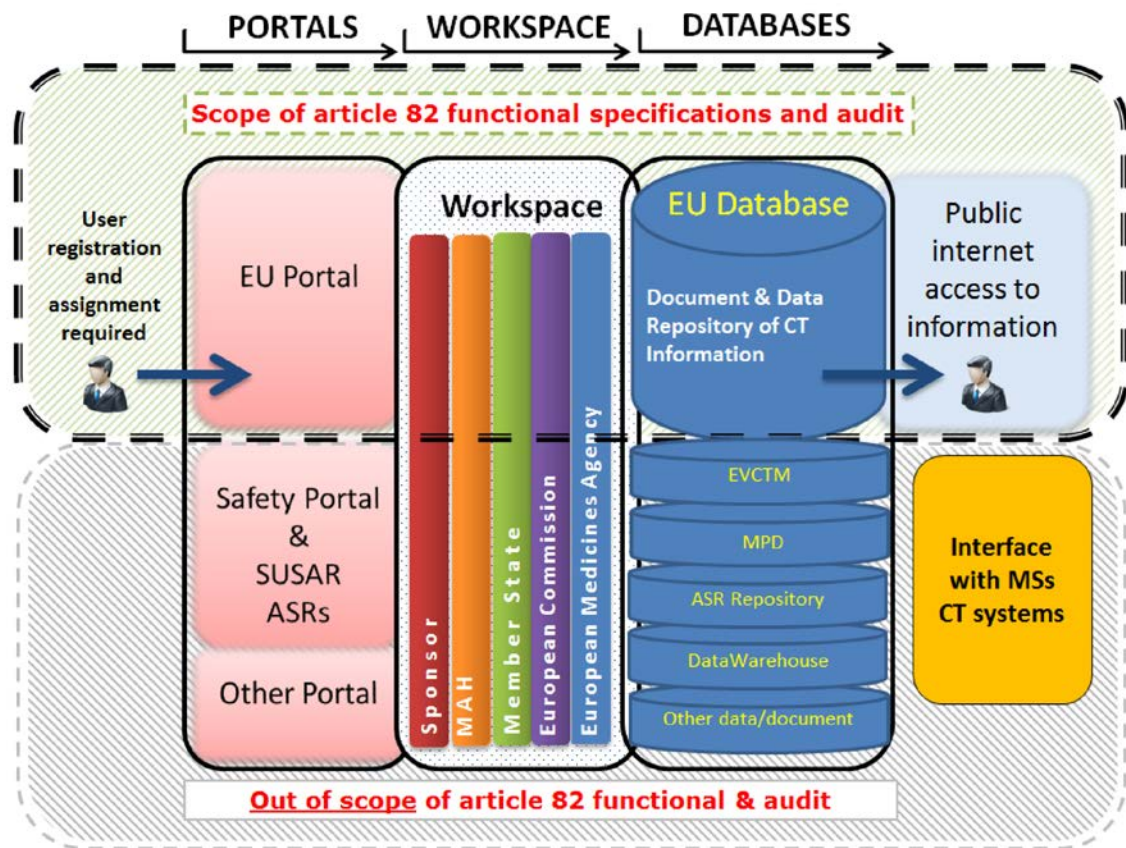


CTA Authorisation process with the new Regulation (2)

- **Reporting MS:** proposed by sponsor but proposal discussed between Member States (MS)
- **Up to MS to decide** how to involve the national competent authority and the ethics committee in Part I and Part II of the assessment to reach single decision;
- **Ethics Committee (EC) role and composition** remains **national decision**, it should take account view of a **layperson** and need to comply with procedure and timelines;
- **Possibility to disagree with Part I conclusions** limited to:
 - CT will lead to patients receiving inferior treatment than normal practice in that MS
 - Infringement of national law (e.g. CT of medicinal product forbidden in that MS)
 - Concerns as regards subject safety, data reliability and robustness.
- **Refusal:** if part I/part II/both negative or if the national ethics committee has issued a negative opinion for that MS
 - Expiration of the authorisation in a member State if no subject included within two years

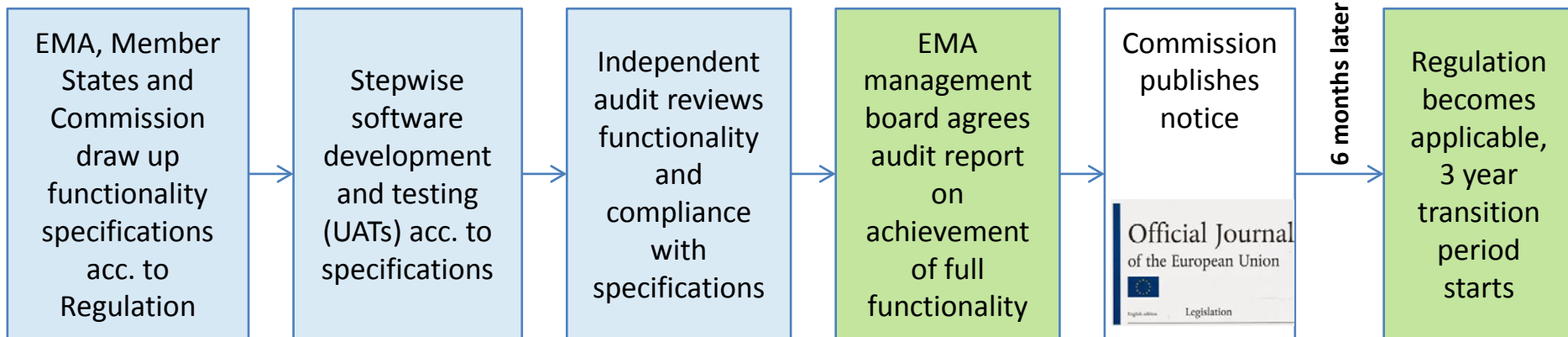
EU portal and EU database (EUPD)

- CTA submission including all documents entirely through EU portal
- Trial related communication between sponsor and RMS and between RMS and MSC entirely through EU portal



Requirements for Regulation (EU) No. 536/2014

- EU portal as a central submission and communication platform: essential for the functioning of the new Regulation
- Therefore, launch of the Regulation is linked to positive review of the EU portal and EU database functionality



Challenges for the NCAs - Interface to IT systems of Member States

- Particular Member States with a larger number of CTAs need an actual overlook about pending and newly arrived tasks when the Regulation becomes applicable
 - New submissions as well as additional information may trigger new deadlines and may shorten others
- Most Member States consider to set up own IT systems particular for the tracking of their ongoing CTAs and for the cooperation with national ECs
- EUPD includes an interface to the Member States IT systems, which will be part of the audit

3 year transition period



Directive 2001/20/EC

Regulation (EU) No. 536/2014

3 year transition period

Start: Regulation becomes applicable

- > First year: CT can be submitted under old (Dir.) or new (Reg.) systems
- > Years 2 & 3: Trials authorised under old system remain under that system

End of legacy

All CTs to switch to new Regulation 3 years after implementation

Challenges for the NCAs -

Short deadlines: tacit approval and withdrawal

- Deadlines of the CTA authorisations processes are short for both the sponsor and MSC
- Deadlines are calculated according to calendar days
 - If RMS appointment requires discussion among MSC, the validation phase could be shortened to 3 effective days for the RMS
 - Initial assessment phase: shortened to 26 days → shorter than current phase under Directive 2001/20/EC (30-60 days)
 - Deadline for the sponsor to provide additional information on request: 12 days → shorter than the current deadlines in most Member States
- If Member States fail to comply with the deadline, in many cases a tacit approval results and vice versa
- If sponsor fails to comply with the deadlines the CTA is deemed to have lapsed in all MSC

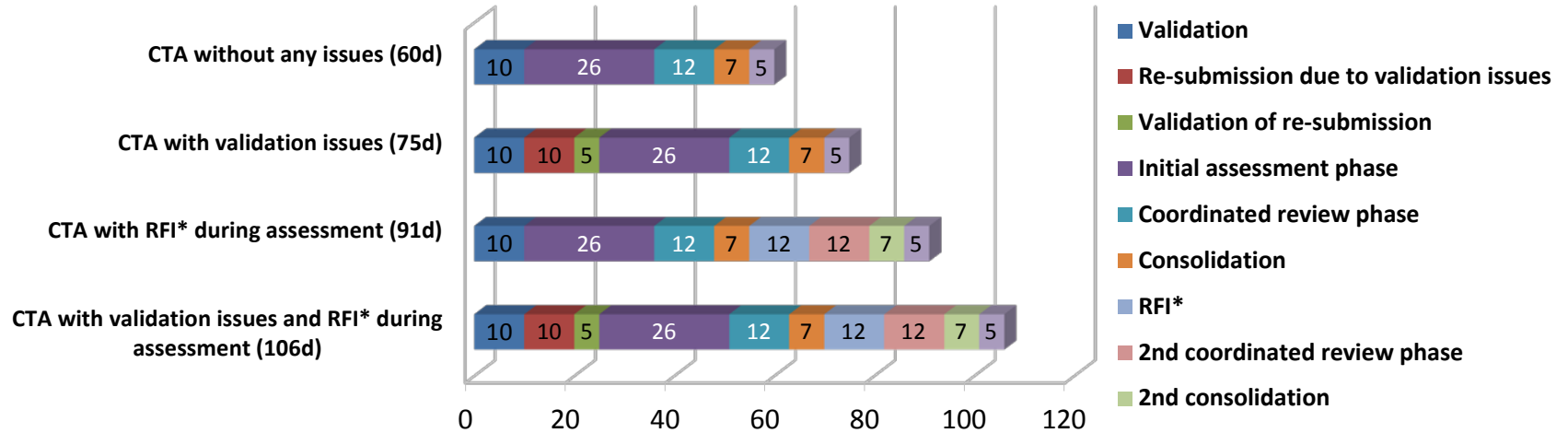
Challenges for the NCAs - Interaction with Ethics committees (EC)

- Most Member States continue to involve ethics committees in assessing and deciding on an application
- Currently, in most Member States EC and NCA work completely independently of each other
 - Particularly when acting as RMS close coordination with the national EC will become necessary
- Some Member States set up pilot projects to foster the cooperation between NCA and EC and to simulate cooperation under Regulation conditions

Deadlines for sponsors and authorities under the new Regulation

Part I

*RFI: Request for (additional) information



Deadlines for Part II comparable to Part I

Example: The German pilot project

- In 2015, BfArM developed a **pilot project for the coordinated assessment of CTAs together with the competent national EC closely following the procedures of the Regulation**
 - Deadlines adapted to those of the Regulation
 - VHP assessment report template
 - Use of IT collaboration tools for information exchange with the EC concerned
 - Joint work on the assessment report for Part I
- According to the current (and future) national laws BfArM and EC **assess Part I jointly** , Part II remains in the solely competence of the EC
- **35 of the 50 German ECs agreed to take part in the pilot project** since 2016
- **81 CTAs were jointly assessed**, in nearly all cases the review deadlines could be met

Conclusions



- **Impact of the Clinical Trial Regulation**

- **Harmonisation:** Further harmonisation of clinical trials in the EU
- **Single dossier, single submission:** Harmonised dossier for all Member States
- **Single opinion:** Only one opinion per Member State (NCA & EC)
- **Facilitation of Multi-State clinical trials:** Joint assessment under coordination of a reporting Member State
- **E-Submission:** Submission of all documents through the new EU portal
- **Enhanced transparency:** Stricter reporting obligations for sponsors
- **Acceleration of decisions:** Shorter deadlines for sponsor and Member States

- **New challenges:** Complex trial designs



Thank you very much for your attention!

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List of abbreviations

CTA	Clinical Trial Application
EC	Ethics Committee
EUPD	EU Portal and EU Database
GCP	Good Clinical Practise
IMP	Investigational Medicinal Product
MSC	Member State Concerned
NCA	National Competent Authority
(R)MS	(Reporting) Member State
UAT	User Acceptance Test
VHP	Voluntary Harmonisation Procedure



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Transparency on Clinical data

2nd International Awareness Session - The EU medicines regulatory system
and the European Medicines Agency

Presented by Karen Quigley on 8 March 2018
Documents Access and Publication Service,
European Medicines Agency



1. **European public assessment reports (EPAR)** Article 13(3) of Regulation (EC) No 726/2004

➤ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:136:0001:0033:en:PDF>

2. **Access to documents (ATD)** Regulation (EC) No. 1049/2001

➤ <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32001R1049&from=EN>

3. **Clinical Data Publication (CDP)** website (Policy 0070)

➤ http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/10/WC500174796.pdf

4. **Clinical Trial Regulation (CTR)** (EC) No. 536/2014

➤ http://ec.europa.eu/health/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf

	ATD	CDP	CTR
Basis	Reg(EC) 1049/2001 Policy 0043	Policy 0070	Reg(EC) 536/2014
What	Any documents held by the EMA	Clinical reports supporting MAA	Data on Clinical Trials conducted in EU
When	Upon request	Pro-actively	Pro-actively
Where	Provided directly to requester	On a website	In an EU database

Regulation 726/2004

The opinion of the Committee shall be made publicly accessible

Applies to withdrawals and refusals of MAA also

Publish the assessment report, if available, after deletion of all information of a commercially confidential nature.

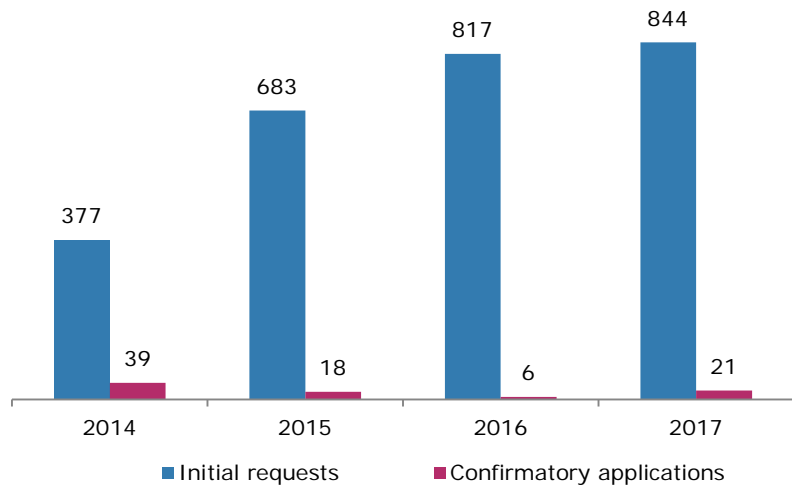
The European Public Assessment Report (EPAR) shall include a summary written in a manner that is understandable to the public.

Summary for public - product information – CHMP assessment report all published on Agency website after Commission Decision issued.

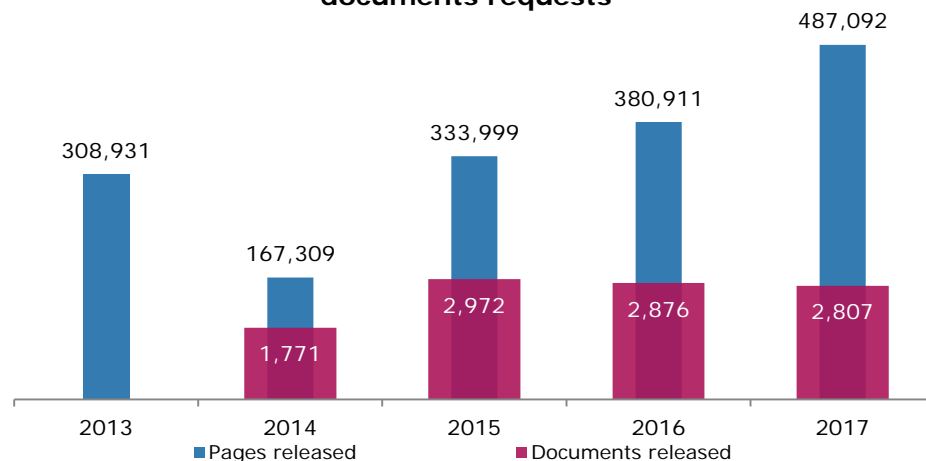


- Requester can submit a request using a **webform**
 - http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/landing/ask_ema_landing_page.jsp&mid=WC0b01ac05806499f0
- Obligation to **acknowledge receipt** of a request
- **15-day procedure** from receipt of clear request – **extendable by a further 15 days** in exceptional cases
- **Third parties are consulted** prior to releasing the requested documents
- High volumes of documents may be released in **batches**
- Summarised in a ***Guide on access to unpublished documents***
 - http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/11/WC500177739.pdf

Requests for access to documents received



Pages and documents released following access to documents requests





Policy 0070:

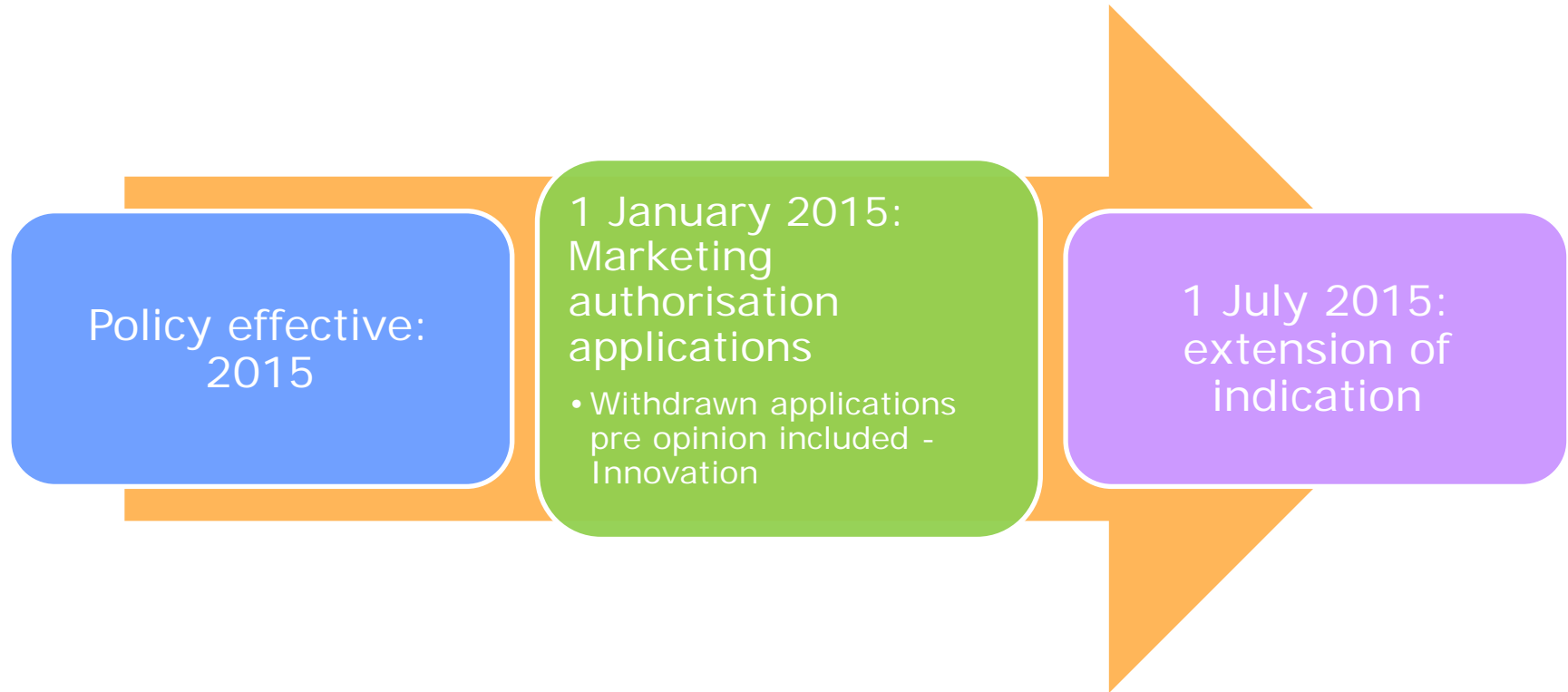
- 2 October 2014, Clinical Data Publication (human medicinal products)

What is it:

- Publication of clinical data supporting CHMP Opinions

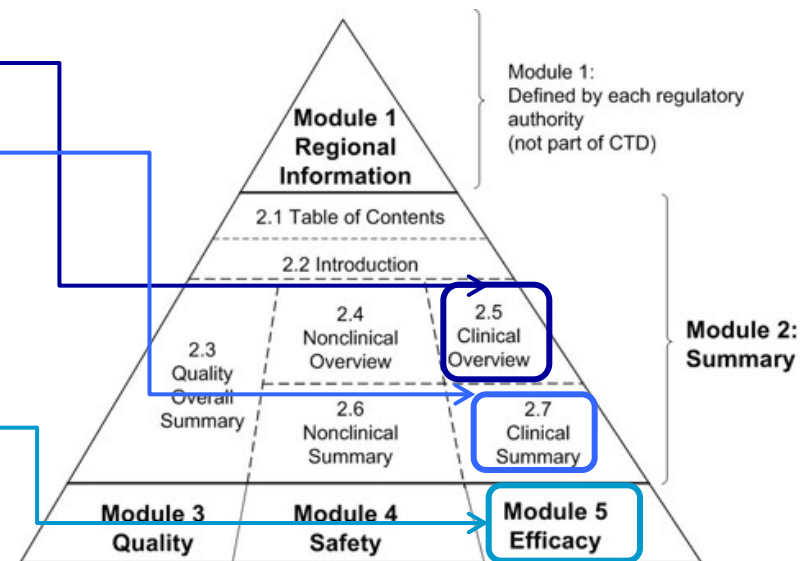
Benefits:

- **Transparency**, continued EMA commitment
- Proactive publication enables **public scrutiny**: establishes trust, confidence
- **Better public information**: Public access enables application of new knowledge in future research, increases efficiency of medicine development, learning from experience
- **Avoids clinical trials duplication**: limits unnecessary patient exposure
- **Enhanced scientific knowledge**/value of secondary analysis: sharing scientific knowledge, contribution to public health



- **Module 2.5 - Clinical Overview**
- **Module 2.7.1 to 2.7.4 - Clinical Summary**
- **Module 5.3 Clinical Study Reports (CSR) - Body of the reports**
- **Module 5.3 Clinical Study Reports – 3 appendices per CSR**
 - 16.1.1 (protocol and protocol amendments)
 - 16.1.2 (sample case report form)
 - 16.1.9 (documentation of statistical methods)

- **Anonymisation report**



- For all applications falling within the scope of Policy 0070 whether studies were conducted in or outside the EU
- No Individual Patients Line (IPD) listings

Introduction, scope, definitions

External guidance on the **procedural aspects** related to the submission of clinical reports for the purpose of publication in accordance with EMA policy 0070

Guidance on the identification and redaction of **commercially confidential information** (CCI) in clinical reports submitted to the EMA

Guidance to pharmaceutical industry on the **anonymisation** of clinical reports for the purpose of publication in accordance with EMA policy 0070

Published on EMA website:

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/12/WC500218567.pdf

The Agency does not accept the redaction of information as CCI if:

1. the information is available in the **public domain** from various sources;
2. it is information that does **not bear any innovative features**;
3. it is information reflecting **common knowledge** shared within the scientific community;
4. the justification provided is **irrelevant** to the text proposed for redaction
5. **commercial harm** (in case of the release of specific information) is **not explained or is insufficiently** explained

- Is the process of turning data into a form that **does not identify individuals** and where identification is not likely to take place
- Will ensure a **very low risk of re-identification** of individuals
- Company's anonymisation report will be published together with the Clinical reports to explain:
 - ✓ The **process**
 - ✓ The **methodology** used
 - ✓ The **impact** of anonymisation on data utility

Type of procedure published

Initial marketing authorisation	36
Extension of indication	18
Line extension	0
Total number of procedures published	54

Documents published

Anonymisation Report	54
Module 2.5	63
Module 2.7.1-2.7.4	160
Module 5.3 (CSR)	3,002
Total number of documents	3,279
Total number of pages	1,308,244

Sharing experience with Health Canada, FDA, Japan

- collaborate with international partners to share our experience with new policy on clinical data publication and transparency initiatives
- examine opportunities for harmonisation
- Staff visits to share knowledge

- 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 foster¹⁴ the innovation capacity of European medical research.



Clinical trials

The European Union Clinical Trials Register allows you to search for protocol and results information on:

- interventional clinical trials that are conducted in the European Union (EU) and the European Economic Area (EEA);
- clinical trials conducted outside the EU / EEA that are linked to European paediatric-medicine development.

Learn [more about the EU Clinical Trials Register](#) including the source of the information and the legal basis.

The EU Clinical Trials Register currently displays **32061** clinical trials with a EudraCT protocol, of which **5170** are clinical trials conducted with subjects less than 18 years old.

The register also displays information on **18700** older paediatric trials (in scope of Article 45 of the Paediatric Regulation (EC) No 1901/2006).

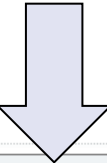


Examples: Cancer AND drug name. Pneumonia AND sponsor name.

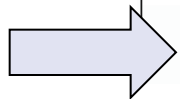
[How to search \[pdf\]](#)

Advanced Search: [Search tools](#)

Additional Paediatric trials also have results posted.



9,761 trials registered as being conducted in EU now have results posted.



Trials with a EudraCT protocol (9,761)

Paediatric studies in scope of Art45 of the Paediatric Regulation (3,885)

9,761 result(s) found. Displaying page 1 of 489.

[< Back to search results](#)[Print](#) [Download](#)**Summary**

EudraCT Number:	2014-000991-25
Sponsor's Protocol Code Number:	Metform03
National Competent Authority:	UK - MHRA
Clinical Trial Type:	EEA CTA
Trial Status:	Ongoing
Date on which this record was first entered in the EudraCT database:	2014-08-13
Trial results	

Index[A. PROTOCOL INFORMATION](#)[B. SPONSOR INFORMATION](#)[C. APPLICANT IDENTIFICATION](#)[D. IMP IDENTIFICATION](#)[D.8 INFORMATION ON PLACEBO](#)[E. GENERAL INFORMATION ON THE TRIAL](#)[F. POPULATION OF TRIAL SUBJECTS](#)[G. INVESTIGATOR NETWORKS TO BE INVOLVED IN THE TRIAL](#)[N. REVIEW BY THE COMPETENT AUTHORITY OR ETHICS COMMITTEE IN THE COUNTRY CONCERNED](#)[P. END OF TRIAL](#)[Expand All](#)[Collapse All](#)**A. Protocol information**

A.1	Member State Concerned	UK - MHRA
A.2	EudraCT number	2014-000991-25
A.3	Full title of the trial	Pre-surgical metformin for women with endometrial cancer: a randomised placebo controlled trial
A.3.1	Title of the trial for lay people, in easily understood, i.e. non-technical, language	Metformin for endometrial cancer randomised controlled trial
A.3.2	Name or abbreviated title of the trial where available	Metformin for endometrial cancer RCT

Summary - Clinical Trial Transparency – and EMA

- Clinical Trials authorised in EU/EEA:
 - Growing body of clinical trial information and results summaries in EU Clinical Trial Register for trials authorised since 2004.
- Contains protocol and results related data for interventional CT started after May 2004
 - Phase II-III-IV trials conducted in adults in the EEA
 - Phase I-II-III-IV paediatric trials in the EEA
 - Only phase I trials conducted in adults & part of a PIP are made public (small %)
- New clinical trial Regulation - Extensive information on clinical trials from authorisation to the trial summary results of all trials authorised in EU/EEA under the new Regulation.



Conclusion

Overview of clinical data transparency at Agency – available on request and proactively

- duplication of clinical trials can be avoided, innovation and development of new medicines will be encouraged;
- public trust and confidence in EMA's scientific and decision-making processes is enhanced
- enables public scrutiny while protecting personal data and commercially confidential information



Public data and information about medicines, their development and authorisation

- **Generate trust** – information is available;
- **Build confidence** – I understand what is happening;
- **Empower** – knowledge enables decision-making

Thank you for your attention

European Medicines Agency

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