Clinical research: where are we with the new (Paediatric) RC trial Regulation

Hugo Devlieger, MD, PhD
Ethical Committee DEEP
Former member of the PDCO EMA
With the aid of Fabio D'Atri European commission
and Anabela Marcal of EMA

The new CT Regulation

- *On 16 April 2014 a new Regulation N°536/2014 of the European Parliament and of the Council on MP for human use was adopted, repealing Directive 2001/20/EC.*
- *It entered into force on 16 June 2014 but will apply no earlier than 28 May 2016*
- *The regulation **applies to all clinical trials** conducted in the EU, this means any clinical study for which the assignment of a subject to a particular therapeutic strategy is decided in advance and that does not fall within normal clinical practice . The regulation **does not apply to non-interventional studies** e.g ADME studies or phase 1 studies and **studies with other than medicinal products** (devices, surgery etc..)*

REGULATION VERSUS DIRECTIVE

- "a directive is a legislative act that sets out a goal that all EU countries must achieve.
- “a regulation is a binding legislative act. It must be applied in its entirety across the EU.”

Why a new CT Regulation?

*The **Clinical Trial Directive (2001/20/EC)** has ensured high level of patient safety,*

but

- *Was **divergently transposed and applied** in the different Member States*
- *ICREL study on the impact of the Directive 2008*
- *It was concluded that it was **unfavourable regulatory framework** for clinical research, thus contributing to a decrease of 25% of clinical trials conducted in the period between 2007 and 2011: in 2007, more than 5000 clinical trials were applied for in the EU while by 2011 the number had dropped to 3800.*

Trends since Directive 2001/20/EC as shown by ICREL „*Impact on Clinical Research by European Legislation*“

- Increase of delay of start of trial: 90%;
- Increase of sponsors's resource needs to handle CT authorisation process: 107%;
- Increase in administrative costs: 98%;
- Increase in costs for insurance fees: 800%, in particular for non-commercial sponsors;
- 25% decrease CT in the EU in the last 5 years;
- Divergent transpositions/implementations in MSs.

Objectives of the new Regulation

- A modern regulatory framework for submission, assessment and regulatory follow-up;
- Addressing the global dimension of clinical trials.
- Overall objective: Make EU attractive for R&D

The new CT Directive: key points

- An **authorisation procedure for clinical trials** which will allow for a fast and thorough assessment of the application by all Member States concerned and which will ensure one single assessment outcome.
- **Simplified reporting procedures** which will spare researchers from submitting largely identical information on the clinical trial separately to various bodies and Member States.
- **More transparency** on whether recruitment for participating in a clinical trial is still ongoing, and on the results of the clinical trial.
- The possibility for the **Commission to conduct controls in Member States and other countries** to make sure the rules are being properly supervised and enforced.

Definitions

- **Clinical trial:**
  - Assignment to therapeutic strategy, not falling within normal practice, is decided in advance
  - Decision to prescribe IMP is taken together with the decision to include the subject in a CT
  - Diagnostic and monitoring procedures in addition to normal clinical practice are applied
- **Low-intervention clinical trials:**
  - IMP is authorised and used according to the MA **or**
  - The use of IMP is **evidence-based and supported by scientific evidence** on safety and efficacy
  - The diagnostic and monitoring procedure does not pose more than minimal risk as compared to normal clinical practice

Clinical trial application

- Each clinical trial should be subject to **prior authorisation** to preserve the rights, the dignity and well being of subjects.
- Each clinical trial should be submitted through a central EU portal.
- In case of clinical trials involving multiple member states one application dossier to a single EU submission portal should be introduced.

Authorisation procedure

3 steps:

- Validation (10 days)
- Assessment (45 days)
- Decision (5 days)

Clinical trial application: timing of validation

- D0: submission of an application dossier by the sponsor to the intended member states through the EU portal. The sponsor propose one of the MS as reporting MS. This MS should notify its acceptance within 6 days through EU portal.
- If the MSs do not agree about the reporting MS, it should be notified through the EUportal within 3 days.
- Within 10 days the reporting MS has to validate the submission taking into account considerations expressed by the other member states (within 7 days) and notify the sponsor whether:
  - It falls within the scope of the regulation or not
  - the dossier is complete

Authorisation procedure – Assessment

The Regulation defines elements that:

- Have to be assessed jointly by concerned MSs (part I);
- Have to be assessed independently by each concerned MS (part II) – national/local elements.

Assessment (part I)

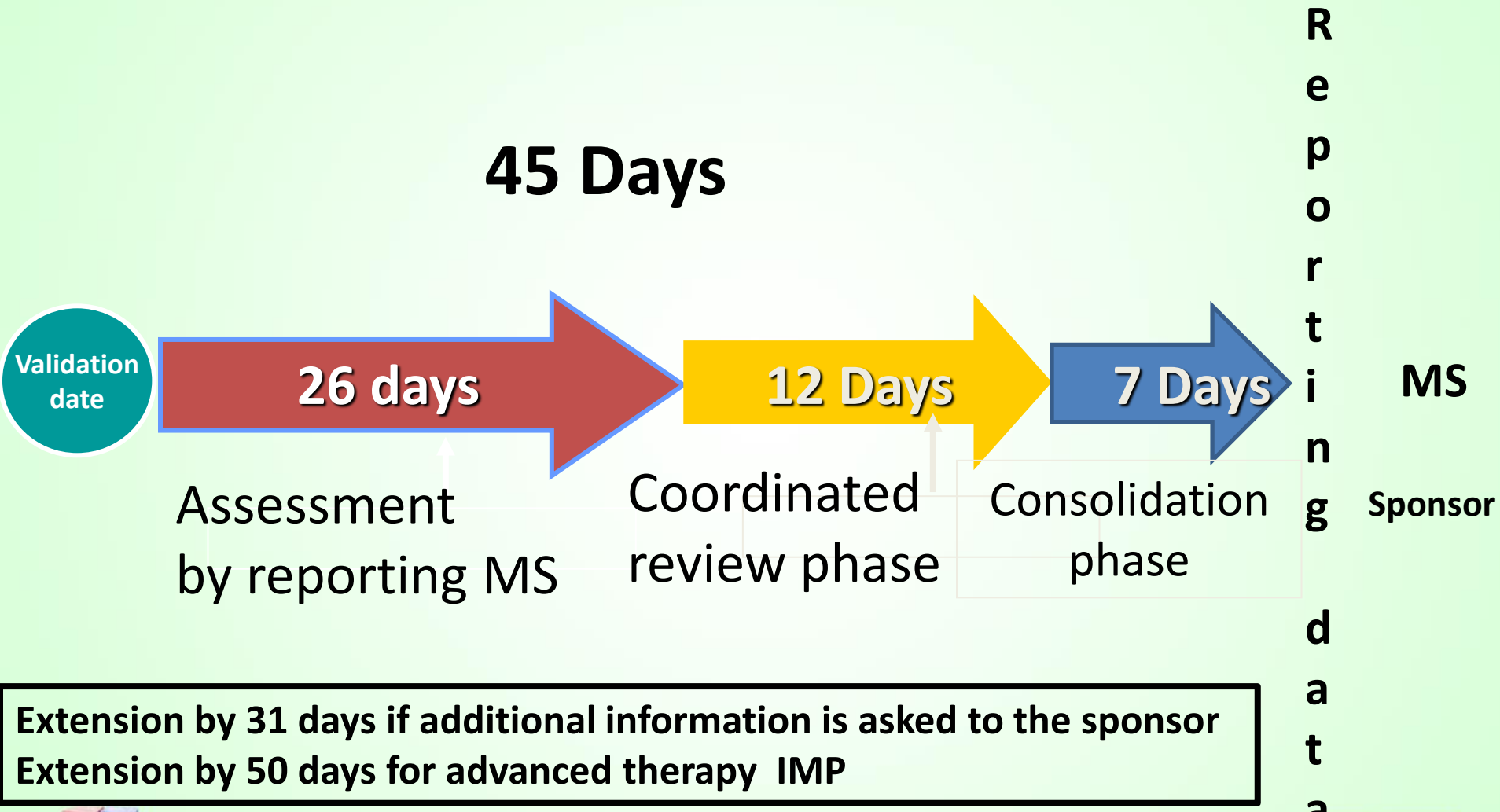
- The reporting MS interacts with the concerned MSs, collects their remarks and asks for clarifications to the sponsor.

- The reporting MS in collaboration with the concerned MS drafts an assessment report on part I.

Assessment report part I by the reporting MS

- Low-intervention CT or not as claimed by the sponsor?
- Compliant with respect to:
  - Anticipated therapeutic and public benefit in terms of knowledge about IMP, relevance of the CT and reliability and robustness of data generated.
  - Acceptable risks and inconvenience as compared with the normal clinical practice and appropriate safety measures, and monitoring taking into account the subject's health posed by the medical condition.
  - Labelling requirements
  - Completeness and adequateness of the investigator's brochure

Timing of the assessment report part I



Extension by 31 days if additional information is asked to the sponsor
Extension by 50 days for advanced therapy IMP

Assessment (part II)

- Each MS prepares independently a report on the national/local elements covered by part II.

- This assessment is carried out in parallel with the assessment of part I.

Assessment report part II

- Each MS concerned shall assess the application with respect to compliance :
  - with requirements for informed consent
  - With arrangements for rewarding or compensating subjects with arrangements for recruitment of subjects
  - With rules for the collection storage and future use of biological samples.
- Each member state has 45 days to send its assessment through the EU portal. This can be extended with 31 days if additional information is needed (12 days for the sponsor, 19 days for the MS).

Decision on the clinical trial

- Each MS notify to the sponsor within 5 days from the reporting date:
  - Authorised
  - Authorised under condition
  - Refused
- When a MS disagrees this should be done through EU portal with detailed justification.
- When the reporting MS conclude as regard part 1 that the trial is not acceptable that conclusion is for all the MS concerned

Authorisation procedure - decision

- Each MS takes a single decision on the conduct of a CT on its territory.
- The decision is composed of conclusions of the assessment of

➢ Part I (possibility for justified 'opt-out' of concerned MS)

- and

➢ Part II

Authorisation procedure - decision

- Refusal:
  - if part I negative,
  - if opt out used,
  - if assessment of part 2 negative,
  - if a “national” Ethics Committee has issued a negative opinion.

- MS shall set up an appeal procedure.

- If trial not started within 2 years authorisation expires.

Ethics committees

- Their role in the assessment and composition follows national rules.
- They will have to work within the given procedures and timelines.
- They have to take into account the views of lay persons (in particular patients/patients' organisations).
- In case of negative opinion by a "national" ethics committee a trial cannot be authorised.

Subsequent addition of a MS

- The sponsor shall submit an application dossier to that MS through the EU portal only after the notification of the initial authorisation decision
- The additional MS has 52 days to notify the sponsor through the EU portal by way of a single decision.

Additional Rules for :

- Authorisation procedure for a substantial modification of the clinical trial part I and Part II
- Content of the Application dossier
- Protection of subjects and informed consent
- Informed consent in cluster trials
- CT on pregnant and breastfeeding women
- CT in emergency situations

Clinical trials in children (minors)

New CT regulation stipulates that CT in minors may be conducted only when:

- the informed consent of their legally designated representative has been obtained;
- the minors have received the information in a way adapted to their age and mental maturity and from investigators or members of the investigating team who are trained or experienced in working with children;
- the explicit wish of a minor who is capable of forming an opinion and assessing the information to refuse participation in, or to withdraw from the clinical trial at any time, is respected by the investigator;
- no incentives or financial inducements are given to the subject or his or her legally designated representative except for compensation for expenses and loss of earnings directly related to the participation in the clinical trial;

New CT regulation stipulates that CT in minors may be conducted only when:

- the clinical trial is intended to investigate treatments for a medical condition that only occurs in minors or the clinical trial is essential with respect to minors to validate data obtained in clinical trials on persons able to give informed consent or by other research methods;
- the clinical trial either relates directly to a medical condition from which the minor concerned suffers or is of such a nature that it can only be carried out on minors;
- there are scientific grounds for expecting that participation in the clinical trial will produce:
  - a direct benefit for the minor concerned outweighing the risks and burdens involved;
  - some benefit for the population represented by the minor concerned with minimal risk or burden in comparison with the standard treatment of the minor's condition.

Legal Framework for clinical trials in Children in Europe up to 2014

Directives

- 1997: The Council of Europe: Convention for the protection of Human Rights and Biomedicine (Oviedo Convention) and the Additional Protocol on Biomedical Research (2005)
- Directive 2001/20/EC related to good clinical practice in the conduct of clinical trails on medicinal products for human use (2004)
- Paediatric regulation (2006)

Guidelines

- ICH guidelines E6 (GCP)
- ICH guidelines E11 (Paediatric)
- Ethical considerations on clinical trials with the paediatric population (EMA 2008)
- Draft Guide for the Research Ethics Committee members (2009)
- Reflection paper on ethical and good-clinical –practice aspects of clinical trials of MP for human use conducted outside of the EU and submitted in MA applications to the EU regulatory authorities (16/4/2012)

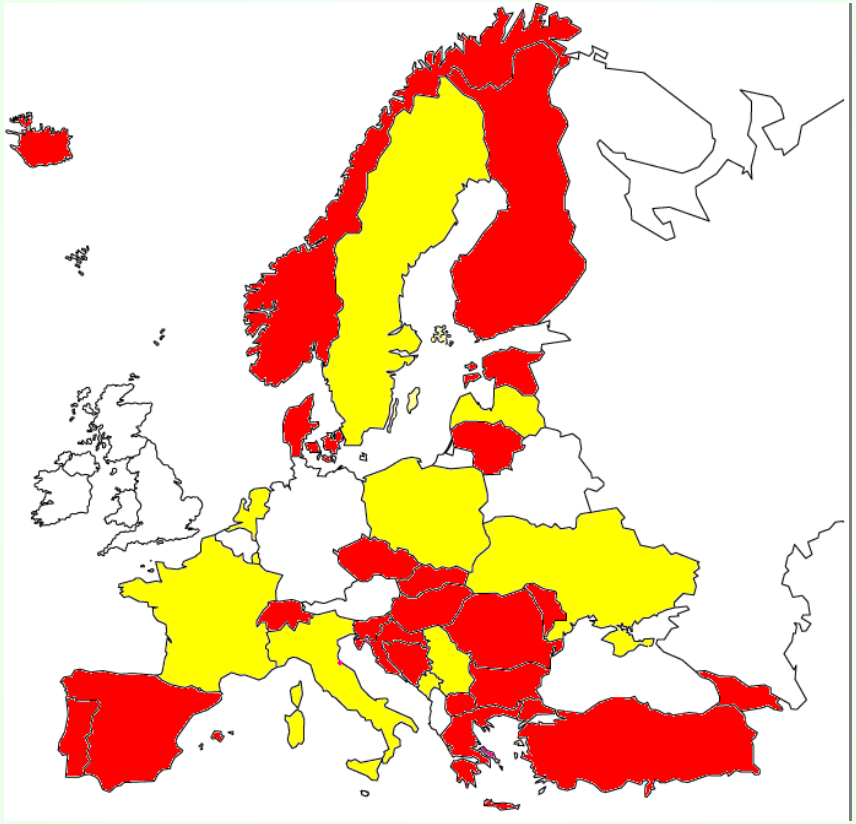
Actual Legal Framework for clinical trials in Children in Europe

A. Paediatric framework before CT-Dir
B. Directive 2001/20/EC
C. Oviedo convention ratification or signed
D. Ethics Committee's devoted to minors
E. Paediatric consent procedure different from Directive provisions
F. Specific provisions ensuring respect of minor's refusal to participate in clinical trial
G. Specific rules ensuring that minor's opinion increasingly carry more weight in the final decision (age limits)

COUNTRY	A	B	C	D	E	F	G
Austria	√	√					
Belgium		√					
Cyprus		√	√				
Czech Republic		√	√				
Denmark		√	√		√		15–17 years
Estonia	√	√	√		√		7–17 years
Finland	√	√		√	√	√	
France	√	√			√	√	
Germany	√	√			√	√	
Greece		√	√				
Hungary	√	√	√				
Iceland		√	√				
Ireland		√					
Italy	√	√		√			
Latvia		√					
Liechtenstein		√					
Lithuania	√	√	√				
Luxembourg		√					
Malta		√					
Netherlands	√	√		√	√		12 years
Norway	√	√	√				
Portugal		√	√				
Slovakia	√	√	√	√			
Sweden	√	√					
Spain	√	√	√		√		12 years
Switzerland				√			
United Kingdom		√					

TEDDY Survey Altavilla et al. 2009

Actual Legal Framework for clinical trials in Children in Europe



Convention on Human Rights and Biomedicine (Oviedo)
Signatures **Ratifications**
updated 15/01/2010

Assent from children from 3 years

Assent from school age children

- Risk and benefit can be understood from the age of 9 but most children are unlikely to understand randomisation as are some parents.
- From school age the assent can be written
- Children with chronic illness have developed increasing capacity in understanding

ETHICAL CONSIDERATIONS FOR CLINICAL TRIALS ON MEDICINAL PRODUCTS CONDUCTED WITH THE PAEDIATRIC POPULATION

Recommendations of the ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use

- Informed consent
- Assent from children, binding?
- Design of the trial, phase I, phase II, PK
- Paediatric control groups: placebo or active comparator
- Pain, distress, and fear minimisation
- Risk/benefit assessment
- Assays in relation to age/body weight and blood sampling
- Trials in healthy children
- Paediatric formulation
- Publication of paediatric clinical trials and results
- Availability of data
- Adverse reactions and reporting
- Inducement versus compensation for children
- Insurance issues
- Trials in non-EU countries and developing countries
- Non-compliance with GCP

Notification of start and end of recruitment of subjects, and of results

- Notification within 15 days after the start or the end in relation to that MS through the EU portal
- Irrespective of outcome of CT, the sponsor shall submit the summary of the results within one year of the end of the CT, except when a longer delay is justified in the protocol.

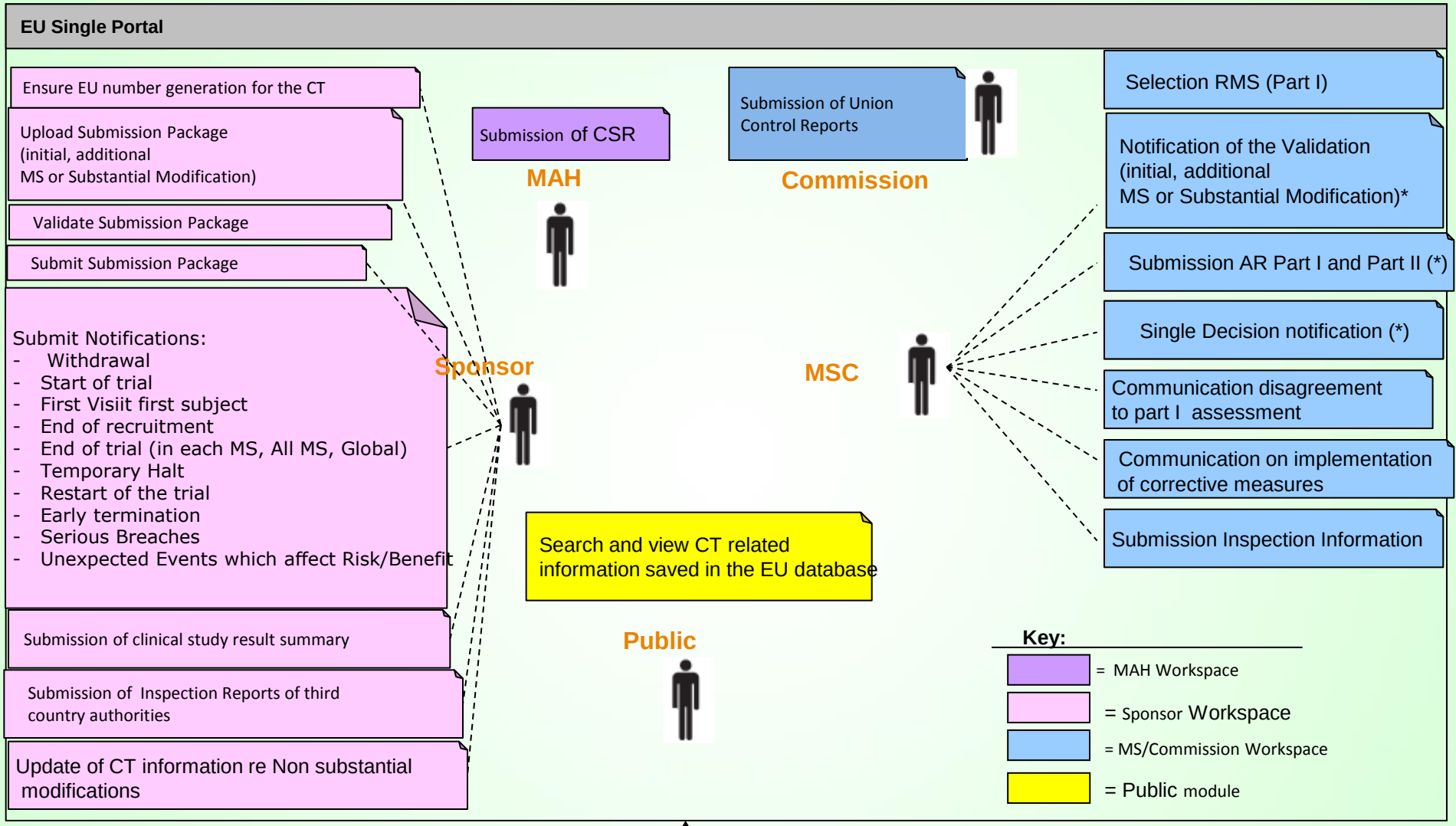
Electronic database for Safety reporting

- Ema shall set up a electronic database: “Eudravigilance database”
- The investigator shall record and document all adverse events-the investigator shall report SAE to the sponsor no later than within 24h
- When relevant, the investigator shall send a follow up to the sponsor to allow the sponsor to assess the impact on the benefit-risk balance of the clinical trial.
- The sponsor shall report electronically and without delay to the Eudravigilance Database
- An annual reporting by the sponsor to the EMA
- EMA forward to the MS, who assess the AE with involvement of the Ethics Committee

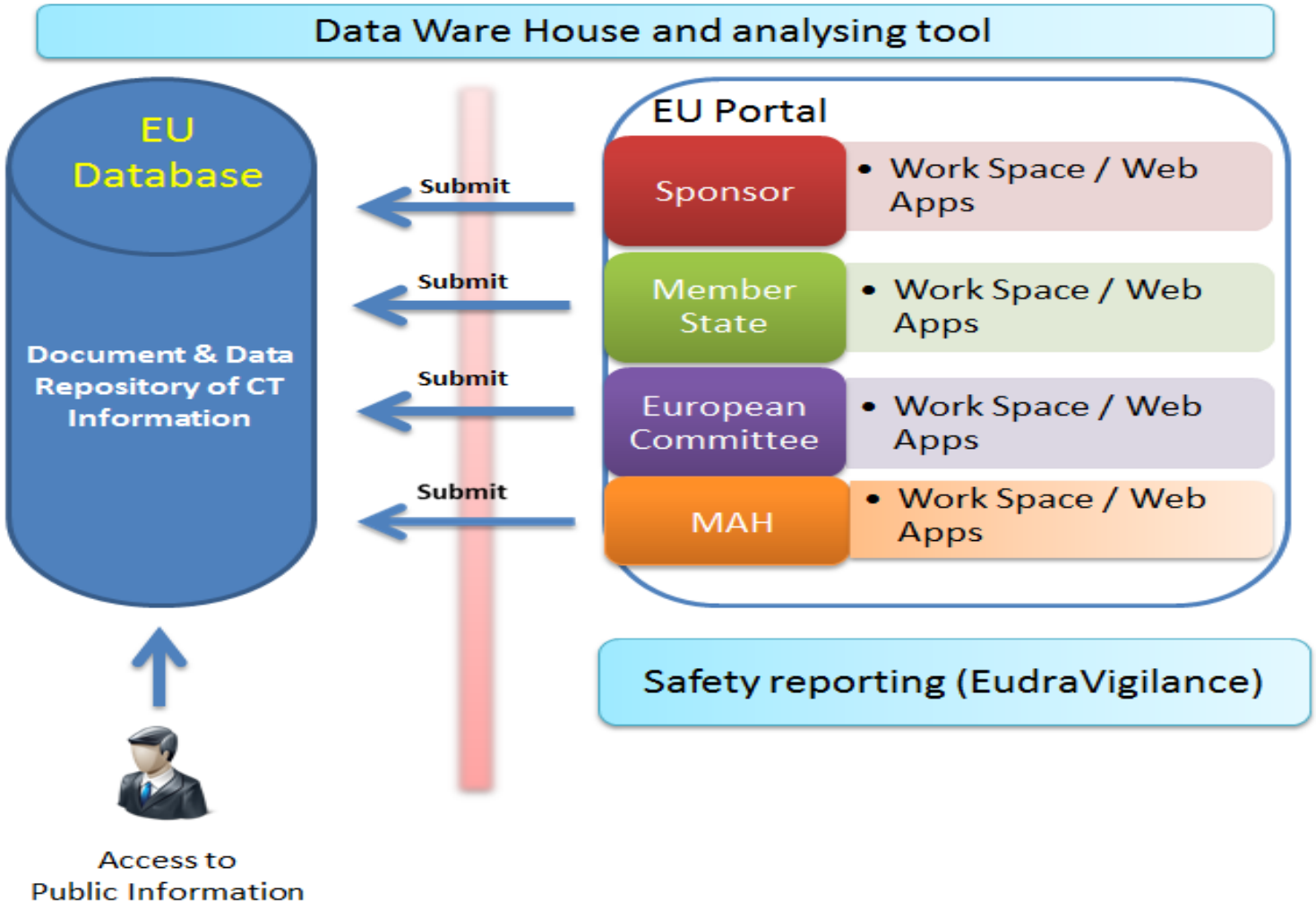
The EU Database – the EU portal

- Will contain all the data and information submitted in accordance with the new CT regulation and all data and information of CT submitted in accordance with the former Directive 2001/20/EC.
- It will contain as a Medicinal Product Dictionary the data contained in the Eudravigilance database
- The EU database shall be publicly accessible unless confidentiality is justified

EU Portal and EU Database (courteously by Anabela Marcal , EMA)



Clinical trial systems (courteously by Anabela Marcal , EMA)



EudraCT

- A European database - EudraCT - contains all ongoing or completed clinical trials falling within the scope of Directive 2001/20/EC, i.e. with at least one investigator site in the EU (incl. the European Economic Area) and commencing after implementation of Directive 2001/20/EC by the Member States. This database gives the competent authorities of the Member States, the EMA and the Commission the necessary information to communicate on clinical trials and to maintain oversight of clinical trials and IMP development.

Transparency of information related to clinical trials

- Union legislation provides that certain information contained in EudraCT is to be made accessible to the public. This public accessibility concerns clinical trials with paediatric as well as non-paediatric participants. It encloses protocol-related information and result-related information. And it covers both negative and positive results.
- With regard to **protocol-related information**, this information is public under clinicaltrialsregister.eu, which is part of the public database EudraPharm.
- With regard to **result-related information**, this information is presently not contained in EudraCT at all.

Conclusions

- The new CT regulation is a major progress to promote multicentre trials between different MS in Europe
- Its binding character will lead to more uniformity in the interpretation and execution of the prescriptions concerning CT
- The fact that the Paediatric CTs have been compliant with the “Paediatric regulation” and the guideline on “Ethical considerations on clinical trials with the paediatric population (EMA 2008)” makes that paediatric trials were the forerunners of this new CT regulation
-


THANK YOU