

The EU Clinical Trial Regulation (CTR) – from assessors (and clinicians) perspectives

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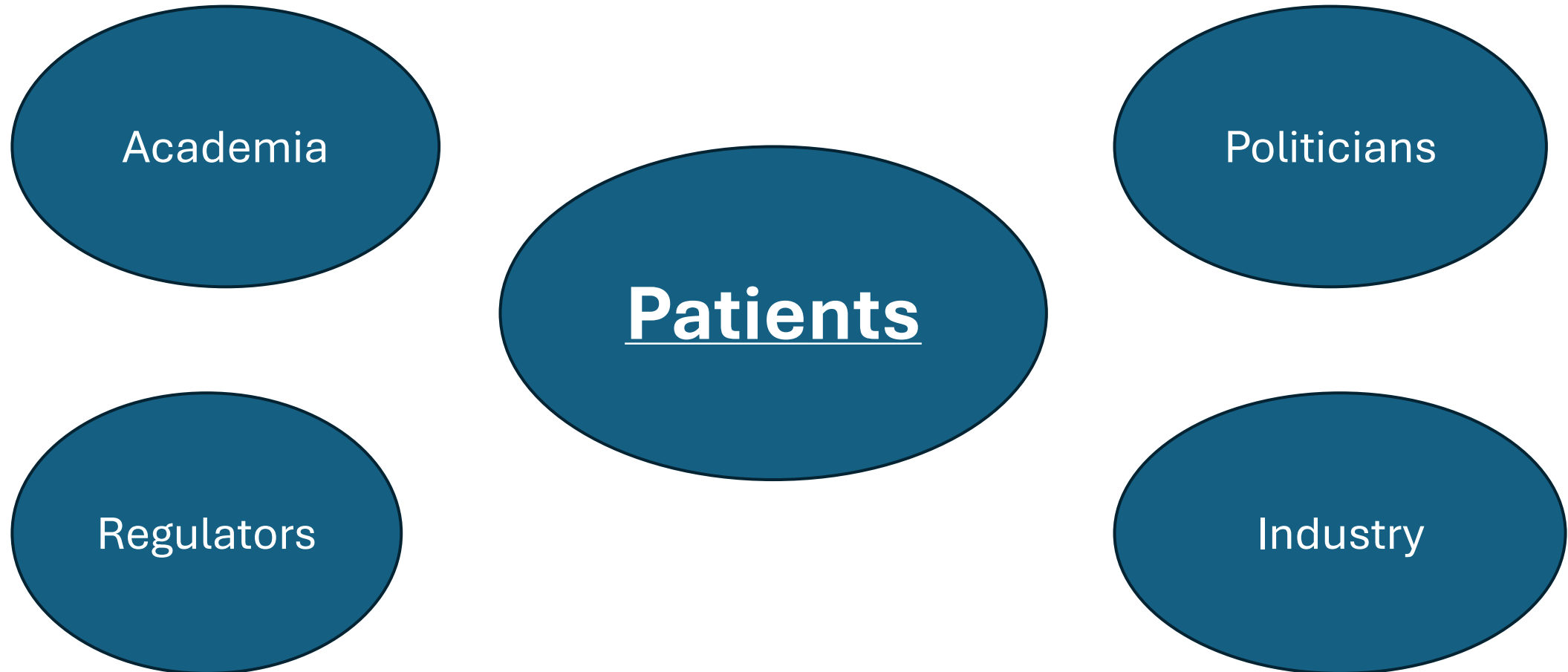
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Disclaimer

- All views are my own

Many stakeholders with interest EU clinical trial regulation (CTR)

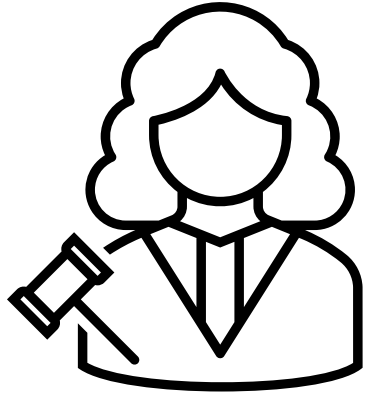




Making all stakeholders
satisfied is a balancing act!

A focus on the patients perspectives

Research is about believes based
on prior knowledge and experience



Believes are not certainty

Regulation does not lead to certainty

Overregulation will limit innovation

Low innovation, less medical advances

DECLARATION OF HELSINKI

Recommendations guiding doctors
in clinical research

Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964

ICH guidelines are provided for:

- Quality
- Safety
- Efficacy
- Multidisciplinary
- Considerations



Regulation should, among other things, ensure

1. Patient autonomy in clinical trials
2. Scientific quality overall/relevance
3. Safe for patients

Safety aspects - example



NCA/Ethics

Authorize a trial – takes a responsibility

Will be asked to explain if major safety issues occur

No direct gains

->More risk adverse decisions?



Sponsor

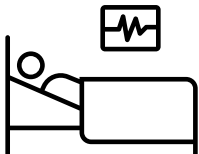
Designs the trial

Will be responsible for safety/conduct

Believes in the idea (bias?)

Direct gains – science/economy

->Less risk adverse decisions?



Patients make the final decisions in full transparency with possible benefit/risks and in accordance with their own believes

Benefit against risk – it is not math

Opportunities/benefit:
Better treatments, better understanding of disease etc.

Safety/ethics – no single person should be
used as a mean to obtain this with
unacceptable risks

Balance has to be assessed
positive

The patient decides if the
balance seems right for them

- (1) In a clinical trial the rights, safety, dignity and well-being of subjects should be protected and the data generated should be reliable and robust. The interests of the subjects should always take priority over all other interests.

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

of 16 April 2014

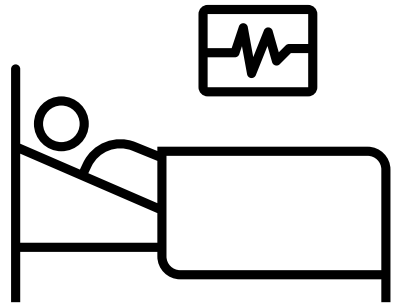
on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

(Text with EEA relevance)

(OJ L 158, 27.5.2014, p. 1)

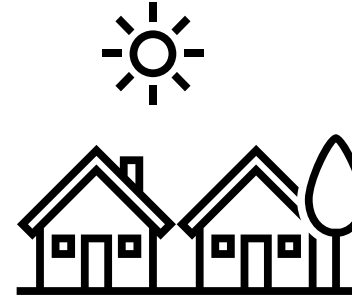
I will not be discussing CTIS functionalities in this presentation

CTR concerns us all



Individual level: Everyone can become a patient

- Easy access to studies
- New treatments
- Research improves SoC
- Contribute to science



Society level: Innovation, clinical research is important for the EU economy



In parallel, regulators should aim to boost the attractiveness of the EU for conducting clinical trials and to expedite access to markets for novel medicines. These goals can be supported, among other things, by reviewing rules for studies combining medicines with medical devices and the application of AI and streamlining guidance across different agencies to industry on unmet medical needs, the design of clinical trials and the use of real-world evidence.

CTR – to streamline and accelerate

EU – 27 member states

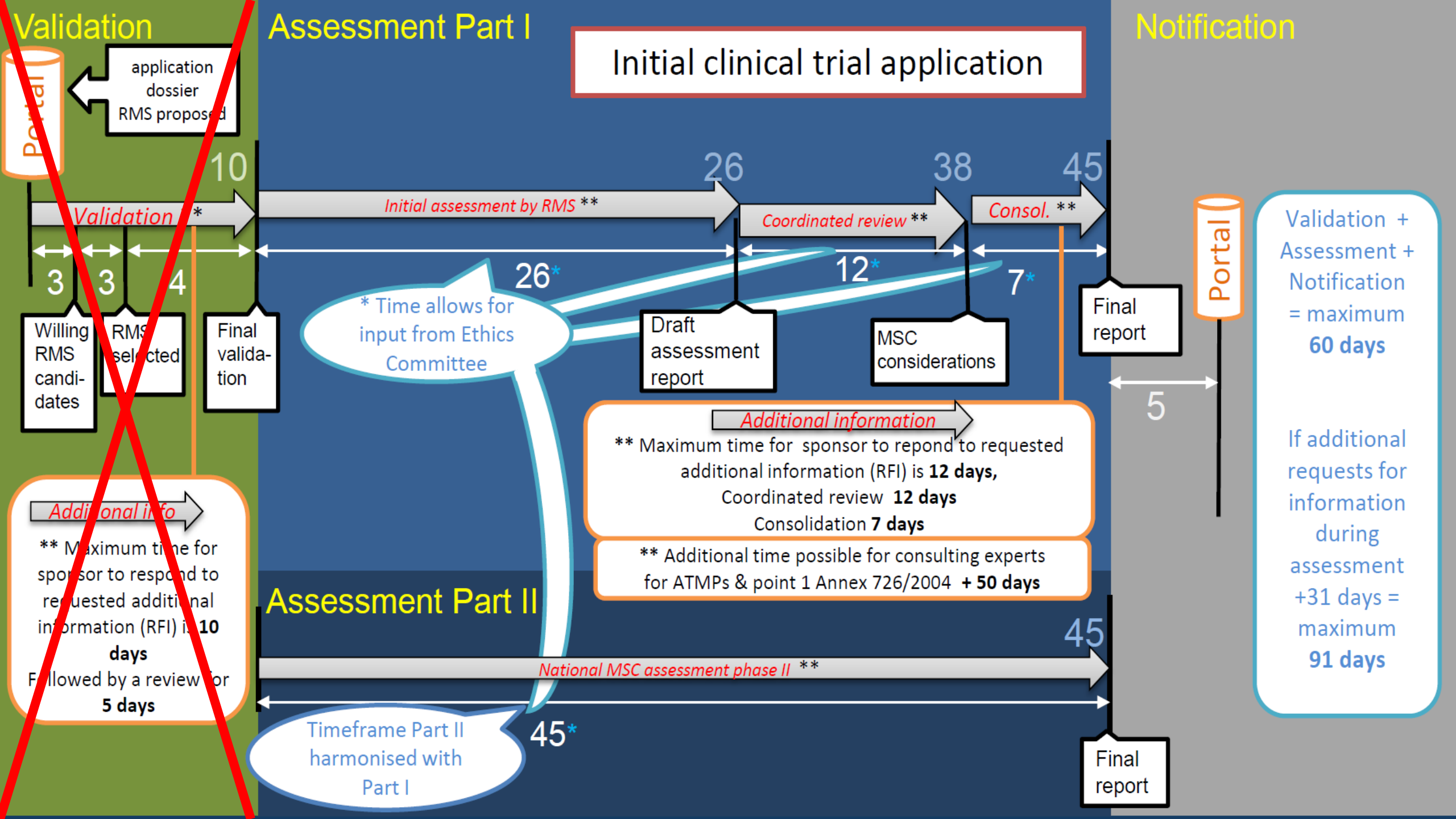
Multinational trials requires harmonization

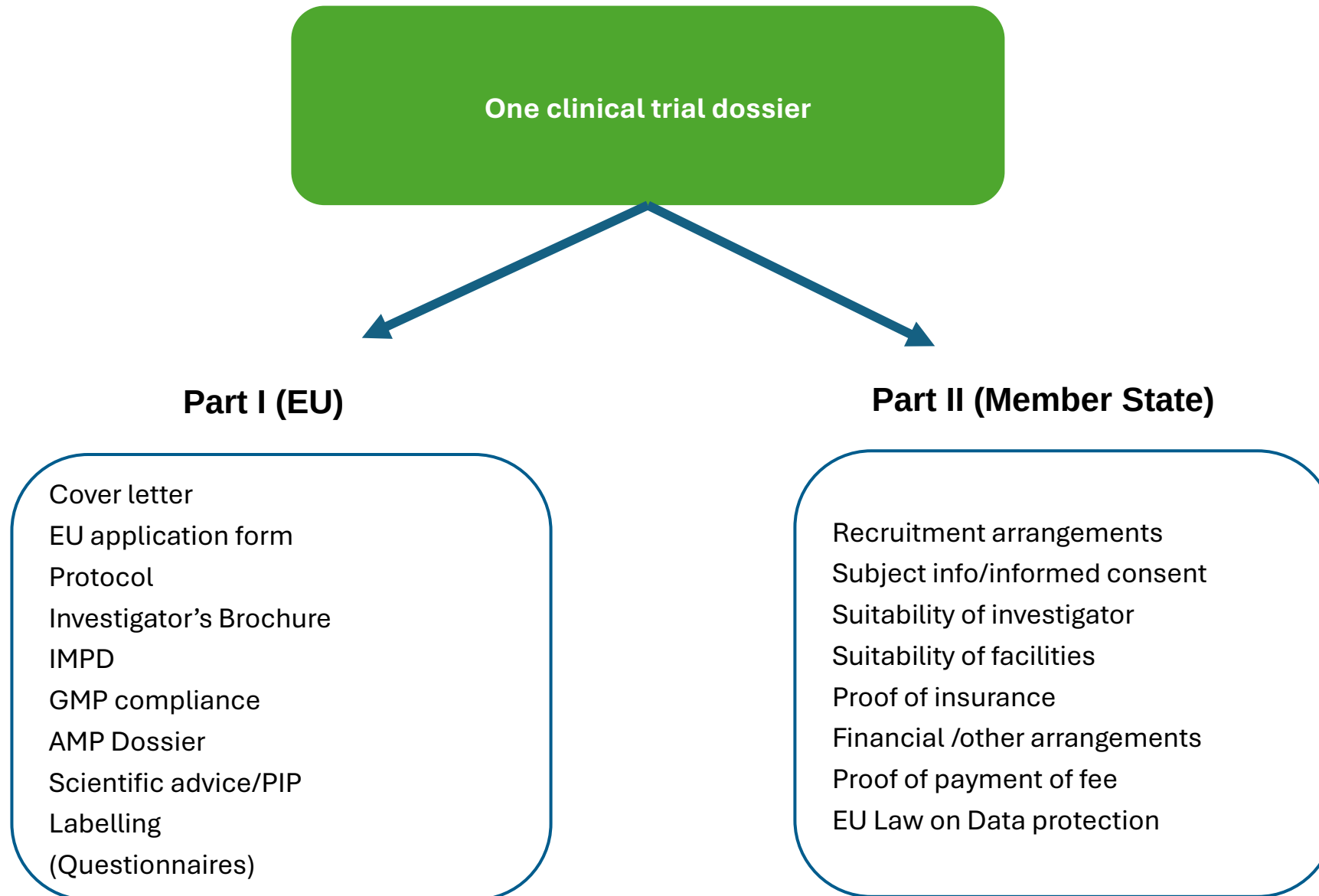
- Large trials/rare disease trials depend on international collaborations

National evaluations were

- Inconsistent – country-specific protocols
- Slow/unpredictable timelines







Part 1 – National competent authorities (NCAs)

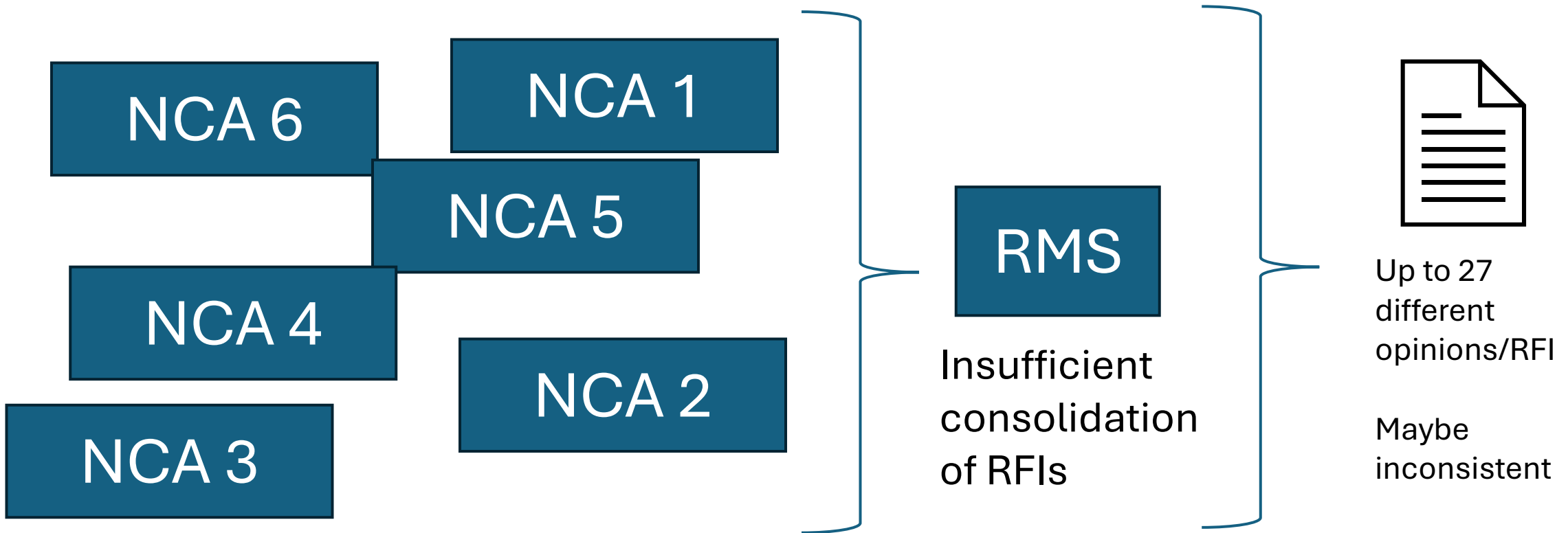
Up to 27 countries
assess (if all are
involved)



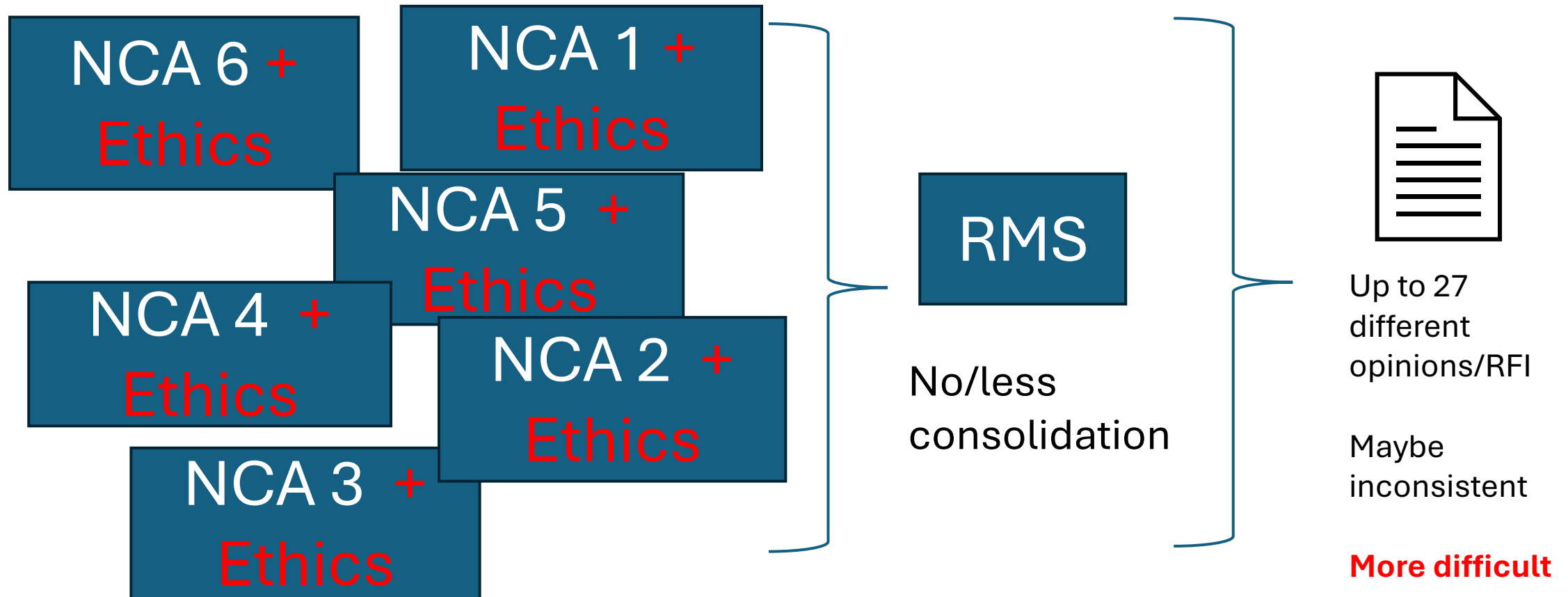
Reporting member
state consolidates
- A consistent report

A good and rational in EU

Part 1 – National competent authorities (NCAs)



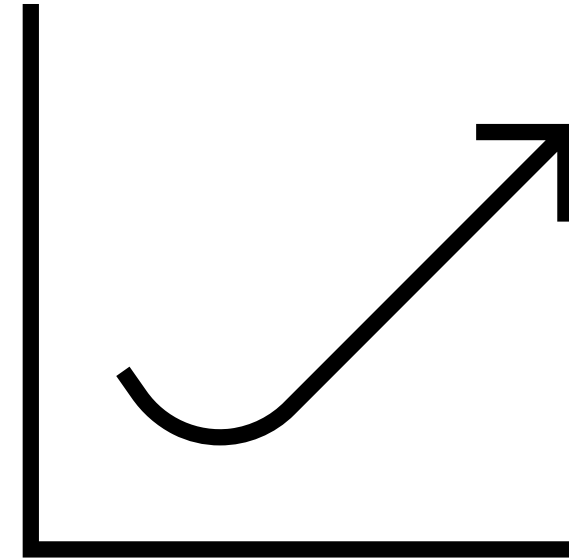
Part 1 – National competent authorities (NCAs)



Often different ethics
within country – with little
internal communication

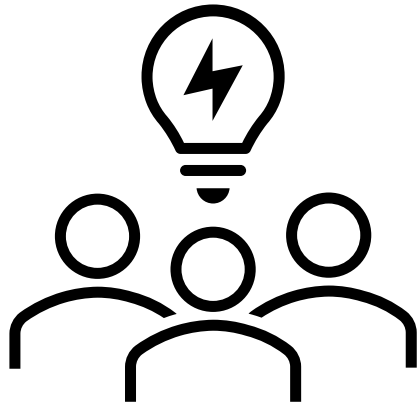
Multiple different NCAs
with time to consolidate

No consistent European
system for collaboration
between ethics and NCAs



**An exponential function in terms of
possible assessment outcomes that
grows with number of countries**

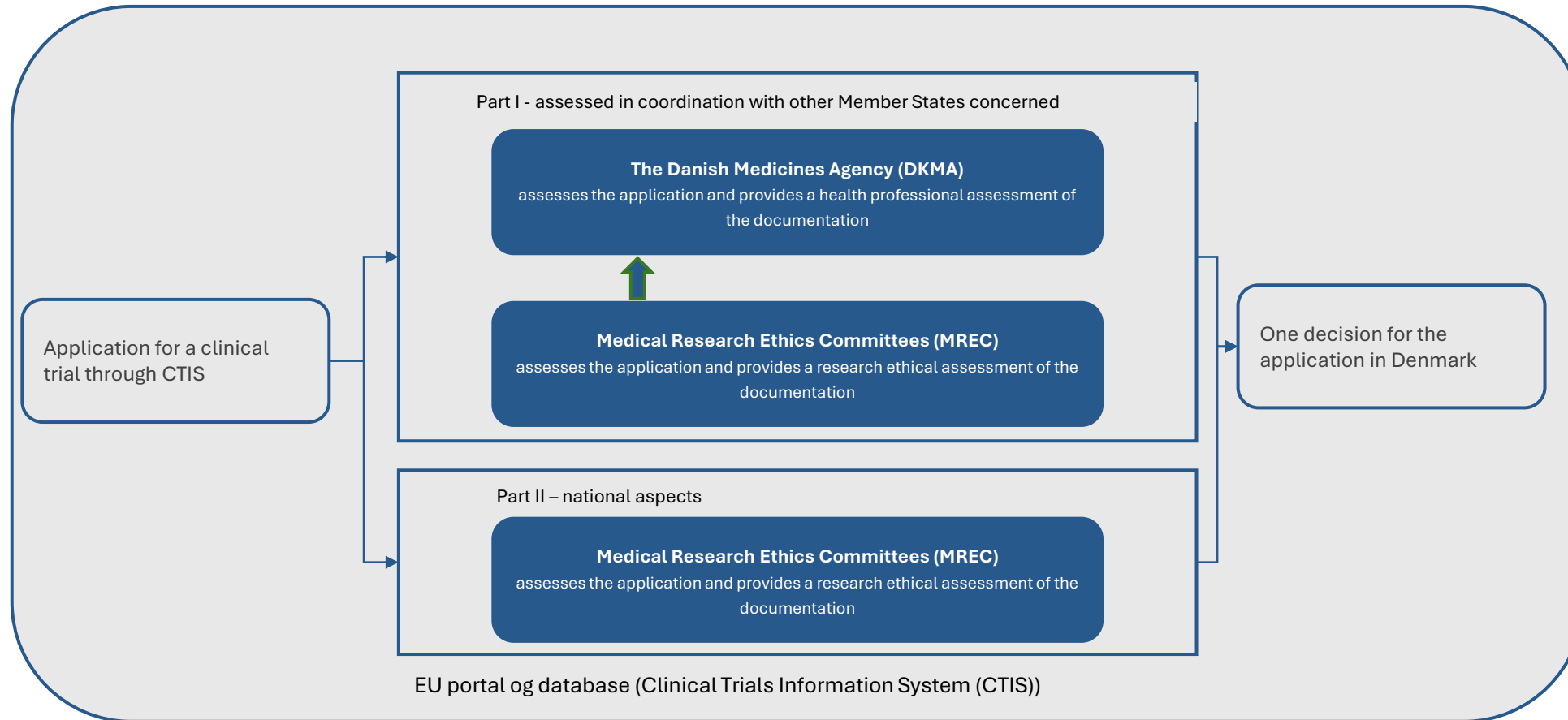
**Too much
unpredictability/inconsistency**

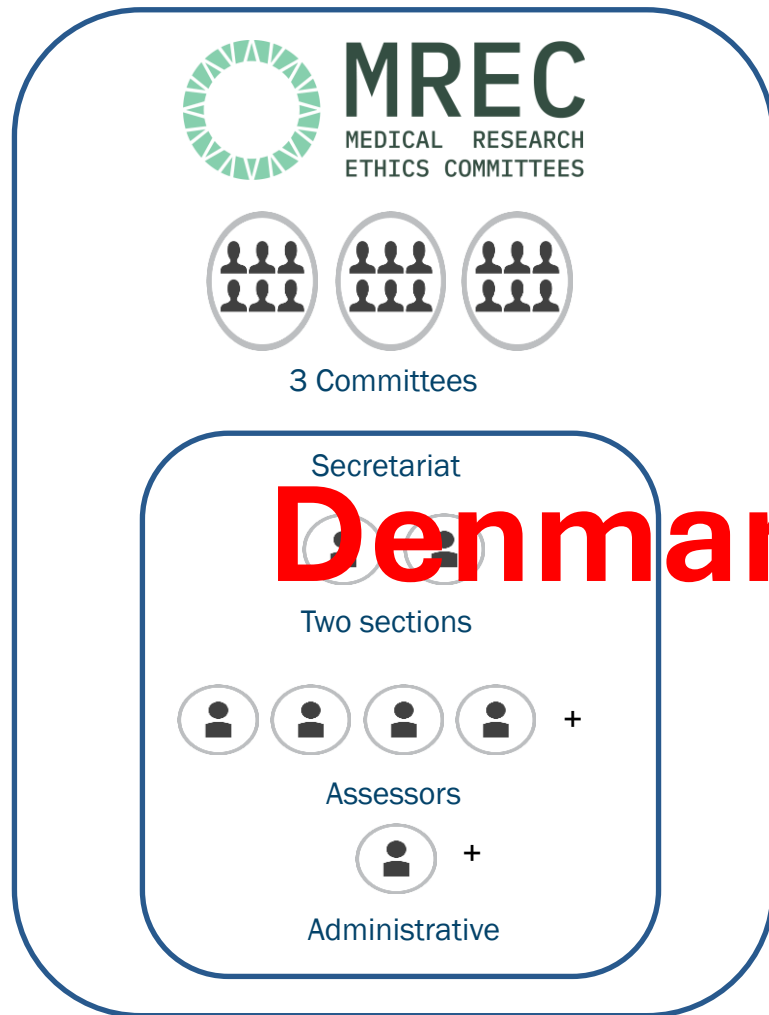


Too little attention to the “how” with CTR

- Expectations and empowerment of the RMS
- Consistencies within countries (between ethics, between ethics and NCAs)
- Consistencies between countries
- Guidance in CTR interpretation

Assessment procedure – in Denmark





National secretariat consists of employees with background in

- Law
- Science
- Philosophy
- Administrative support staff

Denmark is a small country

The medical research ethics committees are centralized

- More consistency in decisions
- Exchange of ideas/decisions between committees

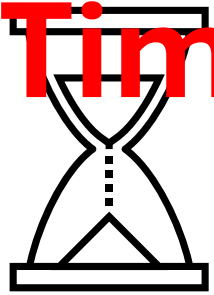
Part I is also assessed by MREC in Denmark, but the Danish Medicines Agency is leading this part

Timelines

Predictable timelines is a major step forward

RFIs returned:

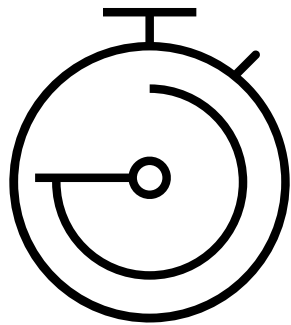
Times are all short for assessors



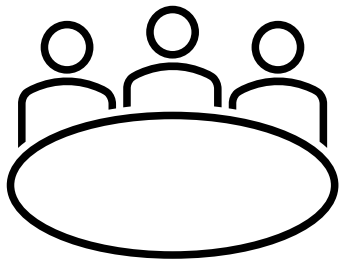
- From more countries?

- Inconsistent?

Few days is too short time for protocol revisions that require work, steering group discussions and agreements etc.



We need a clock-stop opportunity to make best possible assessments and best possible protocol revisions – but should be controlled!



We need opportunities for direct conversations to clarify issues that do not necessarily go through CTIS

CTR is only part of a wider ECO system problem



Individual countries

- National funding opportunities
- Other regulations, contracts/agreements
- How research is prioritized and promoted
- Strained health care systems in most EU countries (staff shortage, high work load)

Individual sites

- Research culture/training
- Infrastructure for research, support for researcher
- Lack of funding for academic research

- CTR provides a legal frame-work for clinical trials in EU
- EU level funding – enough investment in research?
- GDPR – too restrictive?
- Other legal contracts misaligned

Safety reporting - CTR

Article 41

Reporting of adverse events and serious adverse events by the investigator to the sponsor

1. The investigator shall record and document adverse events or laboratory abnormalities identified in the protocol as critical to the safety evaluation and report them to the sponsor in accordance with the reporting requirements and within the periods specified in the protocol.

2. The investigator shall record and document all adverse events, unless the protocol provides differently. The investigator shall report to the sponsor all serious adverse events occurring to subjects treated by him or her in the clinical trial, unless the protocol provides differently.

The investigator shall report serious adverse events to the sponsor without undue delay but not later than within 24 hours of obtaining knowledge of the events, unless, for certain serious adverse events, the protocol provides that no immediate reporting is required. Where relevant, the investigator shall send a follow-up report to the sponsor to allow the sponsor to assess whether the serious adverse event has an impact on the benefit-risk balance of the clinical trial.

3. The sponsor shall keep detailed records of all adverse events reported to it by the investigator.

4. If the investigator becomes aware of a serious adverse event with a suspected causal relationship to the investigational medicinal product that occurs after the end of the clinical trial in a subject treated by him or her, the investigator shall, without undue delay, report the serious adverse event to the sponsor.

Flexibility in safety reporting
guided by the study protocol

NCA/ethics need to agree

Low intervention - CTR

(3) 'Low-intervention clinical trial' means a clinical trial which fulfils all of the following conditions:

- (a) the investigational medicinal products, excluding placebos, are authorised;
- (b) according to the protocol of the clinical trial,
 - (i) the investigational medicinal products are used in accordance with the terms of the marketing authorisation; or
 - (ii) the use of the investigational medicinal products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products in any of the Member States concerned; and
- (c) 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;



Labelling

Monitoring

Advantages a bit unclear

Cluster trials - CTR

Informed consent in cluster trials

1. Where a clinical trial is to be conducted exclusively in one Member State, that Member State may, without prejudice to Article 35, and by way of derogation from points (b), (c), and (g) of Article 28(1), Article 29(1), point (c) of Article 29(2), Article 29(3), (4) and (5), points (a), (b) and (c) of Article 31(1) and points (a), (b) and (c) of Article 32(1), allow the investigator to obtain informed consent by the simplified means set out in paragraph 2 of this Article, provided that all of the conditions set out in paragraph 3 of this Article are fulfilled.
2. For clinical trials that fulfil the conditions set out in paragraph 3, informed consent shall be deemed to have been obtained if:
 - (a) the information required under points (a), (b), (d) and (e) of Article 29(2) is given, in accordance with what is laid down in the protocol, prior to the inclusion of the subject in the clinical trial, and this information makes clear, in particular, that the subject can refuse to participate in, or withdraw at any time from, the clinical trial without any resulting detriment; and
 - (b) the potential subject, after being informed, does not object to participating in the clinical trial.

Simplified consent in cluster trials

- Provided conditions are fulfilled

Emergency trials

Article 35

Clinical trials in emergency situations

1. By way of derogation from points (b) and (c) of Article 28(1), from points (a) and (b) of Article 31(1) and from points (a) and (b) of Article 32(1), informed consent to participate in a clinical trial may be obtained, and information on the clinical trial may be given, after the decision to include the subject in the clinical trial, provided that this decision is taken at the time of the first intervention on the subject, in accordance with the protocol for that clinical trial" and that all of the following conditions are fulfilled:

- (a) due to the urgency of the situation, caused by a sudden life-threatening or other sudden serious medical condition, the subject is unable to provide prior informed consent and to receive prior information on the clinical trial;
- (b) there are scientific grounds to expect that participation of the subject in the clinical trial will have the potential to produce a direct clinically relevant benefit for the subject resulting in a measurable health-related improvement alleviating the suffering and/or improving the health of the subject, or in the diagnosis of its condition;
- (c) it is not possible within the therapeutic window to supply all prior information to and obtain prior informed consent from his or her legally designated representative;



Better opportunities for clinical trials in emergency situations

Conclusions

- CTR is here to stay
- CTR was made with good intentions and contains new opportunities
- More work needs to be done on
 - Alignments within and between countries
 - Procedures
 - CTR revisions
- CTR is not the only obstacle to research in EU



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