
# The European Commission's Regulation Proposal

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# Introduction

- Criticism on effects of Clinical Trials Directive (CTD) 2001/20/EC from all involved stakeholders
- Formal review process of the CTD impact by the European Commission
- Numerous workshops on possible solutions, e.g. “Roadmap Initiative for Clinical Research in Europe”
- 17.07.2012: DG SANCO’s proposal for: “Regulation on clinical trials on medicinal products for human use, and repealing of Directive 2001/20/EC”

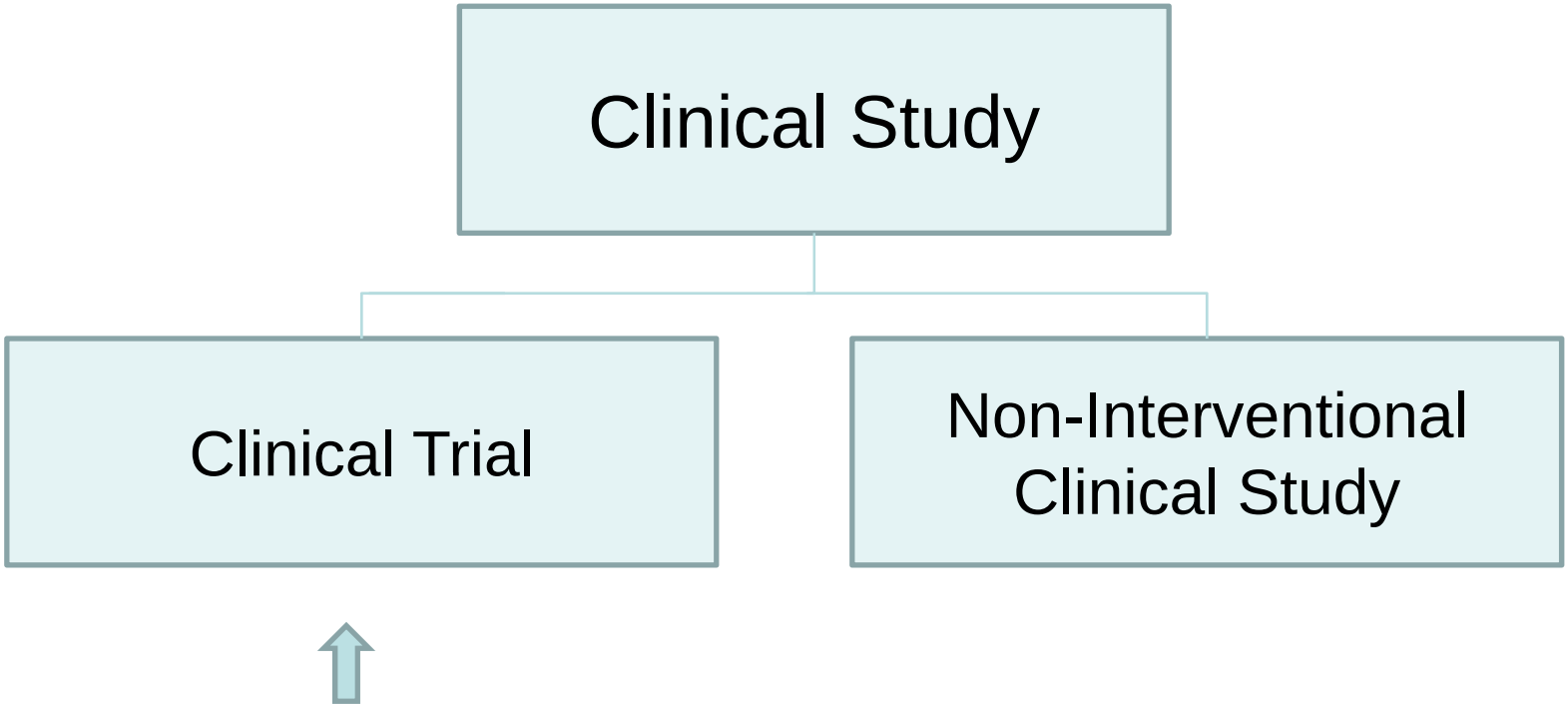
# Introduction

- Structure of the draft Regulation:
  - Extended Explanatory Memorandum
  - Regulation text with 19 Chapters
  - Annex 1: Application dossier for initial application
  - Annex 2: Application dossier for substantial modification
  - Annex 3: Safety reporting
  - Annex 4: IMP and AMP labelling
  - Annex 5: Correlation table (Directive 2001/20/EC versus this Regulation)
  - Legislative Financial Statement

# Key Changes in the Proposal

- It is a REGULATION
- Single portal, single dossier
- Coordination of assessments in multi-national trials shifted from sponsor to competent authorities
- Coordinated 2-Part assessment procedure amongst Member States
- Role of ethics committees
- Single national decision via EU Portal
- Risk-based approach for documentation, approval timelines, monitoring, liability
- Streamlined safety reporting
- New indemnification provisions

# Clinical Study vs. Clinical Trial




**Scope of proposed Regulation**

# Definitions:
# „Low-intervention clinical trial“

- “Clinical trial”: a clinical study which fulfills all of the following conditions:
  - IMP is authorised
  - IMP used within the label or is a standard treatment in any of the Member States concerned
  - The additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned

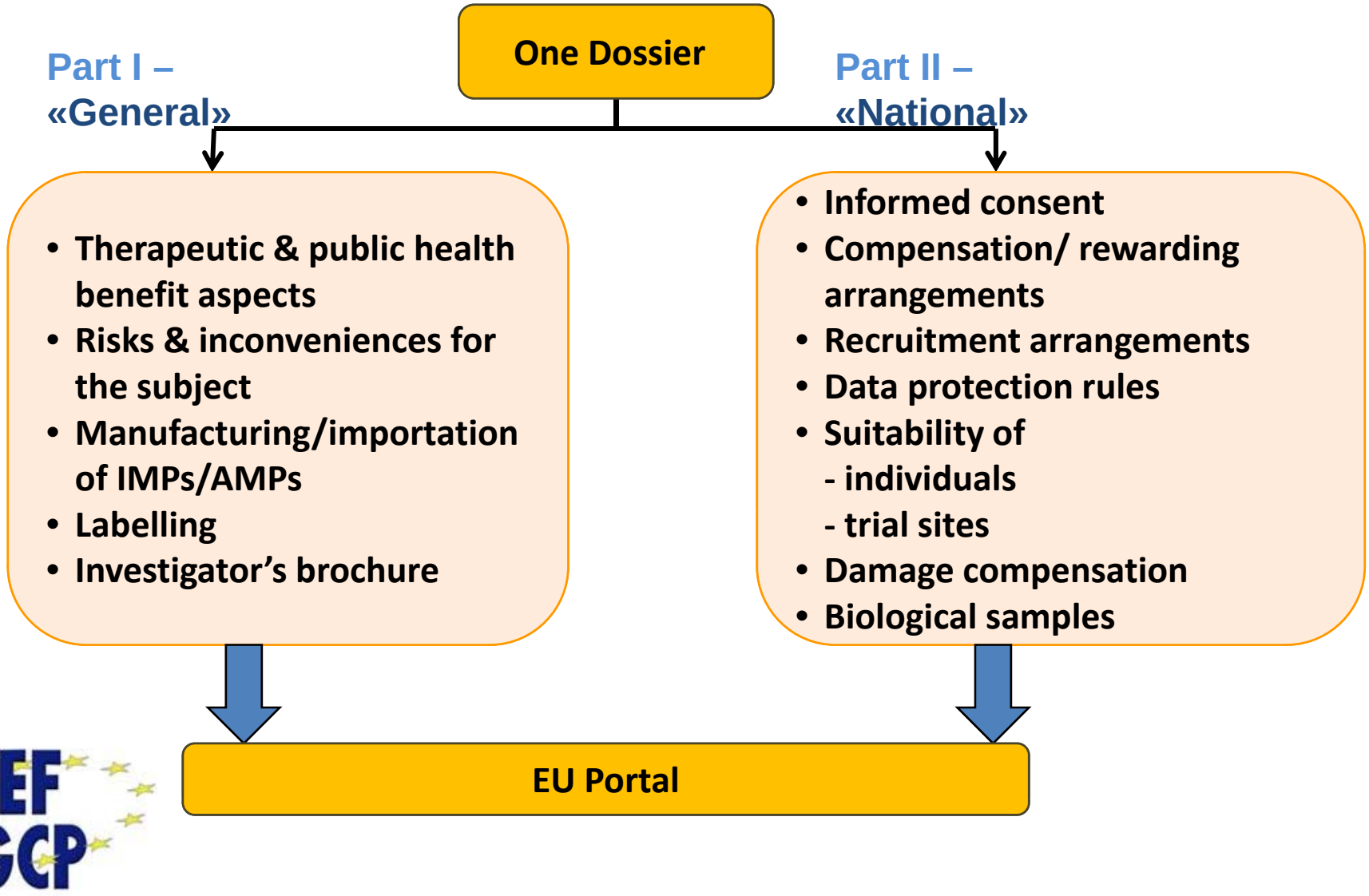
# Single Application Dossier:

- Introduction and General Principles
- Cover letter
- EU application form
- Protocol
- Investigator Brochure
- GMP compliance documents
- IMPD
- Auxiliary Medicinal Product Dossier
- Scientific Advice and PIP
- Content of IMP labelling
- Recruitment arrangements
- PIS and IC
- Suitability of investigators and sites
- Proof of insurance cover or indemnification
- Financial arrangements
- Proof of payment of fee

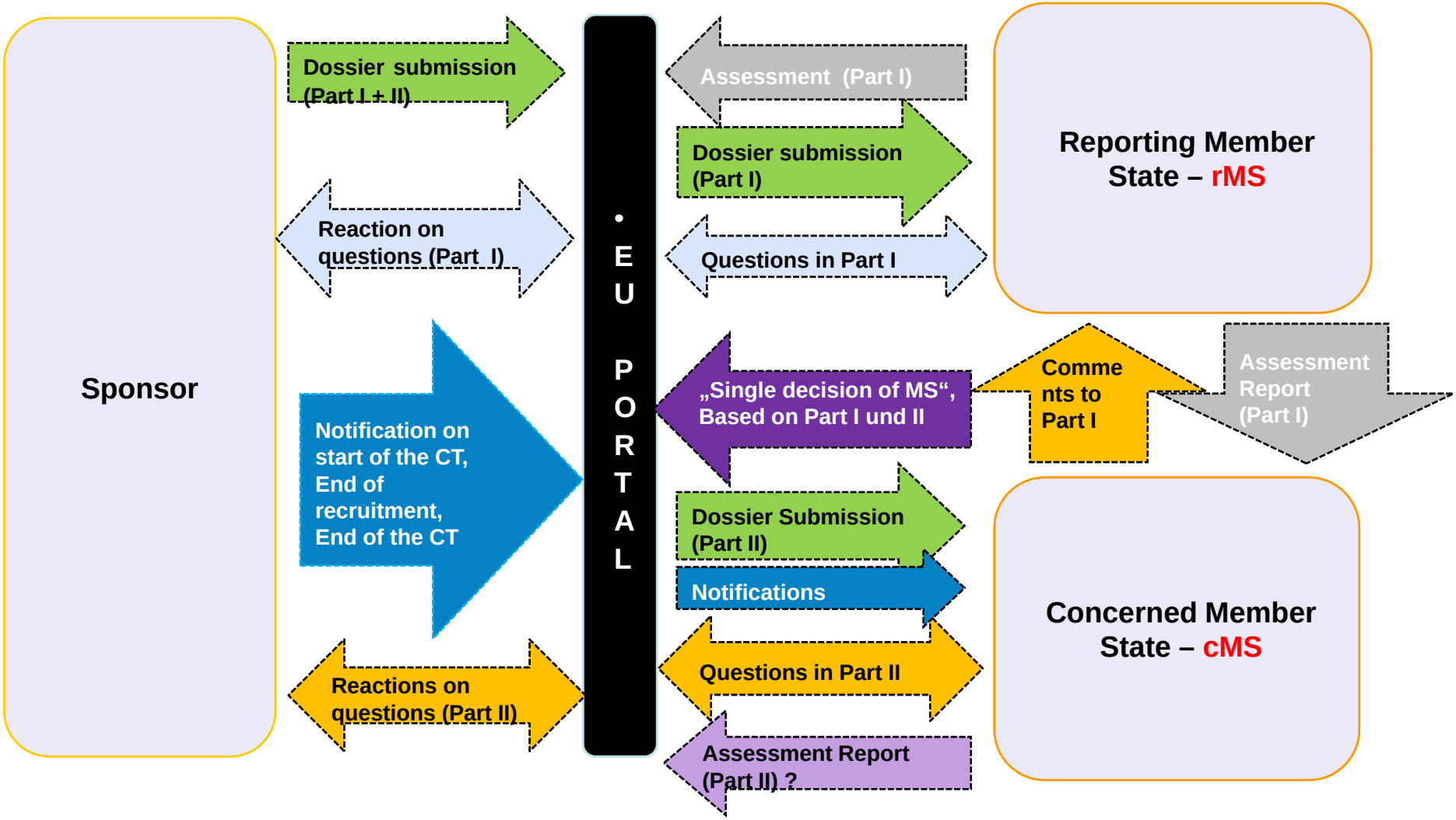
# Single Portal – EU Database

- “The Commission shall set up and maintain a portal at Union level as a single entry point for the submission data and information relating to clinical trials in accordance with the Regulation”.
- “Data and information submitted through the EU portal shall be stored in the EU database”
- Commission will set-up and control an EU Database of submitted information:
  - To enable collaboration between competent authorities
  - To enable sponsors to refer to previous submissions
  - Publicly accessible with exception of personal data, commercially confidential data, inspection information

# Application Dossier – Content & Submission



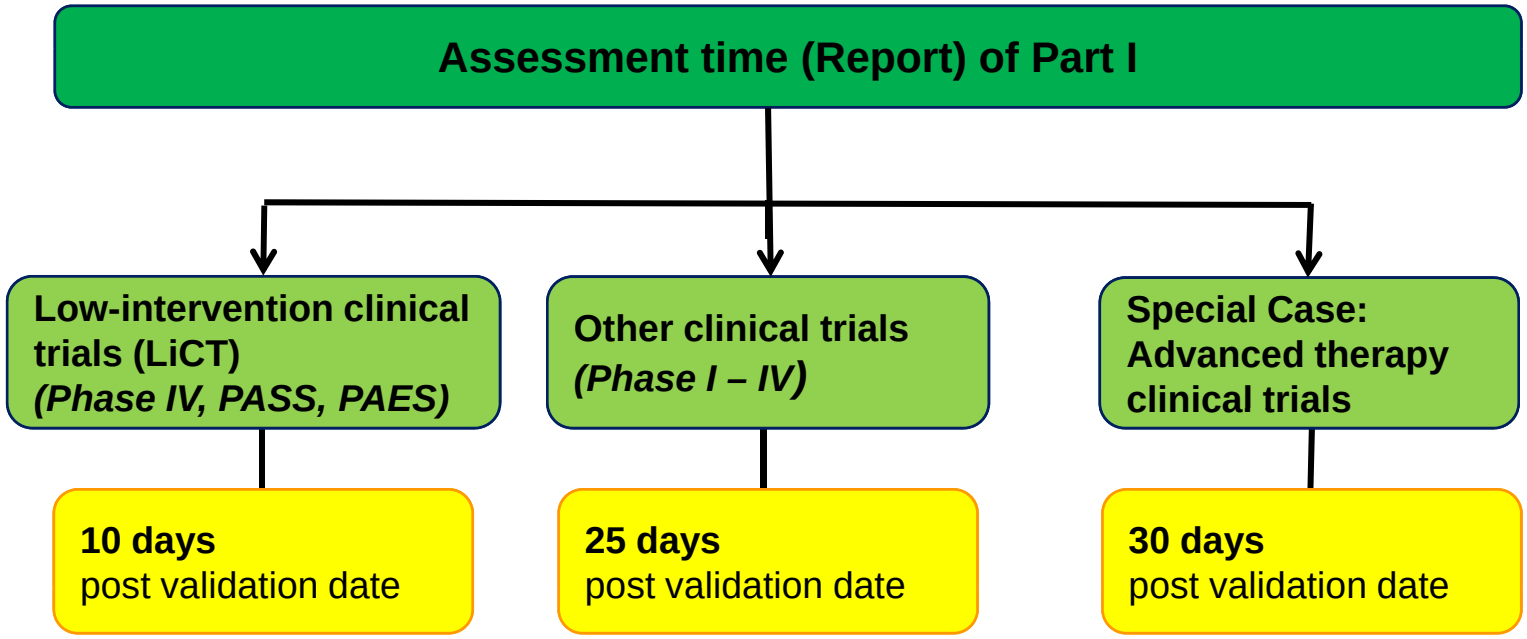
# The EU-Portal



# Persons Assessing the Application

- Member States to ensure that the persons validating and assessing the application
  - Do not have a conflict of interest
  - Are independent of the sponsor, the institution of the investigator and site
  - Are free of any undue influence
- Member States to ensure that assessment is done jointly by a reasonable number of persons who collectively have the necessary qualifications and experience
- In the assessment the view of at least one non-scientific person and one patient have to be taken into account
- Paediatric expertise required for paediatric trials
- For trials with incapacitated subjects expertise in the respective disease and patient population is required

# Risk-based Approach and Impact on Assessment Timelines



# Assessment Timelines Part I

- Validation period: 6 days
- Sponsor validation response time: 6 days
- CA response time to additional information: 3 days (tacit)
- Assessment time Part I (see above) during which cMS can give their comments to rMS
- During assessment time rMS can ask for additional explanations
- Clockstop for 10 resp. 20 days for the sponsor to provide answers
- Upon receipt of information CA can expand response time by 3 resp. 5 days

# Options for Assessment Process

- Sponsor can request that only Part I gets assessed and decided
- Later, sponsor can apply for a Part II assessment only
- Can be helpful to get a better understanding of the acceptability of the study concept before going into national local assessment and approval
- Sponsor may withdraw the application at any time until the assessment date. Will be a withdrawal for ALL Member States involved

# Assessment Timelines Part II

- Validation period: 6 days
- Sponsor validation response time: 6 days
- CA response time to additional information: 3 days (tacit)
- Assessment time Part II: 10 days
- During assessment time cMS can ask for additional explanations
- Clockstop for 10 days for the sponsor to provide answers
- Upon receipt of information CA can expand response time by 5 days

# Decision Making

- Outcome of Part I assessment from rMS, reported to cMSs and sponsor:
  - Conduct is acceptable
  - Conduct is acceptable but subject to compliance with specific listed conditions
  - Conduct is not acceptable
- Each MS notifies the sponsor through the Portal within 10 days after the assessment date about approval, approval under condition or refusal of the CT (tacit)
- Only 2 reasons for refusal:
  - Significant differences in normal clinical practice in the Member State leading to a disadvantage for the patients when participating
  - Infringement of national legislation in CT with IMPs derived from cells

# Modifications: Additional Member State

- Possibility to extend the clinical trial to another MS after notification date of the initial authorisation decision
- Submission to the EU web portal
- rMS remains the same and has to coordinate with the additional country
- Additional MS has to inform sponsor via web portal whether trial is approved (subject to conditions) or not
- Within
  - 25 days for low-interventinal studies
  - 35 days for clinical trials
  - 40 days with advanced therapy products

# Substantial Modifications

- Sponsor submits modification dossier via web portal to all involved MS
- rMS remains the same
- Sponsor defines whether it is a modification to Part I or Part II
- Validation period is 6 plus 6 plus 3 days
- rMS provides assessment report within 15 days to cMS and sponsor
- Opportunity for request for additional information by rMS, sponsor has 10 days to respond
- cMS has to give decision within 10 days after validation date
- Definition of „substantial“ stricter than in CT-1 guidance: impact on safety of rights of subjects or robustness of data (before: scientific value)

# Safety Reporting

- Investigator to report adverse events/lab abnormalities to sponsor (unless the protocol excludes certain adverse events)
- Sponsor to report SUSARs to EudraVigilance (if no resources available, reporting to MS where event occurred, MS to report to EV)
- For IMPs (non-authorised or applied outside terms of marketing authorisation) an annual safety report to be submitted electronically to the Agency
- For authorised IMPs:  sponsor to inform the MAH of all SSARs annually

# Protection of Subjects and Informed Consent

- Detailed description of information and inclusion of
  - Patients in general
  - Incapacitated subjects (legal representative, adaequate info, involvement in IC process as far as possible, presumed benefit)
  - Minors (legal representative, adaequate info from trained individuals, involvement in IC process as far as possible, no incentives except compensation, direct benefit or group benefit)
  - Subjects in emergency situations (IC can be obtained after inclusion in life threatening or other sudden serious medical conditions, no legal representative available, no earlier expressed refusal to join a CT, no group benefit, minimal risk and burden, approval to be sought asap from legal representative and subject)

# Sponsor and Investigator

- Sponsor outside the EU only needs contact point, communication to this contact point is considered as communication to the sponsor
- Co-sponsorship is possible
  - Either in form of equal responsibility for all sponsors

  or

  - Contract amongst sponsors defines responsibilities (minimally: 1. responsibility for authorisation procedure, 2. information to subjects, investigators, authorities concerning the trial, 3. implementing measures concerning early termination)

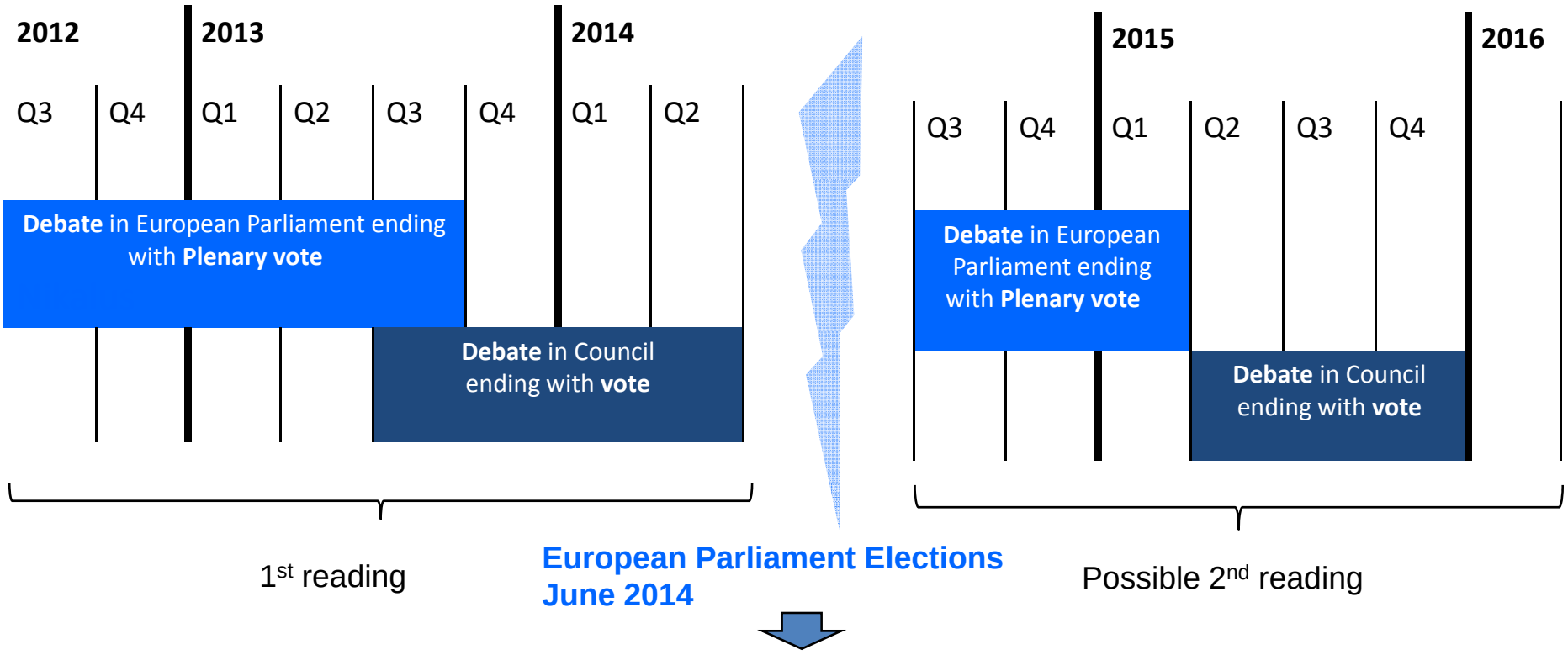
# Damage Compensation and Indemnification

- National indemnification mechanism for compensating damage in low-intervention trials
- Sponsor responsible for damage compensation in accordance with applicable laws on liability of the sponsor and investigator in all other trials according to national requirements
- Sponsor can use national indemnification provision free of charge if the trial is not intended for marketing authorisation
- Sponsor can be asked to pay a fee if he wants to use national indemnification provision. Member States need to calculate the fee on not-for-profit basis and take into consideration the risk of the trial, the potential damage and the likelyhood of damage

Source : EFPIA presentation

# EU Legislative Process

## Estimated Timelines for Ordinary Legislative Procedure by European Parliament and Council of the EU

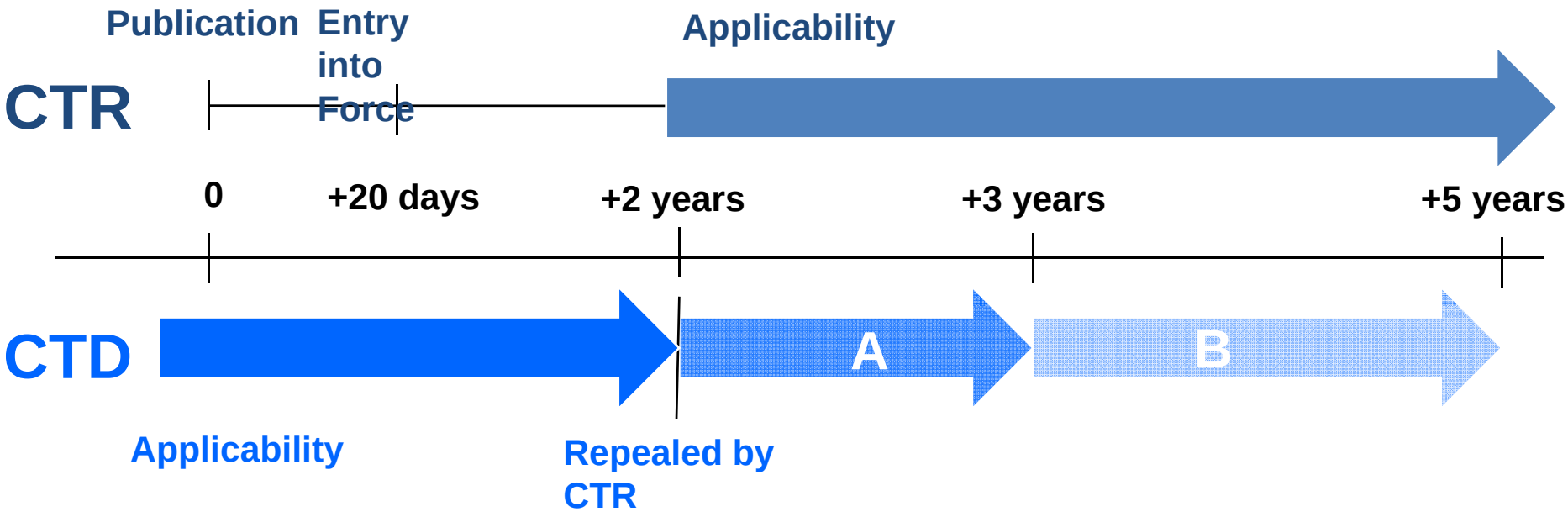



Elections likely to have an impact on the process

# Implementation / Transition Period

Source : EFPIA presentation

**Implementation of the New Clinical Trials Regulation (CTR) and Transition Period for the Existing Clinical Trials Directive (CTD)**




**A: Clinical trials may still be submitted and started under CTD**
**B: Clinical trials submitted under A may continue to be governed by CTD until year +5**


# Thank you!

# Any questions?

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Thank you!

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