Changes in Clinical Trial Regulations

Analysis of the latest regulatory initiatives in EMEA (536/2014) impacting clinical trials today

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Agenda

- ✓ GCPpl Overview
- ✓ Clinical Trials Landscape in EMEA
- ✓ Scope of Regulation (EU) No. 536/2014
- ✓ Key changes in CTR
- ✓ Transparency
- ✓ EU Clinical Trial Portal and Database
- ✓ Conclusions & Discussion

Polish Association for Good Clinical Practice: Overview

- Established in 1997
- Non-Government Organisation of proffesionals involved in organisation and conduct of clinical trials
- >1000 members (pharma/CRO employees, investigators, site personel, students)
- National Board and Working Groups
- Most activities related to education
- Co-operation with the legislator, regulator, ethics committees, investigators/sites
- Co-operation with two further organisations focusing on clinical trials:
  - Employers' Union of Innovative Pharmaceutical Companies INFARMA
  - Polish Employers' Union of Contract Research Organistions POLCRO

Polish Association for Good Clinical Practice: Education

"Clinical Trials" handbook, 2015

17 educational workshops/seminars for various stakeholders, including clinical sites and patients, over just last 3 years

LIDERZY BADAŃ KLINICZNYCH

Clinical Trial Leaders:
National award for clinical operations proffesionals (last edition: 2019)

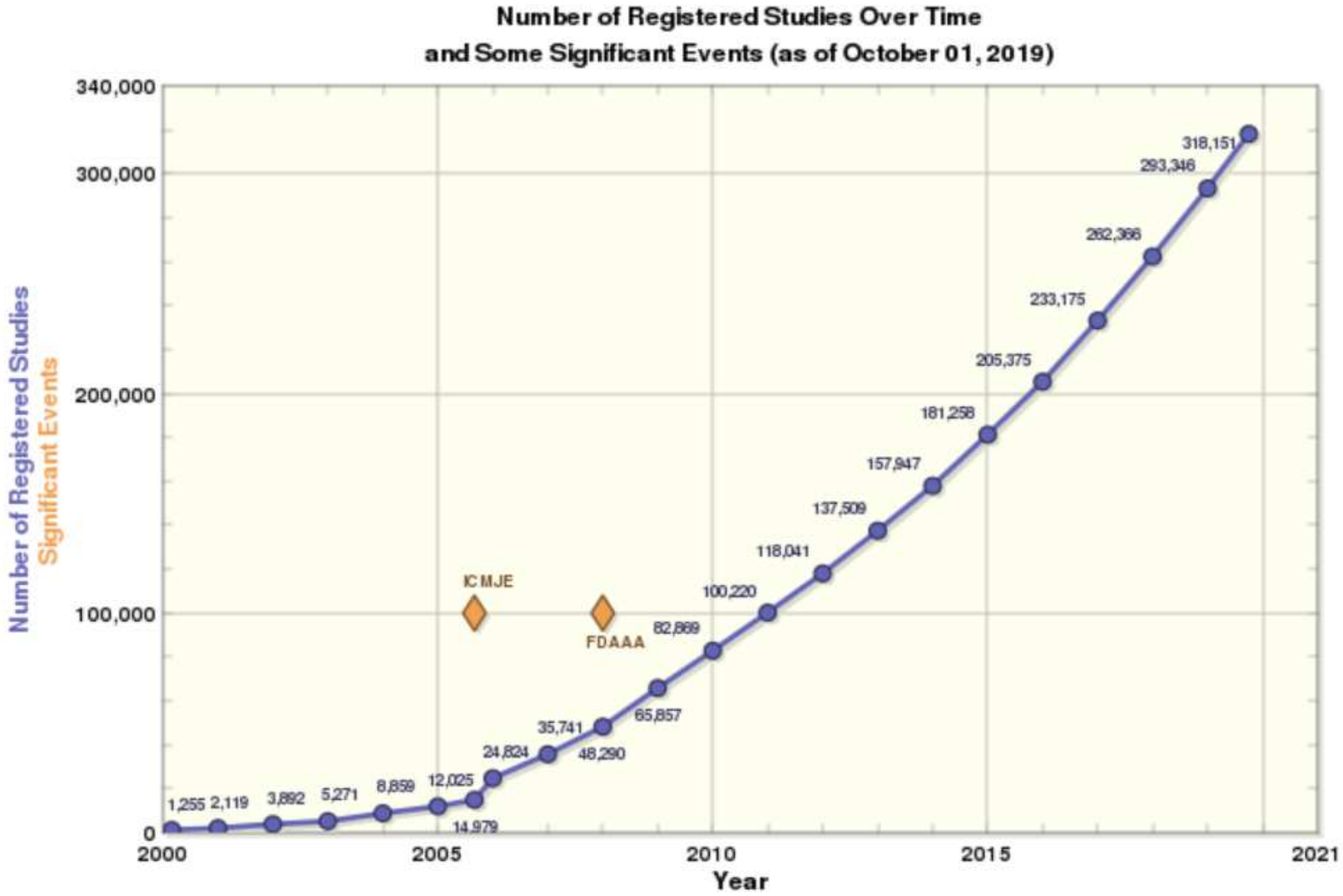
www.gcppl.org.pl

International Clinical Trials Day – Poland's conference, 6th edition

Save the date: 20th May 2020

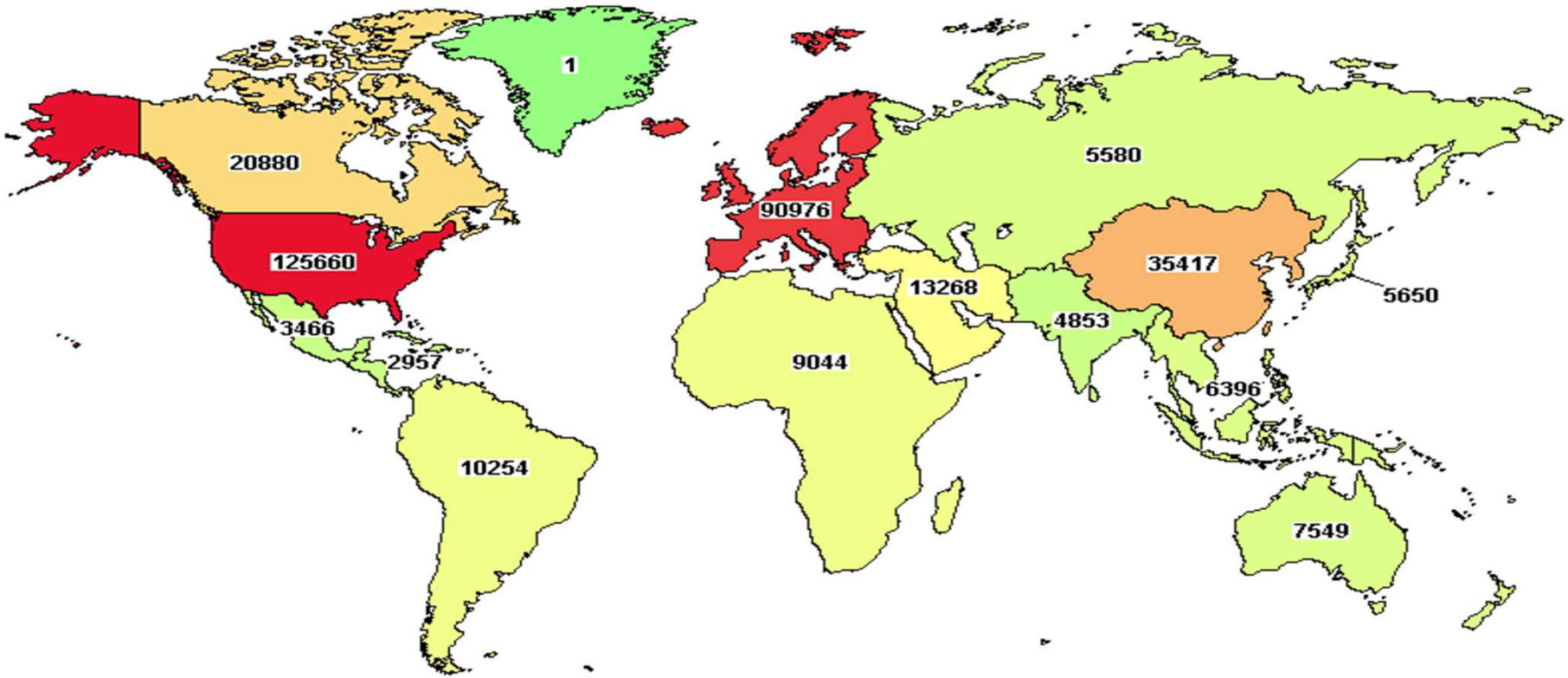
www.gcppl.org.pl

Landscape of clinical trials – growing market



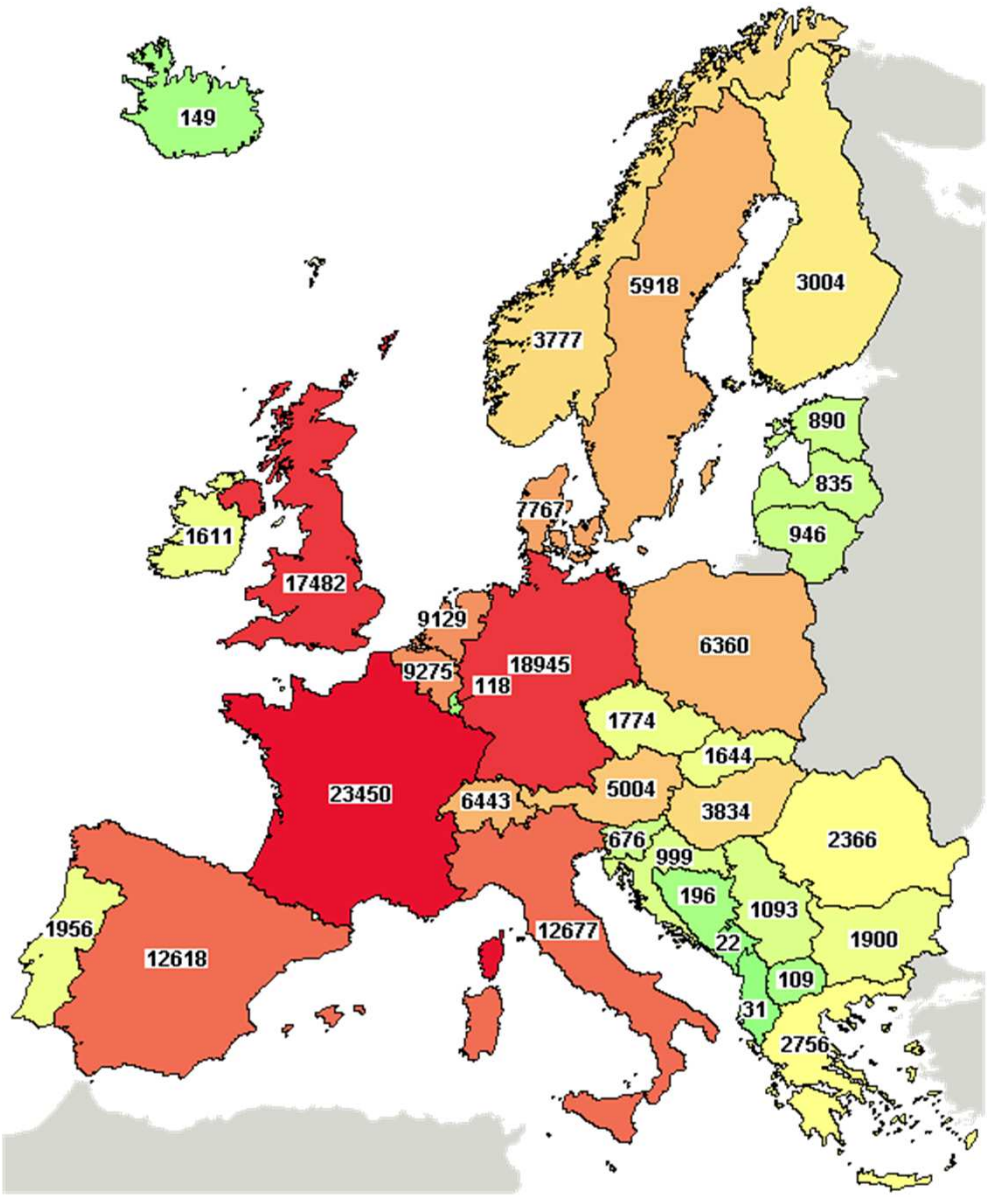
Source: https://ClinicalTrials.gov

ClinicaTrials.gov:
319,371 CTs (including 252,080 interventional CTS) registered since 2004 r.



EMEA Region

90,976 CTS since 2004 r.



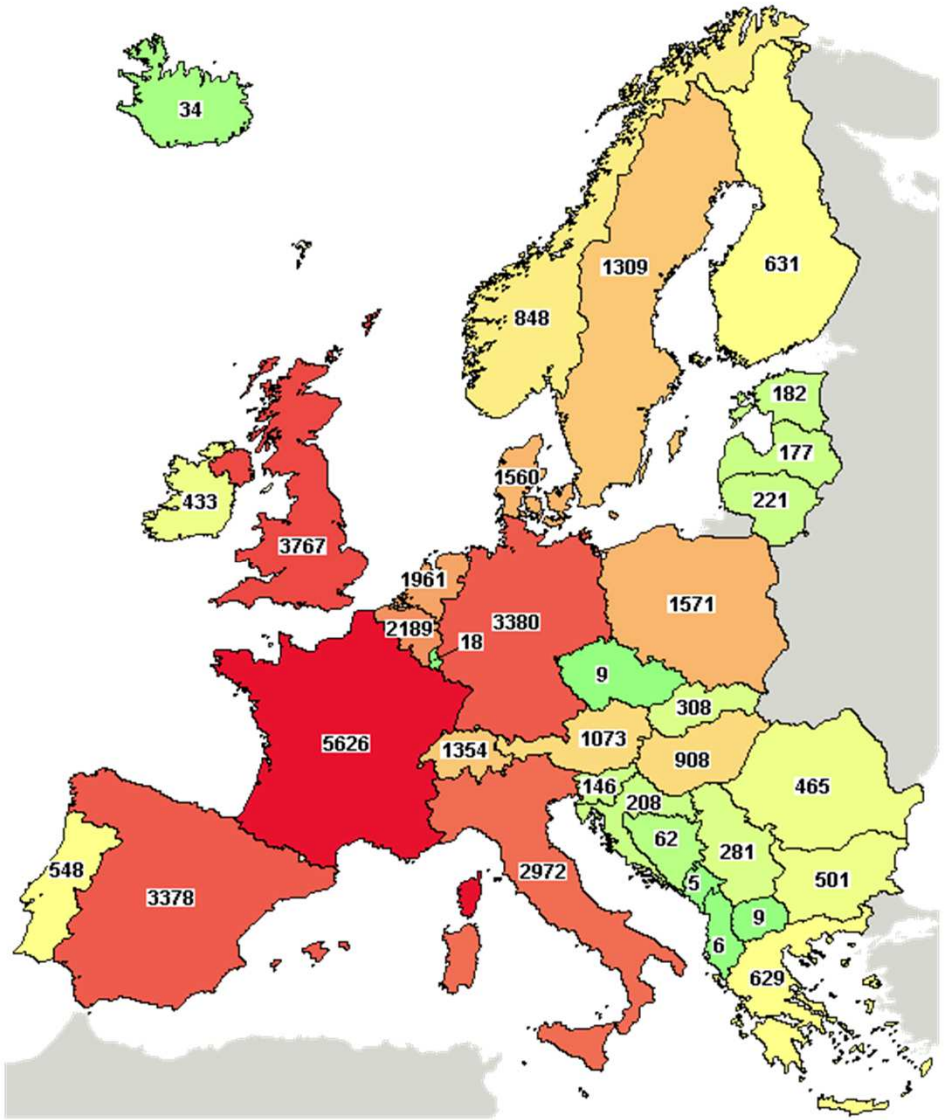
EU Clinical Trials Register

31 821 CTs registered since 2004 r.

Sponsor class:	
Non-commercial	No (%) 14 408 (45.3)
Commercial	16 964 (53.3)
Mixed	265 (0.8)
Blank	181 (0.6)

Source: https://www.bmj.com/content/362/bmj.k3218

Clinical Trials Landscape in Poland

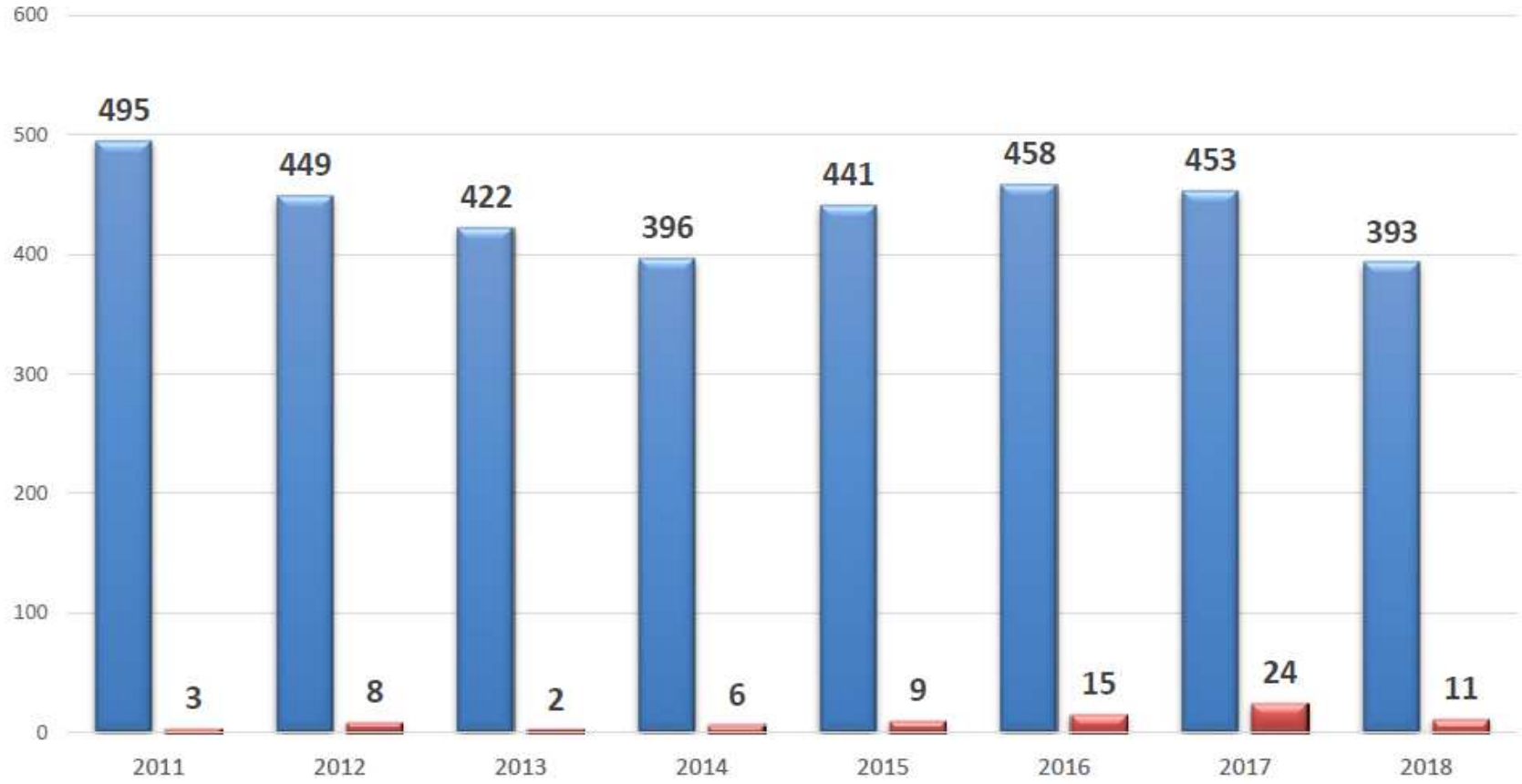


- **1571 - open active clinical trials**
- **885 - active recruiting**
  - Oncology - 280
  - Cardiovascular Diseases – 209
  - Paediatric population – 194
    - (limited peadiatric CTs)
  - Neurology disorders – 179
  - Pulmonary diseases - 172
  - Psychiatric disorders – 66
  - Infectious diseases – 73
  - Ophthalmology - 35
  - Phase I - 57

Source: www.clinicaltrials.gov 09Oct2019

Clinical Trials registered in Poland

comercial vs non-comercial



Evolution in Clinical Trials Regulation

27.5.2014 EN Official Journal of the European Union L 158/1

I

(Legislative acts)

REGULATIONS

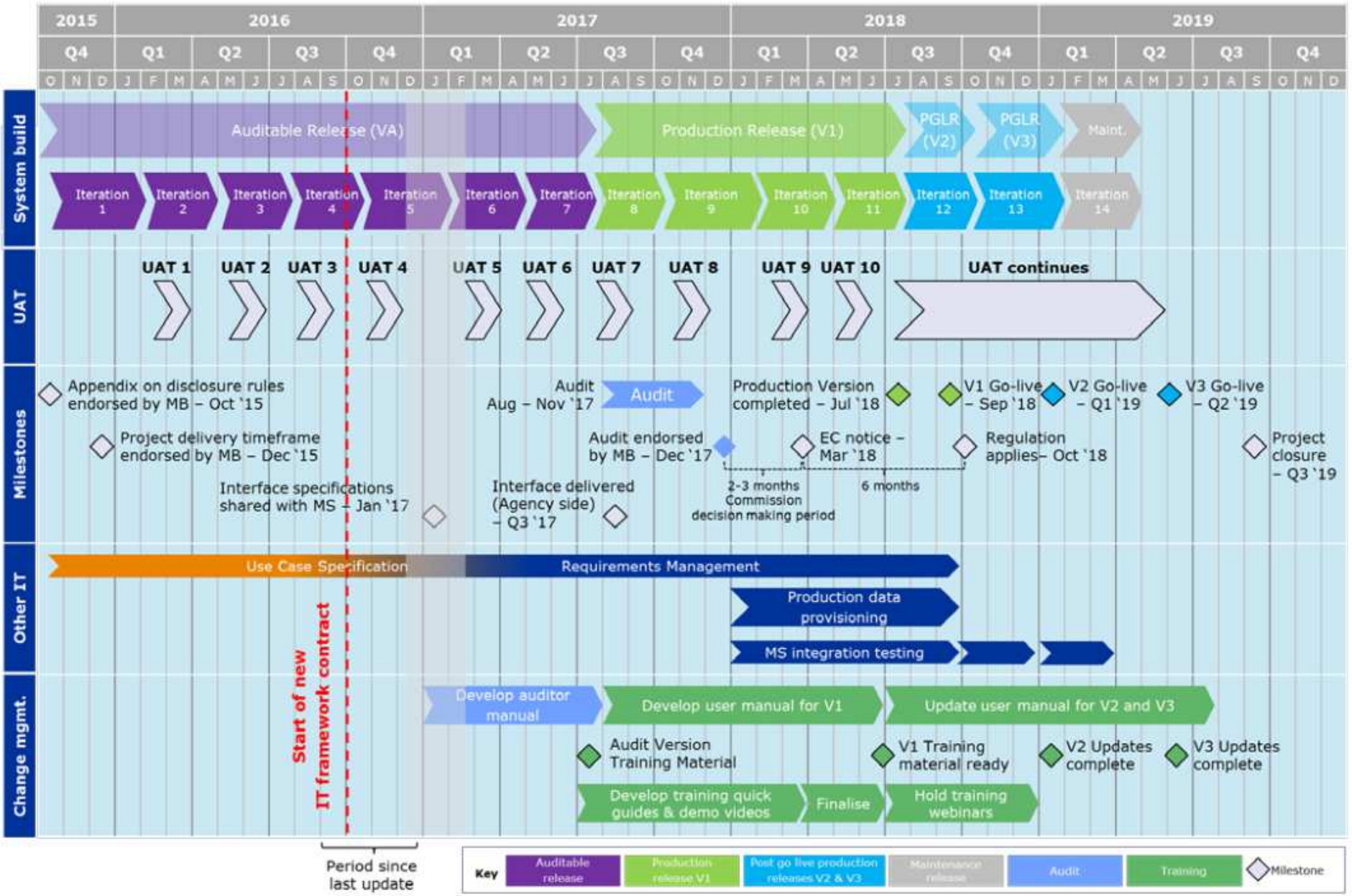
REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 16 April 2014

on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

(Text with EEA relevance)

- ✓ Replaced **Directive 2001/20/EC**
- ✓ Entered into force on **16 June 2014**
- ✓ The timing of its application depends on the development of a fully functional **EU clinical trials portal and database,**
- ✓ **The functionality of EU Portal** will be confirmed by an independent audit.
- ✓ It becomes applicable **6 months** after the European Commission publishes a notice of this confirmation.
- ✓ An initial timelines of CTR application was estimated on **2019**
- ✓ Audit of EU Portal still ongoing
- ✓ Expected delay till **March 2021?**


2015
2016
2017
2018
2019
Q4
Q1
Q2
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O N D J F M A M J J A S O N D J F M A M J J A S O N D J F M A M J J A S O N D J F M A M J J A S O N D
System build
Auditable Release (VA)
Production Release (V1)
PGLR (V2)
PGLR (V3)
Maint.
Iteration 1
Iteration 2
Iteration 3
Iteration 4
Iteration 5
Iteration 6
Iteration 7
Iteration 8
Iteration 9
Iteration 10
Iteration 11
Iteration 12
Iteration 13
Iteration 14
UAT
UAT 1
UAT 2
UAT 3
UAT 4
UAT 5
UAT 6
UAT 7
UAT 8
UAT 9
UAT 10
UAT continues
Milestones
Appendix on disclosure rules endorsed by MB – Oct '15
Project delivery timeframe endorsed by MB – Dec '15
Interface specifications shared with MS – Jan '17
Audit Aug – Nov '17
Audit
Interface delivered (Agency side) – Q3 '17
Audit endorsed by MB – Dec '17
Production Version completed – Jul '18
2-3 months Commission decision making period
EC notice – Mar '18
6 months
V1 Go-live – Sep '18
V2 Go-live – Q1 '19
V3 Go-live – Q2 '19
Regulation applies– Oct '18
Project closure – Q3 '19
Other IT
Use Case Specification
Requirements Management
Production data provisioning
MS integration testing
Change mgmt.
Start of new IT framework contract
Develop auditor manual
Develop user manual for V1
Update user manual for V2 and V3
Audit Version Training Material
V1 Training material ready
V2 Updates complete
V3 Updates complete
Develop training quick guides & demo videos
Finalise
Hold training webinars
Period since last update
Key
Auditable release
Production release V1
Post go live production releases V2 & V3
Maintenance release
Audit
Training
Milestone

15th Nov 2019 Dutch authorities have handed over to EMA its newly built tailor-made premises, located in the Zuidas area of Amsterdam!!!!!

Clinical Trials Regulation - What's new?

History of harmonization

CPMP/ICH/135/95	ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP)
2001/20/EC	EU Directive, 4 April 2001 (the Clinical Trial Directive)
2003/94/EC	EU Directive, 8 October 2003 (the GMP Directive)
2005/28/EC	EU Directive, 8 April 2005 (the GCP Directive)
536/2014	Regulation (EU) No 536/2014 on clinical trials (effective 2016 and repealing Directive 2001/20/EC)

The Clinical Trial Regulation: what is new?

EUROPEAN MEDICINES AGENCY

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

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

Published on 27 May 2014.

Application 6 months after confirmation published in the OJ of full functionality of EU portal and EU database, in any event not earlier than 28 May 2016.

Transitional arrangements.

Scope of 536/2014 Regulation

Regulation EU 536/2014 is designed to:

- Ensure that the procedures for authorization are efficient and rapid;
- Increase the uniformity of rules
- Simplify specific sponsor obligations;
- Guarantee public access to information regarding clinical trials.

Regulation EU 536/2014 applies to:

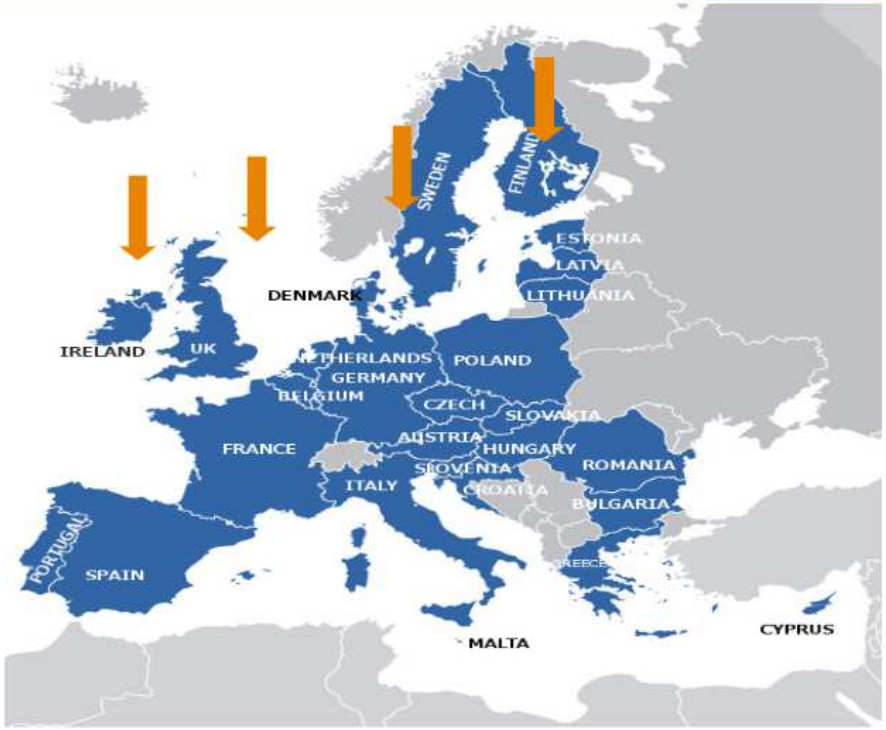
- Interventional clinical trials with medicinal products for human use
- Comercial and non-comercial Clinical trials
- New category of low-intervention clinical trials with adapted requirements

Not covered:

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

Directive versus 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.

Key changes

The regulation focuses on the difference between a study without intervention, clinical trial, clinical trial with limited intervention and a clinical study.

- ✓ Clinical Studies:
  - ✓ To discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products;
  - ✓ To identify any adverse reactions to one or more medicinal products;
  - ✓ To study the absorption, distribution, metabolism, and excretion of one or more medicinal products;
  - ✓ With the objective of ascertaining the safety and/or efficacy of those medicinal products.
- ✓ Clinical Trials (interventional studies):
  - ✓ The assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within the normal clinical practice of the Member State concerned;
  - ✓ The decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study;
  - ✓ Diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects.
- ✓ Low-intervention clinical trials – non-interventional study by design, which includes some form of additional diagnostic or monitoring procedures that carry minimal risk or impact on patients (e.g. study-specific blood draw).

Key changes

- ✓ The Regulation prescribes a precise and detailed procedure for the submission, assessment, and evaluation of requests for authorization of clinical trials (strict timelines)
- ✓ In the application dossier, the Sponsor will be required to propose one of the Concerned Member States (CMS) as the Reporting Member State (RMS) who will coordinate the validation and evaluation of the application.
- ✓ Introduce the concept of Co-sponsorship
  - ✓ Sponsor is the health center/person responsible for a clinical trial.
  - ✓ Co-Sponsors – health center/person who shares the same responsibilities unless a different arrangement is set out in a written contract.

Key changes

Informed consent - new provisions for:

- ✓ Broad consent (use of data outside the protocol)
  - ✓ Consent for further future analysis, which the patient can at any time revoke
- ✓ Simplified consent for certain cluster trials
  - ✓ Trials comparing standard (authorized) treatments, and where randomization is not for patient but for Clinical Center, will be admitted.
- ✓ For trial in minors and incapacitated subjects
- ✓ For trials on pregnant and breastfeeding women
- ✓ Special cases where, due to the urgency conditions, it is not possible to obtain ICF

Key changes

- ✓ Single e-submission to all MSCs via an EU portal (accessible to MS NCAs and Ethics Committees);
- ✓ The new EU portal and database for clinical trials with medicines will replace EudraCT
- ✓ The Clinical Trials Information System will serve as the single entry point for submitting clinical trial information in the EU.
- ✓ Harmonised dossier (Annex I to the Regulation / language of the documents decided by each MSC);
- ✓ Coordinated assessment between Reporting MS and MS Concerned;
- ✓ One single decision per Member State Concerned;
- ✓ Option to have tacit/implicit decision for the MS single decision (vs tacit approval in Dir. for NCA)
- ✓ All the information will be accessible to the public
- ✓ Clear transparency and disclosure rules

Key Changes

- ✓ Introducing a risk adapted approach by applying less stringent rules to those trials conducted with medicines which are already authorized and which pose only minimal risk compared to normal clinical practice;
- ✓ Increasing transparency as regards clinical trials and their outcomes;
- ✓ Simplifying safety reporting requirements
  - ✓ The protocol may provide that not all adverse events (AE) and serious adverse events are recorded and reported.
  - ✓ For a clinical trial involving more than one investigational medicinal product (IMP) a single safety report can be submitted in the Clinical Trial Eudravigilance database.
  - ✓ Suspected unexpected serious adverse reactions (SUSARs) can be reported via the database.
- ✓ Greater involvement of the public and patients, with the mandatory introduction of a patient into the testing team (Patient Engagement approach)
  - ✓ Member States should ensure the involvement of laypersons, in particular patients or patients' organisations in the assessment of the application to conduct a clinical trial
- ✓ Reinforcing supervision of clinical trials by introducing Union Controls in Member States and third countries to ensure that the Regulation is properly supervised and enforced;

Transparency in the CT Regulation

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

General principles for disclosure

- 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;
- 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);

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

16 March 2015
EMA/129363/2015 Final
Compliance and Inspections

Revision of section 6 of the "Functional specifications for the EU portal and EU database to be audited - EMA/42176/2014" setting out features to support making information public

What is proposed NOT to be made public?

- The IMPD quality section will not be made public as it remains commercially confidential even after the marketing authorization has been given;
- Draft assessment reports (outside the EU database);
- Names of the Member States experts (outside the EU database);
- Personal information identifying sponsor staff (protection personal data);
- Personal information identifying MAH/applicant (protection personal data);
- Direct contacts of clinical investigators, sponsors or MAH personnel (protection personal data);
- Agreements between the sponsor and the investigator site;
- SUSARs and Annual Safety Reports (outside the EU database- in EV)

Summary key of changes

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 MSC: to NCA 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

Areas not covered by CTRT
- to be regulated by local laws of the Member States

- ✓The system of ethical evaluation and organization of ECs
- ✓The scope of ethical evaluation of the application documentation
- ✓Terms of liability / insurance and compensation
- ✓Language requirements of the application documentation
- ✓Appeal procedures
- ✓Identification of the national competent authority
- ✓Finance procedures

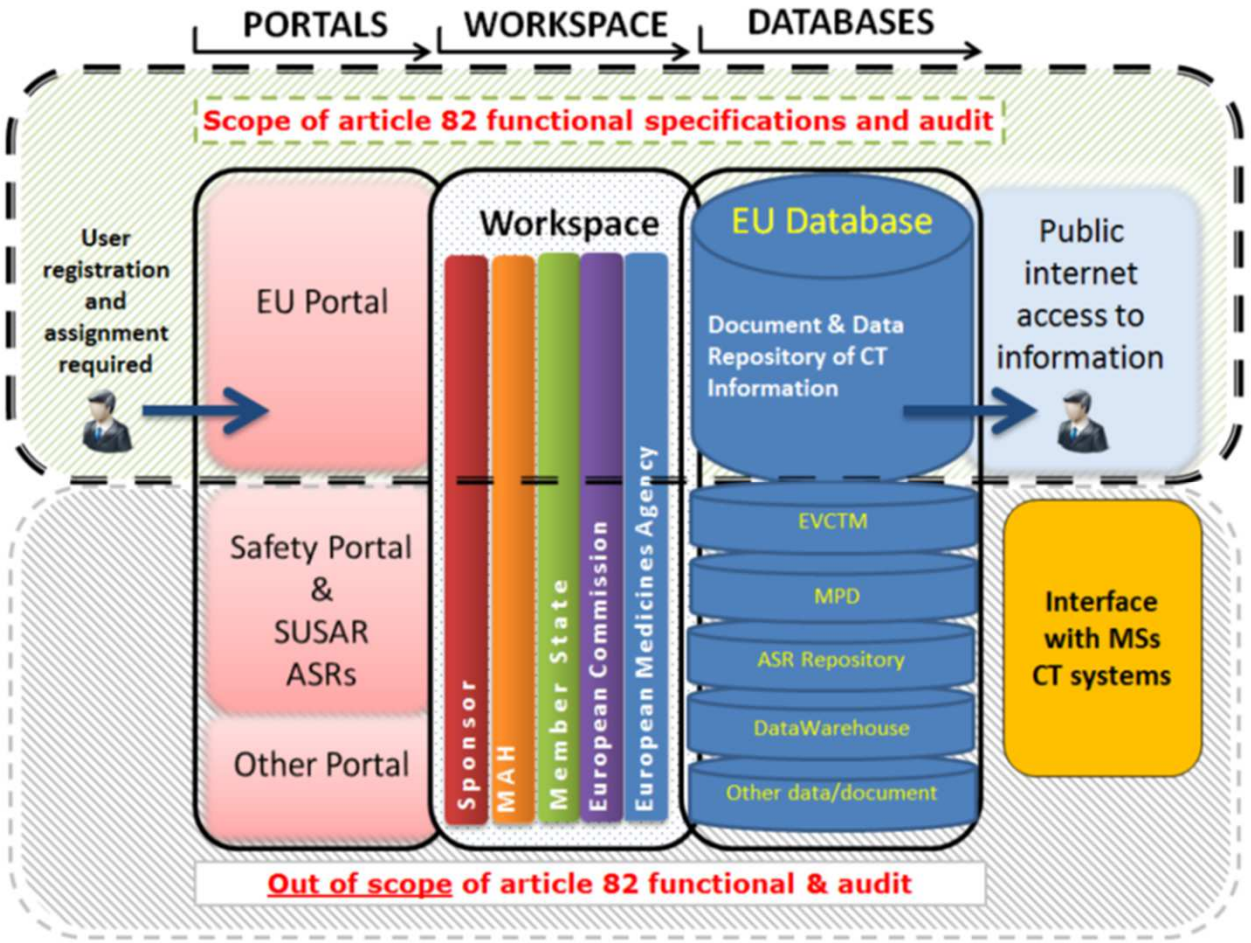
- ✓ Labeling and packaging of the medicinal product
- ✓ Provisions regarding sanctions
- ✓ Determining the legally appointed representative of persons unable to consent and minors
- ✓ Identification of the person authorized to provide information on the clinical trial and conduct the initial interview

Transition Period

Directive 2001/20/EC

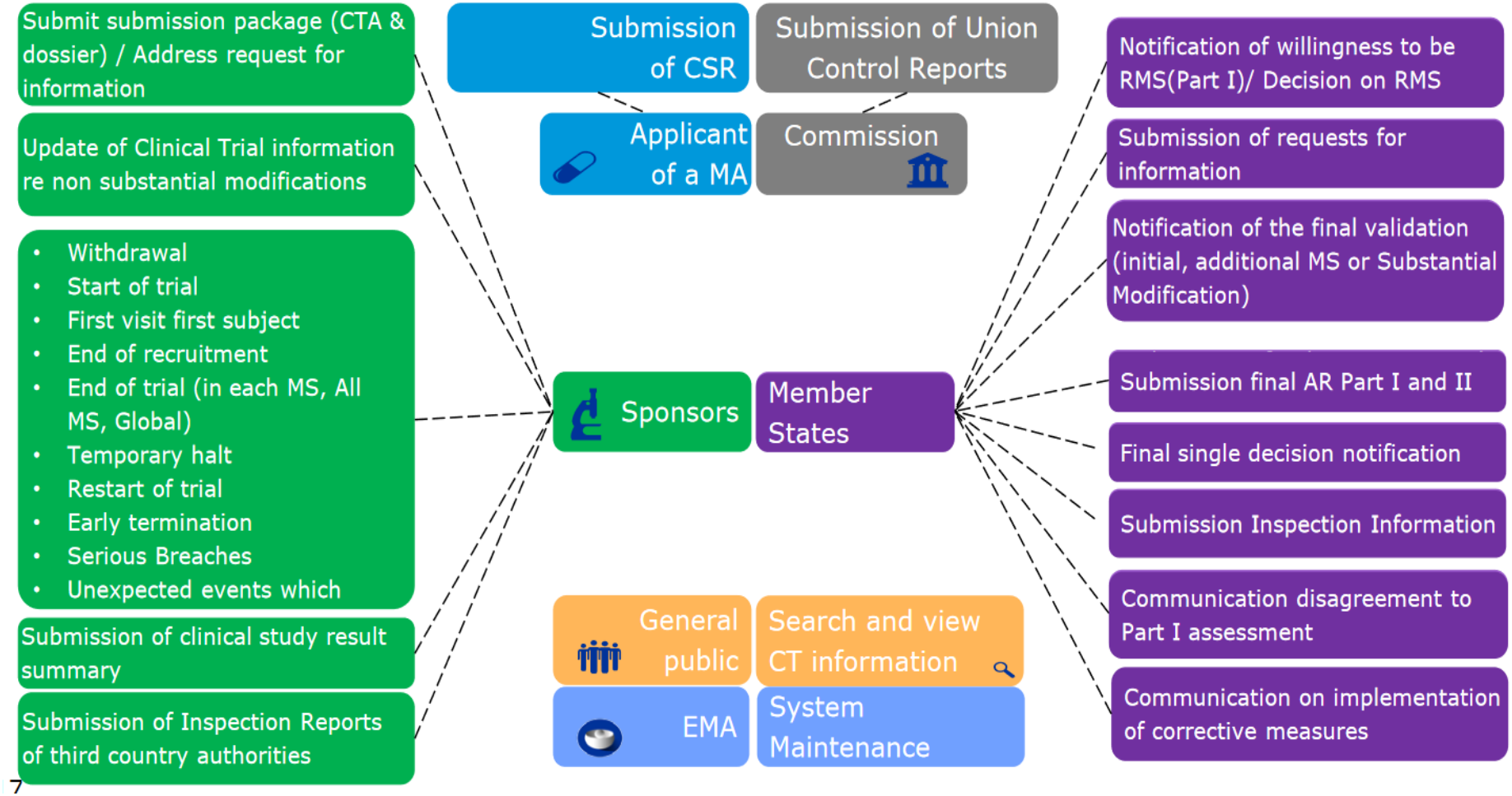
Regulation (EU) No. 536/2014

- ✓ 3 year transition period
- ✓ Starts when Regulation becomes applicable (2021?)
- ✓ First year: CT can be submitted under old (Dir.) or new (Reg.) systems,
- ✓ Years 2 & 3: trials authorized under old system remain under that system.
- ✓ End of legacy
- ✓ All CTs to switch to new Regulation 3 years after implementation.



EU Clinical Trial Portal and Databases

EU Portal and database project



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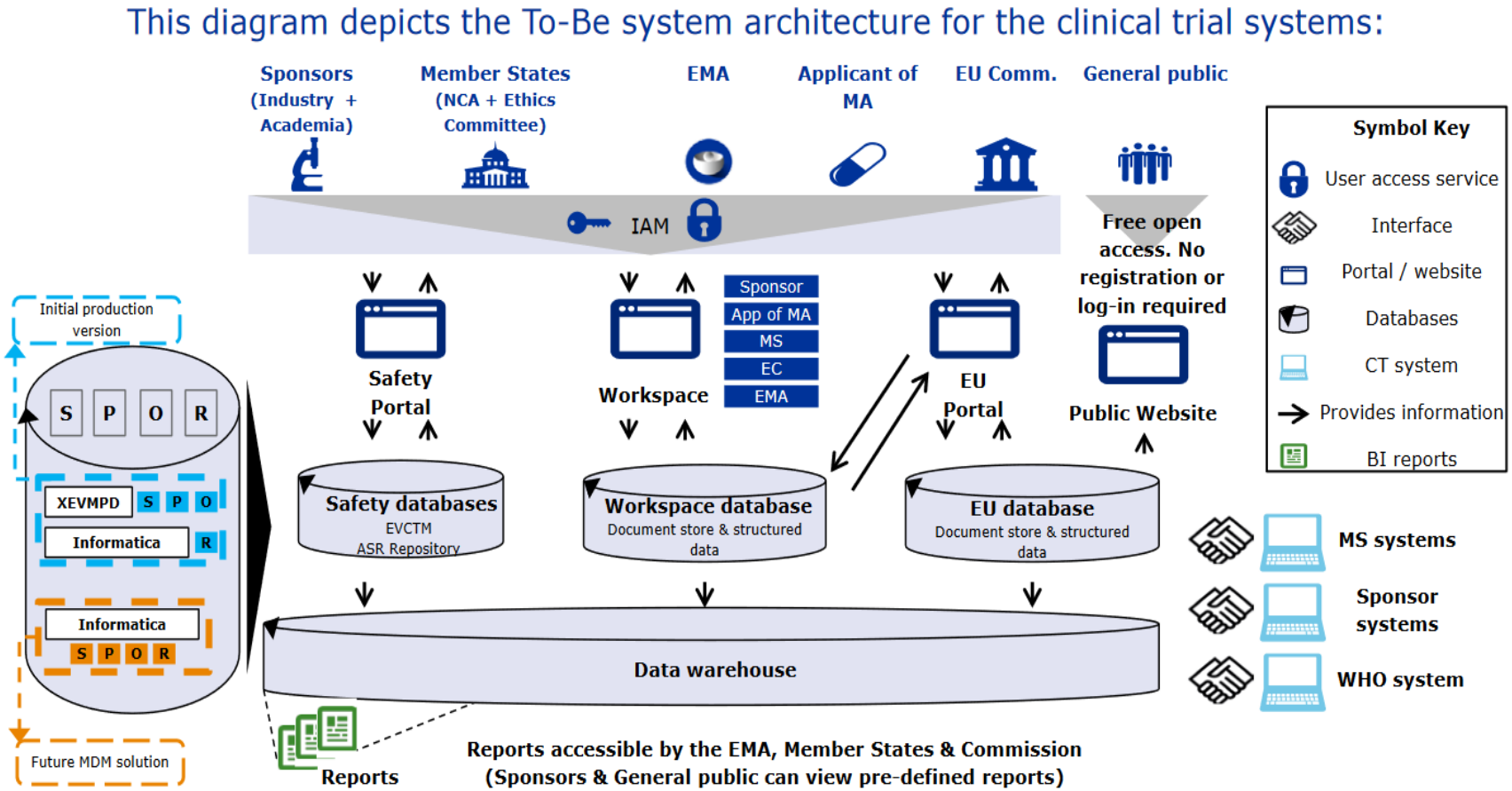
EU portal and database project – business context view



Positive Impact of the Clinical Trial Regulation

Further harmonization of clinical trials in the EU

- **Harmonised and streamlined procedures**
  - ✓ Single dossier, one single submission for authorisation of a clinical trial to National Competent Authority & Ethics Committee and for public registration (primary register of clinical trials);
- **Member state Collaboration and communication path**
  - ✓ Facilitation of Multi-State clinical trials: Joint assessment under coordination of a reporting Member State
  - ✓ Single opinion: One decision per Member States (NCA & EC)
- **Standardized IT Platforms:** EU Portal and Databases
- **E-Submission:** Submission of all documents through the new EU portal
- **Enhanced transparency:**
  - ✓ Stricter reporting obligations for sponsors
  - ✓ Public data and information about medicines, their development and authorization
  - ✓ To generate trust – information is available
  - ✓ To build confidence – I understand what is happening
  - ✓ To empower – knowledge enables decision-making
- **Acceleration of decisions:** Shorter deadlines for sponsor and Member States
- **Acceleration of availability of innovative therapies in the future**

Positive legal environment in Poland

Medical Research Agency

AGENCJA BADAŃ MEDYCZNYCH

- Plans to fund about 100 non – commercial trials within 10 years
- The main areas of research: oncology, cardiology, paediatrics, rare diseases
- Focus on research site network development and research staff training
- Educational and informational initiatives for sites and patients
- Systemic support for sites engaged in clinical research

Local Legislation changes

- New Ministry of Health Decree- joint efforts from government, CRO & Pharma experts and Patients Organizations in Poland
- Development Plan for Clinical Trials in Poland – official government policy signed by Ministry of Heath and Primary Minister
- Increasing transparency in financial obligations between Sponsors and public health providers with respect to commercial clinical trials
- New regulations regarding clinical applications- no signed contracts needed

Growing market of clinical trials

Pacjent w badaniach klinicznych

Strong Patients' voice

- Patient engagement in educational initiatives

www.pacjentwbadaniachklinicznych.pl

- Active patient involvement in legal changes
- Patients actively seeking clinical trials
- Patient centricity models in clinical research

Open dialog between all stakeholders

- Enhanced communication and cooperation- public campaigns in media, meetings for patients, medical professionals, etc.
- Engagement of experts from MH, NHF, MRA, RA, IEC, CRO, Pharma and Patients Organizations

EUPATI Conference , Brussels 2016

Jan Geissler, EUPATI Director,
EPF (European Patients Forum)

Please contact me in case of any questions

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