Clinical Trial Data Transparency

Environment & Expectations

EMA Policy - Clinical Trials Regulation

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Overview

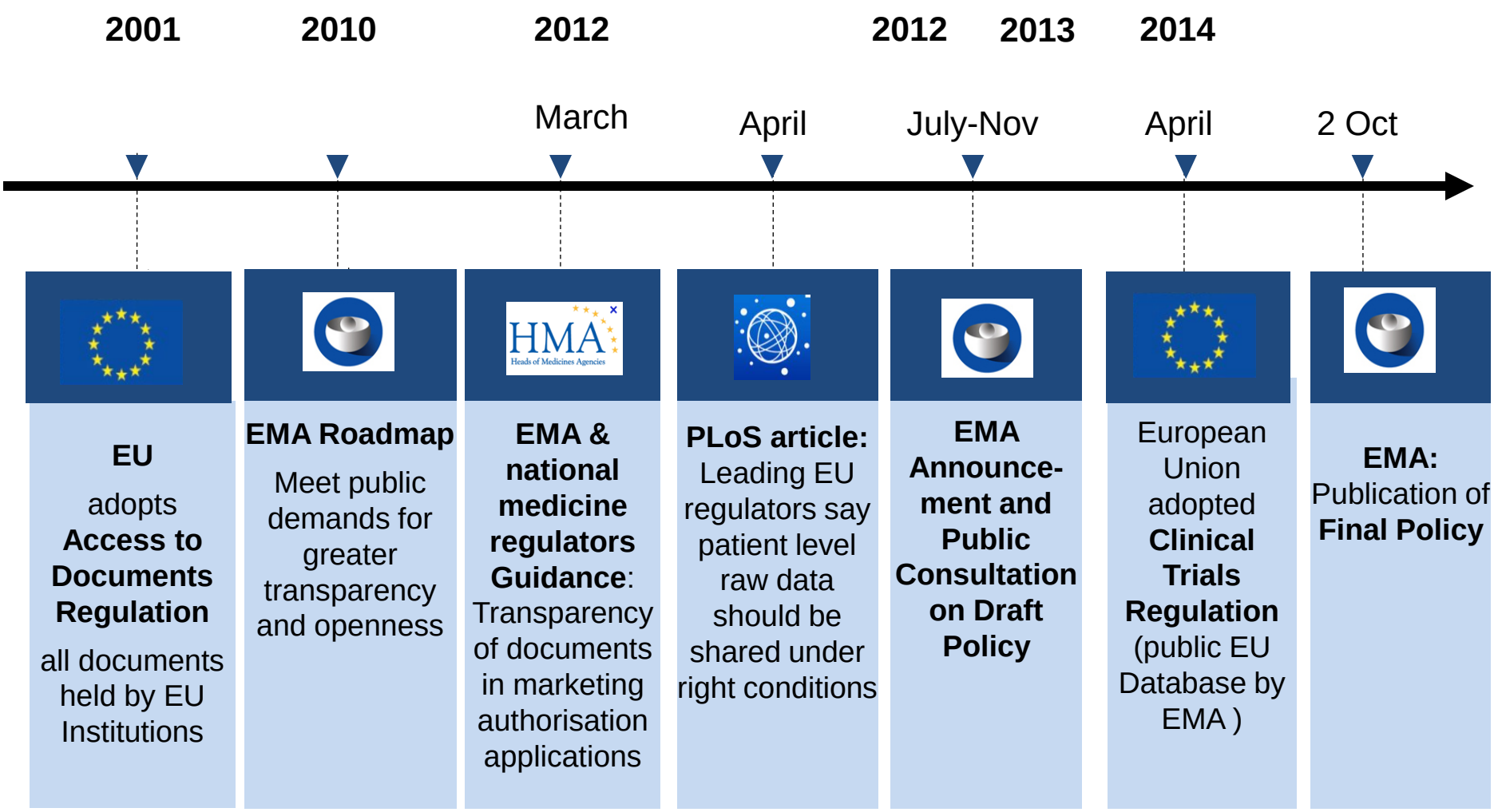
1) Context – EU Transparency Roadmap
2) Transparency Measures by European Medicines Agency (EMA)
3) Clinical Trials Regulation
4) Industry Commitments

1) Context – EU Transparency Roadmap

Background - EU Legal & Political Environment

- EU Treaty calling for more openness in all policy areas
- **Access to documents Regulation (EC) 1049/2001**
  - Relevance for all EU Institutions and Agencies
  - Applies to all documents submitted to/ generated by them
  - Any person in EU can request documents
  - Documents must be released unless they contain
    - commercially confidential information (CCI)
    - protected personal data (PPD)
- European Ombudsmann – several decisions and interventions in debate by EMA
- EMA under pressure for more transparency

Context - Transparency Activities – EU Roadmap



2) Transparency Measures by EMA

EMA – Key elements of Transparency Framework

1) **Access to documents Regulation (2001)**

2) **EMA Roadmap and Policies**
   - Roadmap 2010-2015
   - EMA/HMA Gudiance from 2012
   - New EMA Policy on Publication of Clinical Data (2 Oct 2014)

3) **Clinical Trials Regulation (EU) 536/2014**
   - Adopted in April 2014, published in May 2014
   - EMA responsible for set up and maintenance of EU Portal/ Database
   - Will become applicable with the confirmed functionality of the EU Portal/ Database (earliest mid 2016)
   - Specific Transparency provisions included

Access to Clinical Trial Data under different Schemes (1)

	EMA Access to Docs Policy (AtD)	New EMA Policy	Clinical Trials Regulation CTR
Type of documents	**Documents submitted as part of MA application** (incl. CSRs)	*Step 1* – **Clinical Reports** - Clinical overviews - Summaries - CSR & selected Annexes (Protocol, sample CRF, Statistics) *Step 2* – **patient data IPD** (deferred)	**Documents submitted to EU Portal** (e.g. application dossier CSRs, summary results, layfriendly summaries, assessment reports for CT)
Application	**Legacy data**	**Prospectively** CT Data submitted as part of - new MA (Art. 58) application as of **Jan 2015** - of extension of indications/ line extensions as of **Jul 2015**	**Prospectively** Submissions of CTs and results as of application date: **expected mid 2016**
Release of CSR	**Immediate** (already applied)	**Earliest upon approval of product, i.e. mid 2016** (150-210 days after submission)	**Earliest upon approval of product, i.e. 2019** (150-210 days after submission)
Scope	studies in **EU and**	studies in **EU and non-EU**	Studies in **EU only**

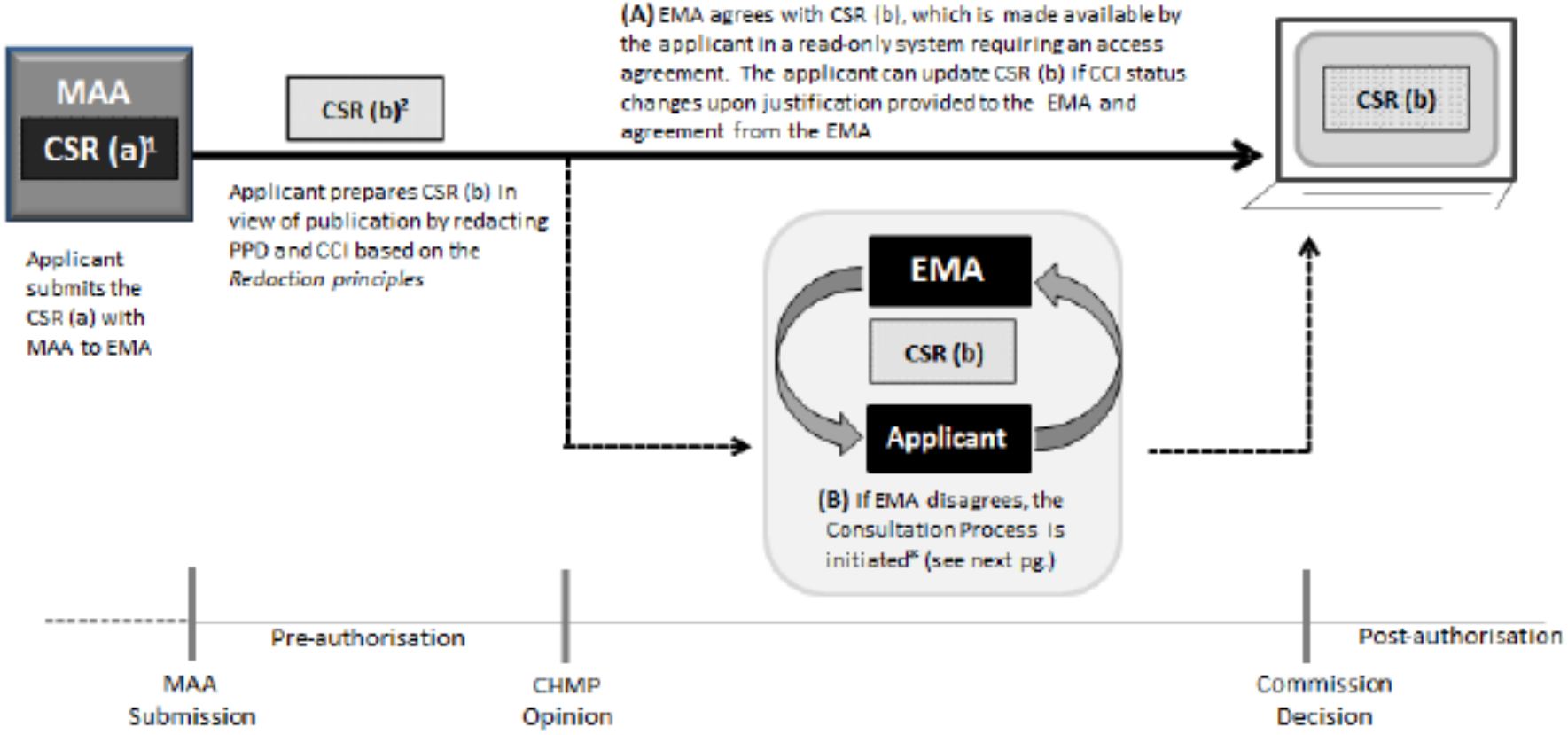
Access to Clinical Trial Data under different Schemes

	EMA Access to Docs Policy (AtD)	New EMA Policy	Clinical Trials Regulation CTR
Requester	ID needed: based in EU ID will only be released upon agreement by requester	Simple access: undefined Downloads: ambiguous but ID with adress in EU No release of requester ID	Open - tbd
Redaction for Personal data (PPD) Commercially Confidential Information (CCI)	PPD - by EMA CCI - by companies	PPD - to be determined CCI - by EMA after consultation with companies (specific process) Parallel submission of full and redacted version.	PPD and CCI: process and criteria currently being discussed (EMA consultation by 03/2015 planned)
CCI Criteria	New EMA policy will have repercussions on CCI definitions	**Defined in new policy:** Categories which may be CCI	New EMA policy will have repercussions on CCI definitions
Publication process	Paper copies/ pdf	**On screen only** for general info purpose Simple registration process **Downloadable info** for research purposes	To be determined (stakeholder discussion ongoing)

Access to Clinical Trial Data under different Schemes (3)

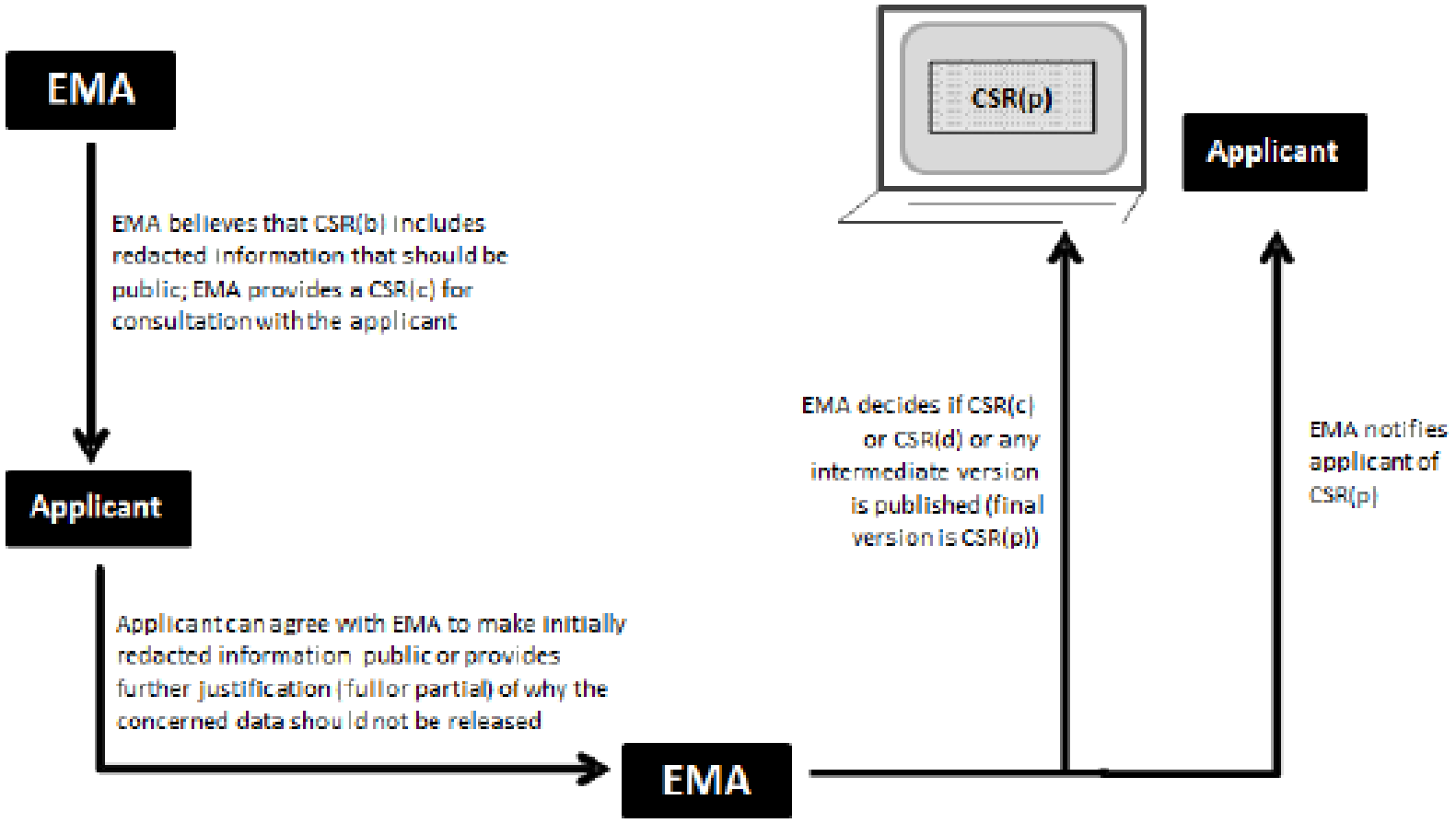
	EMA Access to Docs Policy (AtD)	New EMA Policy	Clinical Trials Regulation CTR
Conditions	**No Terms of Use**	**Different Terms of Use (ToU) for** **1)General information purposes** – simplified access **2)Use for academic and other non-commercial research** - downloads	**No terms of Use foreseen in legislation**, access under discussion by EMA and stakeholders
		User shall/may not - seek re-identification of subjects - use CR to support an application - make any unfair commercial use - (…)	
		No enforceability of ToU by EMA (MAH responsibility) Jurisdiction: Courts of England and Wales	

EMA - Process for publication of clinical reports



1. CSR (a) = CSR in accordance with EMA guidance (1995 and 2004)
2. CSR (b) = CSR available under the EMA policy

EMA – Consultation Process with Applicants



3) New EU Clinical Trials Regulation (CTR) – (EU) 536/2014

HTTP://EUR-LEX.EUROPA.EU/LEGAL-CONTENT/EN/TXT/PDF/?URI=CELEX:32014R0536&FROM=EN

From Directive to Regulation – In a nutshell…

- **Single submission of a CT dossier**
  containing a scientific part and a national part to the new EU Portal/Database

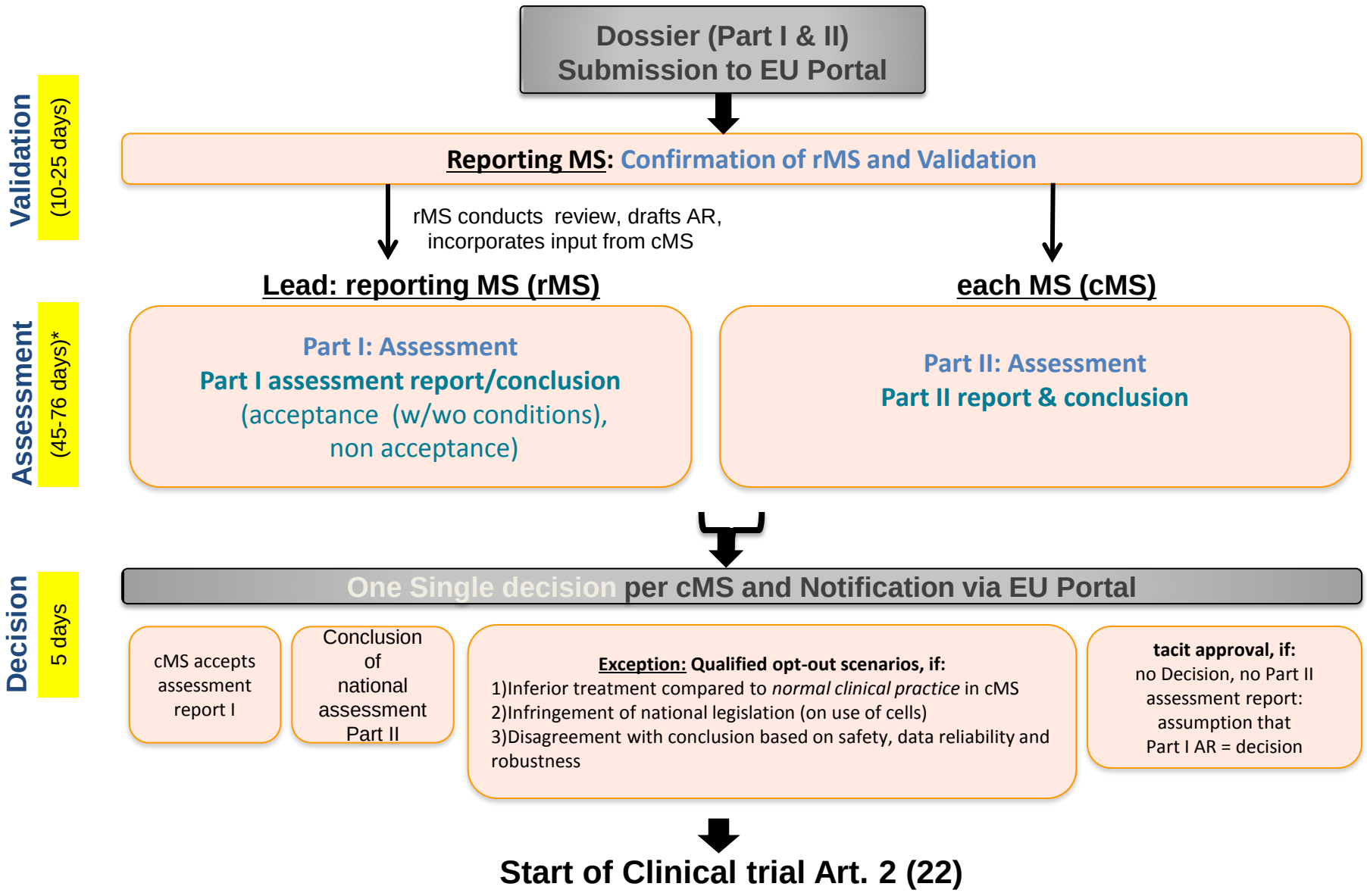
- **Single CTA Assessment –**
  - scientific aspects (Part I): reporting Member States(which can be proposed by the sponsor) coordinates joint assessment by the countries involved in the trial
  - national aspects (Part II): assessment by each country in parallel.
  - Of note: Member States organise and coordinate review by authorities and ethics committees (→ need to revise national laws)

- **Single CT authorisation for each participating EU country**
  based on the common scientific assessment by concerned EU competent authorities[HA] and review by ethics committees[EC]

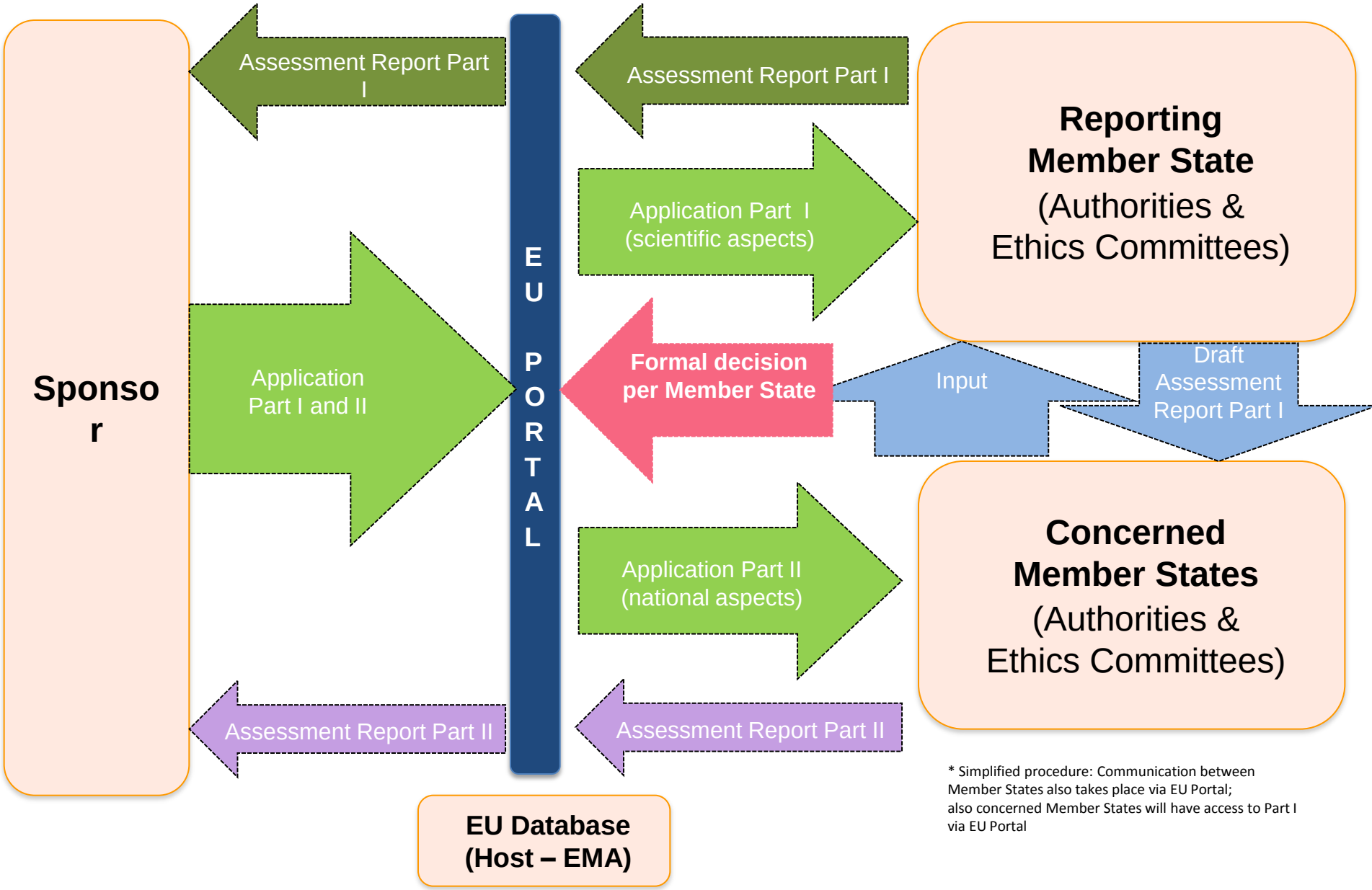
- **Single Safety reporting** streamlined and simplified via EudraVigilance for all participating countries

- **Transparency:** EU Portal/EU Database information will be made publicly available unless confidentiality is justified on defined grounds

CT Authorisation Process (simplified)

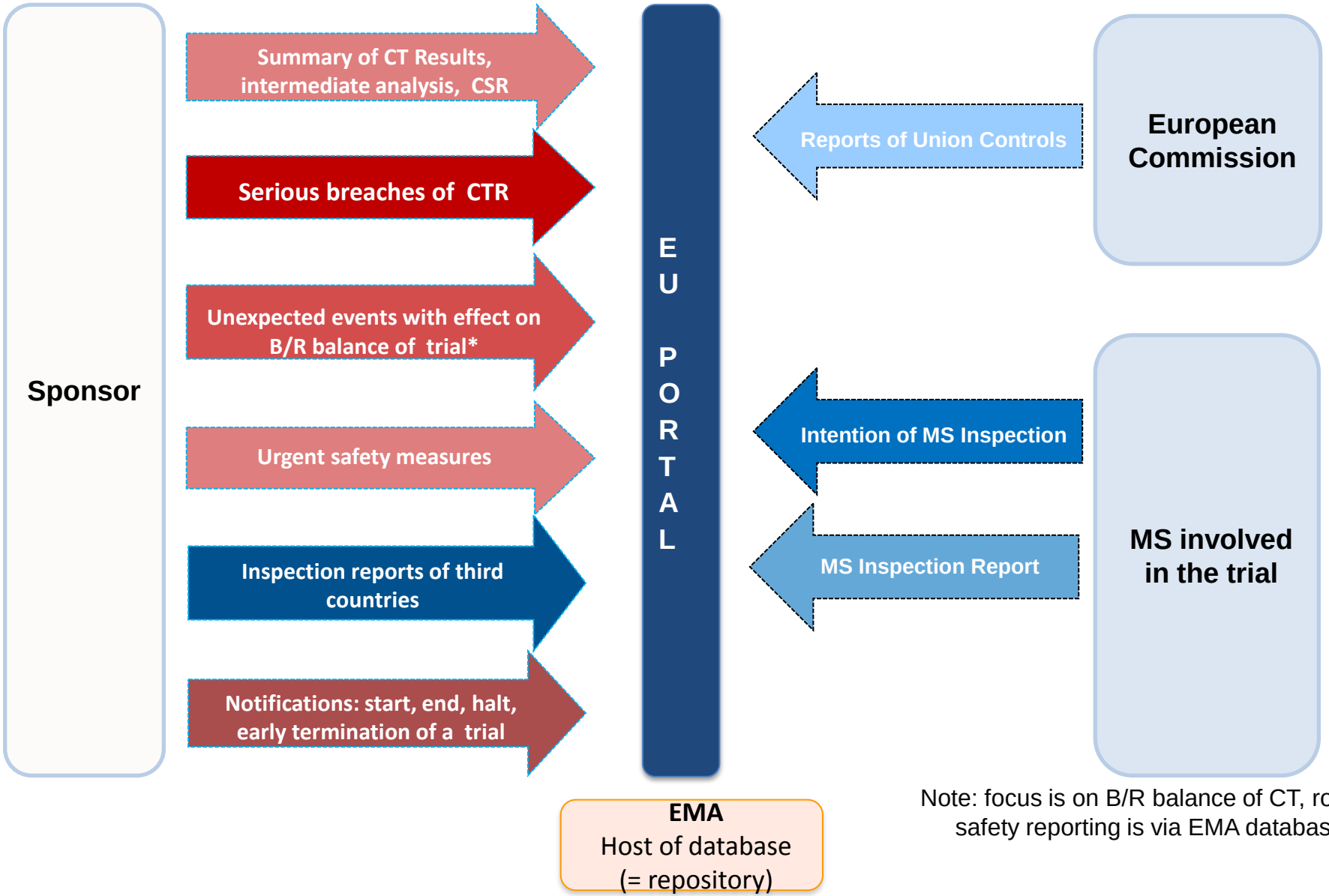


New Assessment Procedure for Clinical Trials via EU Portal/ Database (earliest 2016)*



* Simplified procedure: Communication between Member States also takes place via EU Portal; also concerned Member States will have access to Part I via EU Portal

EU Portal & Database
Exchange of Additional Info



Note: focus is on B/R balance of CT, routine safety reporting is via EMA database!

EU Portal & Database: Results

- **Summary results and layfriendly summary**
  - ≤ *1 year* from end of trial *in all MS concerned*
  - > *1 year* only when scientific reasons & justification detailed in protocol
- **Summary of intermediate data analysis** (as per protocol)
  - ≤ 1 year of intermediate analysis date
- **Clinical Study Reports (CSR)**
  - in cases where trial intended for obtaining a marketing authorisation
  - ≤ *30 days*
    - after marketing authorisation has been granted or
    - completed decision-making process for marketing or
    - withdrawal of marketing authorisation application
- **Non-reporting/ posting will be subject to penalties**
- **Of Note: No submission of patient level (raw) data required**
  - But - COM to produce guidelines for voluntary data sharing schemes

EU Portal & Database: Transparency

- **EU Database publicly accessible** unless confidentiality is justified
  - to protect **personal data**
  - to protect **commercially confidential information**, taking into account marketing authorisation status of a medicinal product
  - to protect **confidential communication between MS**
  - to ensure effective **supervision**

- In general, **data included in CSR should not be considered commercially confidential** once
  - a marketing authorisation (MA) has been granted
  - decision making process on an MA has been completed
  - application for a MA has been withdrawn

- **Of note:** similar database/ transparency concept being discussed for clinical performance studies under new EU Medical Device & IVD Legislation.

4) Industry Commitments

EFPIA/ PhRMA Commitments

1. **Enhancing data sharing with researchers**
   - request by qualified researchers
   - submission of research proposal
   - review by independent scientific review board
   - anonymisation of patient-level data
   - after approval of drug
2. **Enhancing public access to clinical study information**
   - to CSRs filed after 1 Jan 2014 and after approval of product and indication:
     - At a minimum: synopses of CSRs
     - At company discretion: full CSRs, including patient and study level data
   - redaction of commercially confidential information and personal data
3. **Sharing results with patients who participate in clinical trials**
4. **Certifying procedures for sharing clinical trial information**
5. **Reaffirming commitments to publish clinical trial results,** at minimum
   - from all phase 3 clinical trials and
   - from discontinued development programs

Commitment No. 1 - Implementation
Multi-sponsor platform for patient level data access

ClinicalStudy DataRequest.com

https://clinicalstudydatarequest.com/

- A Partnership of

- Public website that gives fully transparent overview of all requests approved, denied, and in progress

efpia

Other access concepts for patient level data

Yale University Open Data Access (YODA) - Partnership witl

- Yale University performs independent scientific reviews of investigator requests for Janssen's Clinical Study Reports and participant-level data

- Reviews requests for all products currently available on the market, not only products developed in 2014 and beyond

Other stand alone concepts

- Submission to Pfizer online portal and assessment by Pfizer

- Requests declined by Pfizer will be submitted to an independent review panel for final binding decision

Some expectations about greater transparency

1) **Meta-analysis**
   - Can suggest a trial is not needed
   - validate surrogate endpoints
   - well characterised historical controls (rare diseases)
   - Speed up development (Ex.: colorectal cancer, HIV, further potential in cancer, schizophrenia)

2) **Lessons on heterogeneity of treatment effects**
   - Allow focused drug development (identification of population with high unmet medical need)
   - May enhance drug value

3) **Indirect methods for use in comparative-effectiveness assessments**

4) **Mitigate patient exposure to clinical trials**

5) **Save resources**

Reference: Eichler, Petavy, Pignatti, Rasi, NEJM (2013)

Summary and Perspectives

1) The European Union has established transparency provisions leading to an enhanced **transparency policy by the European Medicines Agency** including information on clinical trials.

2) Following a **separate industry commitment**, companies are in the process of establishing enhanced clinical trial data access schemes, translating principles into practice.

3) In the future, enhanced transparency on **anonymised real world data** from patient registries, hospitals, general practitioners will be of key importance for the establishment of real world evidence.

4) Enhanced transparency serves **patients, researchers, industry, regulators, HTA bodies and the public**. The journey has just started. **We will have to learn through experience.** In all different areas.

Doing now what patients need next