where science and ethics meet

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The New EU CT Regulation: European and International Perspectives

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Conclusions GCP Workshop 2011

- **There is much clearer and more common understanding of what is going wrong at the moment**
- **There is much common understanding between academic and commercial sponsors on how the situation should be improved**
- **DG Research strongly supports the interests of the academic researchers**
- **DG SANCO is in the process of achieving as much improvement as possible through guidelines and makes first attempts towards new legislation**
- **The Heads of Agencies make strong efforts to improve the situation of CTAs within the current legal framework**
- **However, new legislation will be required to force the Member States to apply strictly the same rules for clinical trial authorisation and safety reporting to enhance the performance of multi-national clinical trials in in the interest of patients‘ rapid access to new treatments**

EU-Commission‘s Consultation and Legislation Preparation Process

- 2009 - ICREL Study
- 2009 - Concept Paper for public consultation: “Assessment of the functioning of the Clinical Trials Directive 2001/20/EC”: 106 respondants (60 non-commercial)
- 2011 – Concept Paper for public consultation: “Revision of the Clinical Trials Directive 2001/20/EC”: 143 respondants, most answers from academia
- 2012 - Impact assessment report on the revision of the Clinical Trials Directive 2001/20/EC

EU-Commission‘s Consultation and Legislation Preparation Process

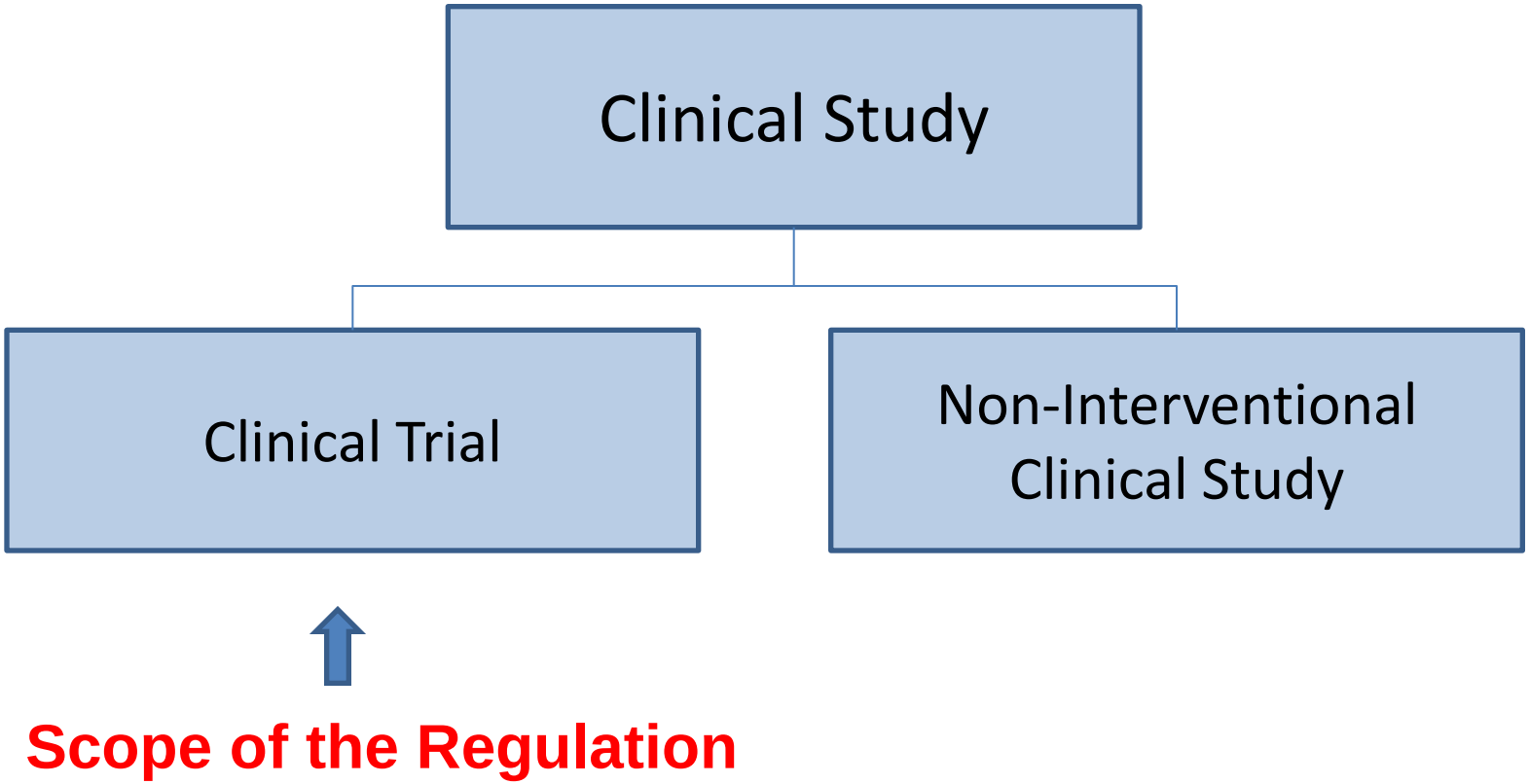
- 17. July 2012 – EU-Commission released the first proposal for a Clinical Trial Regulation
- 31. January 2013 – EU Parliament (ENVI) published its Final Report
- 29. October, 2013 – Council of the European Union published an amendment of the proposal
- 17. December 2013 – TRIAGE agreed on final text of the Regulation
- 4. April 2014 – EU Parliament adopted this text
- 16. May 2014 – The Council of the European Union signed the Regulation
- 27. May 2014 – Regulation 536/2014 published in the the Official Journal of the European Union
- 16. June 2014 – Regulation 536/2014 came into force

Structure of the Regulation 536/2014

- 85 recitals as Explanatory Memorandum
- Regulation text with 19 Chapters with 99 Articles
- Annex 1: Application dossier for initial application
- Annex 2: Application dossier for substantial modification
- Annex 3: Safety reporting
- Annex 4: Content of the summary of the results of the clinical trial
- Annex 5: Content of the summary of the results of the clinical trial for laypersons
- Annex 6: Labelling of IMP and auxilliary medicinal products
- Annex 7: Correlation table Directive 2001/20/EC vs Regulation 536/2014

Key Changes in the Regulation

- 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 (“Low-intervention trial”) for documentation, monitoring, liability
- Co-sponsorship permitted
- Conditions for trials in vulnerable populations



Scope of the Regulation

Definition of a Clinical Trial

"Clinical trial": a clinical study which fulfills any of the following conditions:

- Assignment of subjects to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of this Member State
- Decision to prescribe the IMP is taken together with the decision to include the subject into the trial
- Diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subject

Definition of a Low-intervention Clinical Trial

"Low-intervention Clinical Trial": a clinical trial which fulfills all of the following conditions:

- IMP, excluding placebo, is authorised
- IMP used within the label or is an evicence-based 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

Definition and Roles of Ethics Committees

- "Ethics Committee": an independent body established in a MS in accordance with the law of this MS and empowered to give opinions for the purposes of this Regulation, taking into account the views of laypersons, in particular patients and patients' organisations.
- Article 8.4: the responsible Ethics Committee has a veto right for its cMS and if it is the rMS, for the whole trial.

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

Single Application Dossier (cont.):

- 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
- Proof that data will be processed in compliance with data protection directive

Options for Assessment

- Sponsor can request that only Part I gets assessed and decided
- Within 2 years, 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

Persons Assessing the Dossier (Recital (18))

- It should be left to the MS concerned to determine the appropriate body or bodies to be involved in the assessment of the application… and to organise the involvement of ECs….. When determining the appropriate body or bodies, MS should ensure the involvement of lay persons, in particular patients or patient organisations…. They should ensure that the necessary expertise is available…. The assessment should be done jointly by a reasonable number of persons who collectively have the necessary qualification and experience.

Persons Assessing the Dossier (Article 9)

- MS shall ensure that the persons validating and assessing the application do not have conflicts of interest, are independent of the sponsor, of the clinical trial site and the investigators involved and of persons financing the clinical trial, as well as free of any other undue influence.
- In order to guarantee independence and transparency….persons …have no financial or personal interests…. Annual declaration of their financial interests.
- MS shall ensure that the assessment is done jointly by a reasonable number of persons who collectively have the necessary qualification and experience
- At least one lay person shall participate in the assessment

Protection of Vulnerable Populations (Chapter V)

- Article 28: General rules
- Article 29: Informed consent incl. info on final report summary
- Article 30: Informed consent in cluster trials
- Article 31: Informed consent in incapacitated subject
- Article 32: Informed consent in minors
- Article 33: Clinical trials on pregnant or breast feeding women
- Article 34: Additional national measures (concerning dependent persons)
- Article 35: Clinical trials in emergency situations

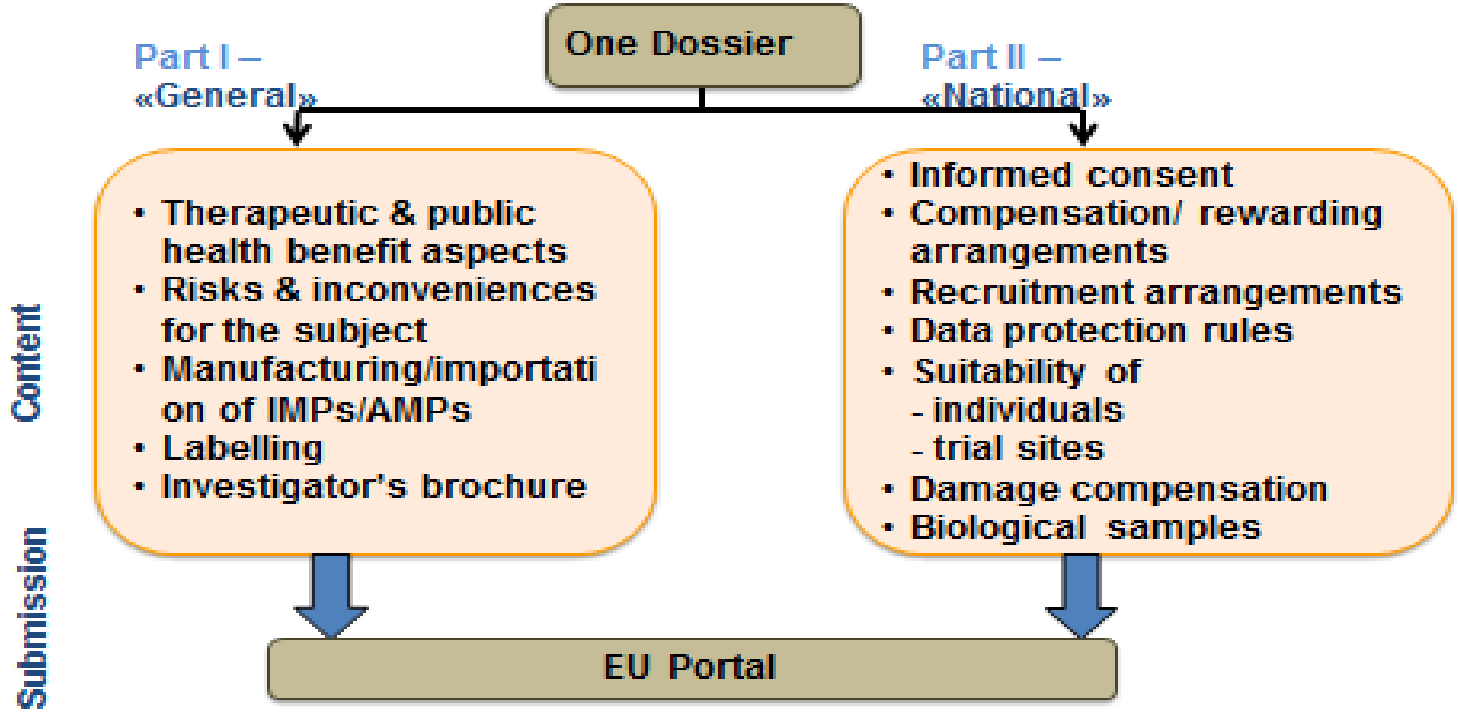
Single Portal

- “The Agency shall set up and maintain a portal at Union level as a single entry point for the submission of 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”

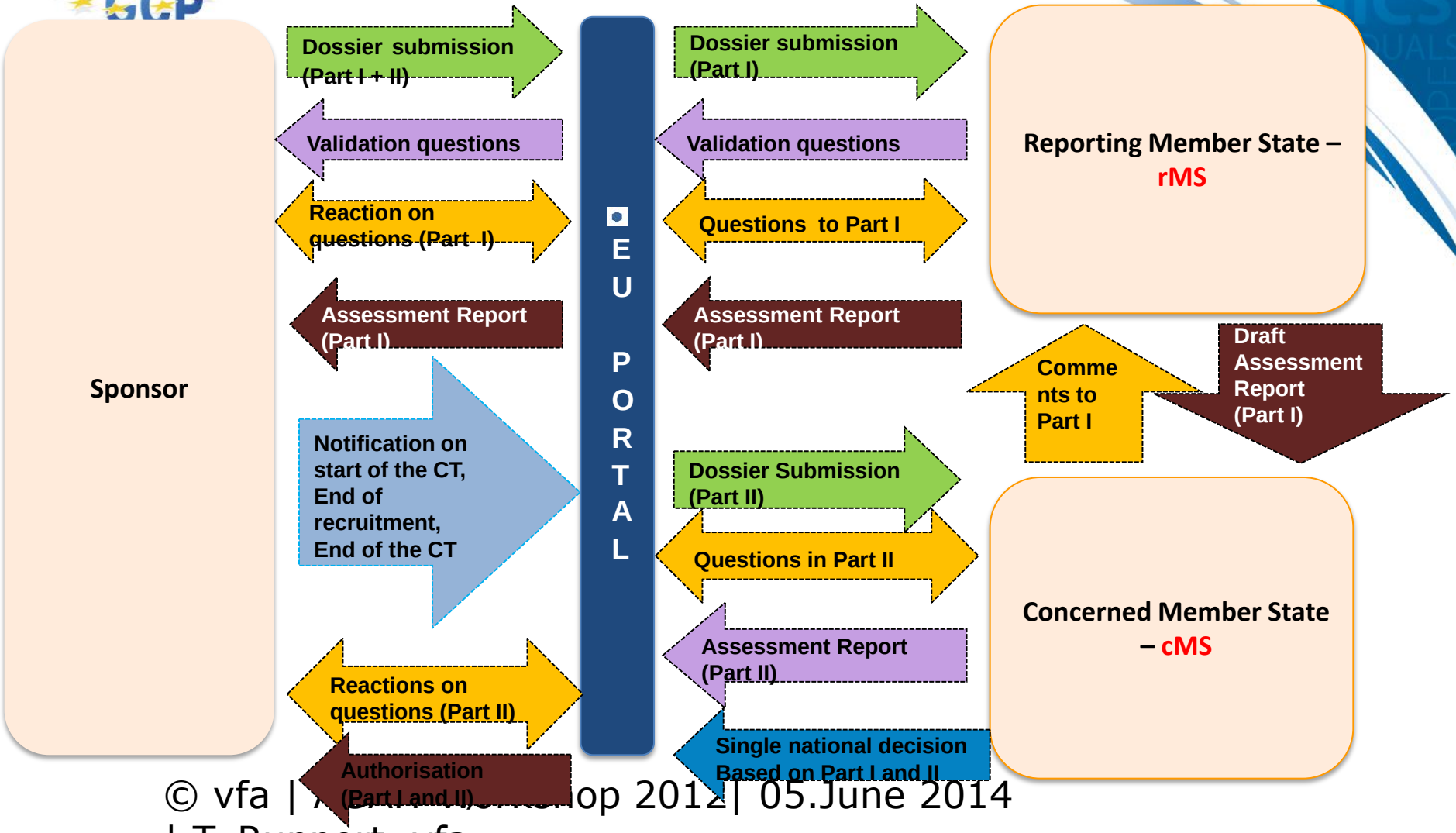
EU Database

- The Agency shall set-up and maintain an EU Database of submitted information:
  - To enable cooperation between competent authorities
  - To enable communication between sponsors and competent authorities
  - To enable citizens to have access to the information about IMPs
  - To enable sponsors to refer to previous submissions through a medicinal product number for IMPs without MA and a EU active substance code for IMPs with MA
  - Publicly accessible with exception of personal data, commercially confidential data, communication in relation to assessment preparation, communication on supervision of conduct
  - User interface available in all EU languages
  - EudraCT and EudraVigilance databases will remain

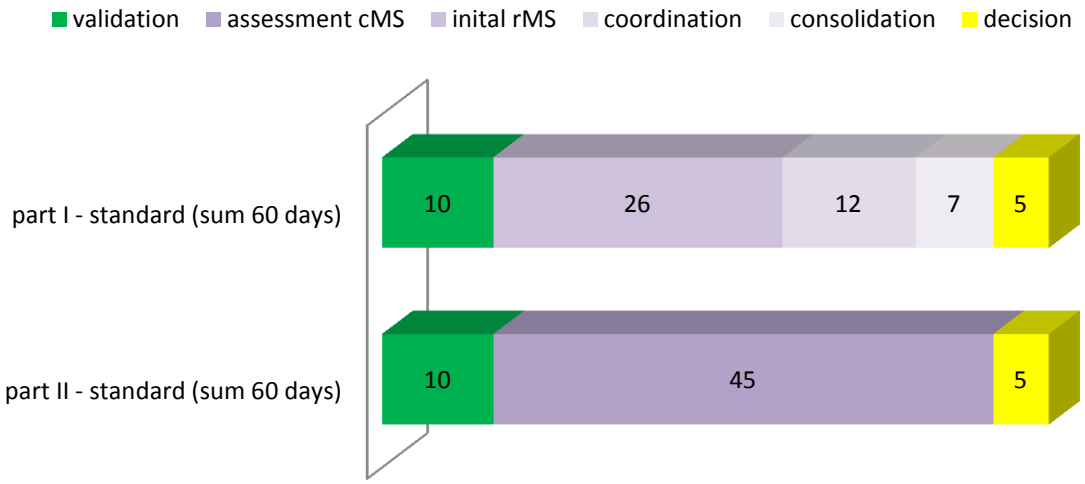
Application Dossier – Content & Submission



The EU-Portal



Timeline parallel assessment report for multiple MS (part I & II)



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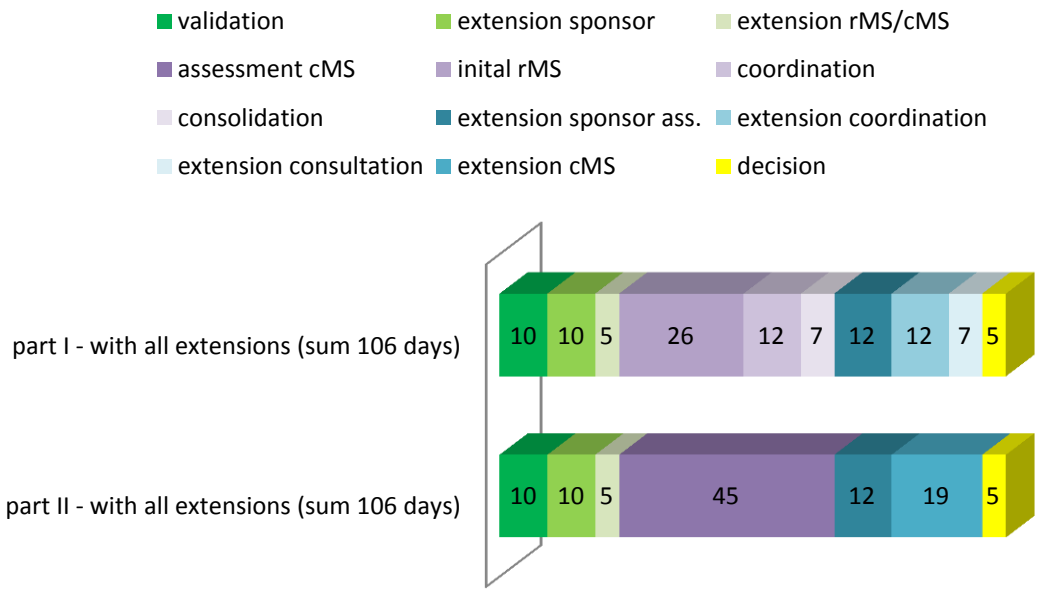

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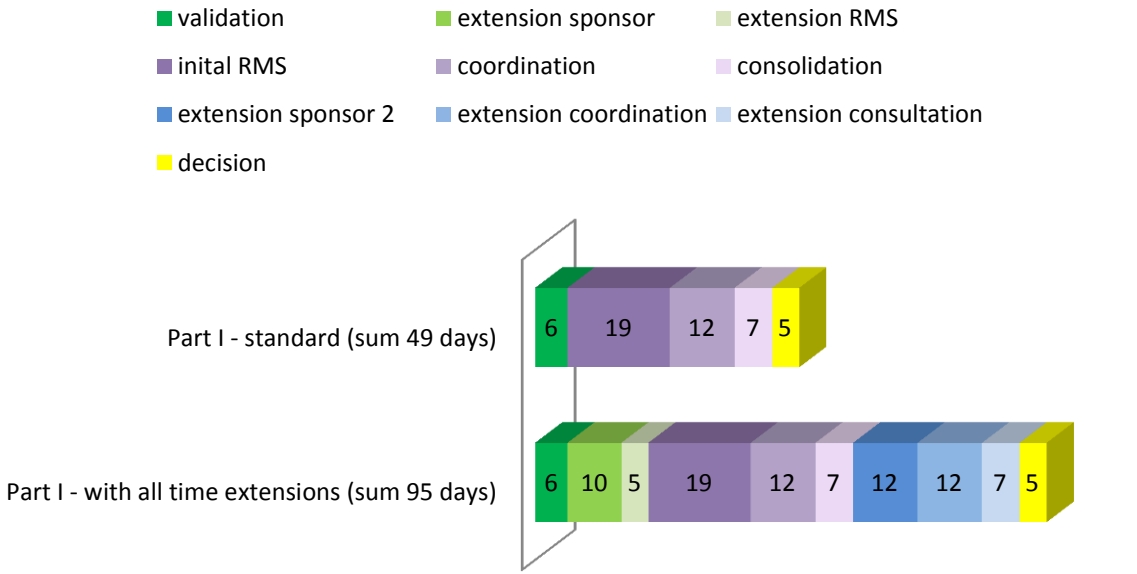
Decision Making

- Outcome of Part I assessment from rMS, reported to cMSs and sponsor:
  - Clinical trial is authorised
  - Authorised subject to conditions
  - Authorisation refused
- Each MS notifies the sponsor through the Portal within 5 days after the reporting date, resp. assessment date, whether the CT is acceptable, acceptable subject to compliance with specific conditions, or not acceptable
- Only 3 reasons for refusal:
  - Participation in CT would lead to inferior treatment than normal clinical practice in the Member State
  - Infringement of national legislation in CT with IMPs derived from cells
  - Considerations as regards subject safety and data reliability and robustness

Approval of 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 10 plus 5 days
- rMS provides assessment report within 19 days to cMS and sponsor
- cMS has to give decision within 12 days after validation date
- rMS has 7 days for consolidation
- Opportunity for request for additional information by rMS, sponsor has 12 days to respond

Timeline assessment of substantial modification for multiple MS (Part I)



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Implementation Timelines

- Coming into force: 17.06.2016

  However: only if EU-Database is fully functional, otherwise 6 months after functionality has been formally confirmed

- After that date the CTD is still in force for 3 years and the sponsor can choose the legislation for his trial

- Regulation's final coming into force as sole CT legislation: 28.05.2019 (or later if database functionality is delayed)

Conclusions

- We received a second chance to come to an efficient European system for study approval while ensuring reliable patient protection
- It is up to the Member States to establish an assessment system that provides DoH-compliant ethical review in collaboration with the competent authorities to come to one joint opinion on Part I and II and to national approval
- Voluntary harmonisation of assessment approaches would help to come to a simple system
- Member States have limited time to develop their assessment system and to adapt their legislation
- What we get now will determine clinical trials in Europe for the next 15 to 20 years