2023 – When the CTR will be in force for all – Let's be prepared

Early Phase Trials under the EU Clinical Trial Regulation –
What changes in the interaction between competent authorities
and ethics committees?

An overview of changing aspects for national Phase I trials under the EU Clinical Trial Regulation

Ingrid Klingmann, MD, PhD, FFPM, FBCPM, GFPM
Pharmaplex bv, EUFEMED
Brussels, Belgium

Changing Aspects for Phase I Trials

The European Union's Legislative Options

The legislations released by the European Commission have different "legal weight":

- "*Regulation*": text has to be implemented in national legislation as it stands
- "*Directive*": the principles have to be implemented in national legislation but leave the member states flexibility of interpretation and adaptation to national legislation *(leads to different conditions for many aspects of clinical trials in the different Member States)*
- "*Guidance*": defines in detail execution aspects and requirements generally lined out in the Directive or Regulation

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The New Clinical Trial Regulation EU 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

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Regulation EU 536/2014

Single Application Dossier to be entered into the Single Portal

- Introduction, General Principles
- Cover letter
- EU CTA 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
- Proof that data will be processed in compliance with GDPR

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EU DATABASE ‘CTIS’ (Clinical Trial Information System)

EMA has set-up and maintains 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

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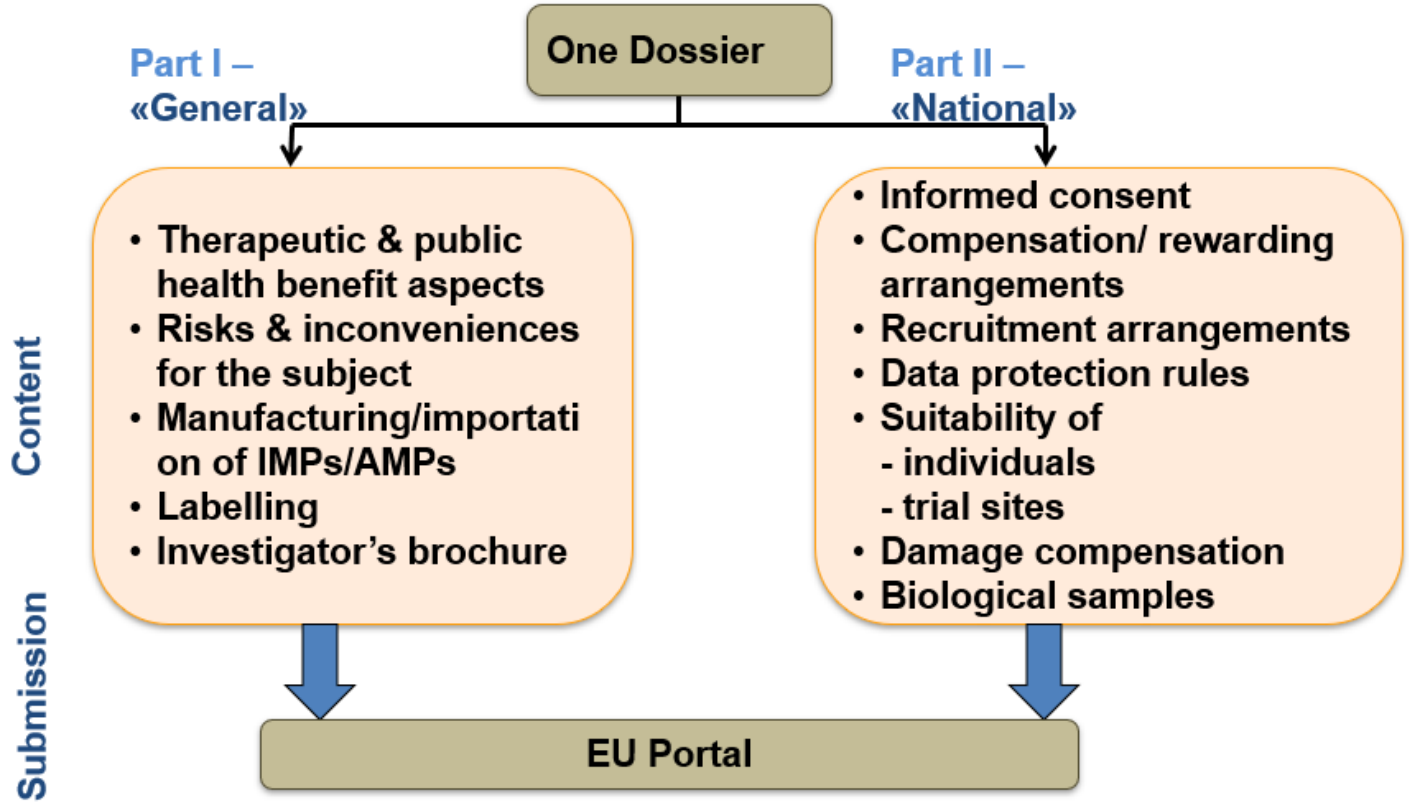
Application Dossier – Content & Submission



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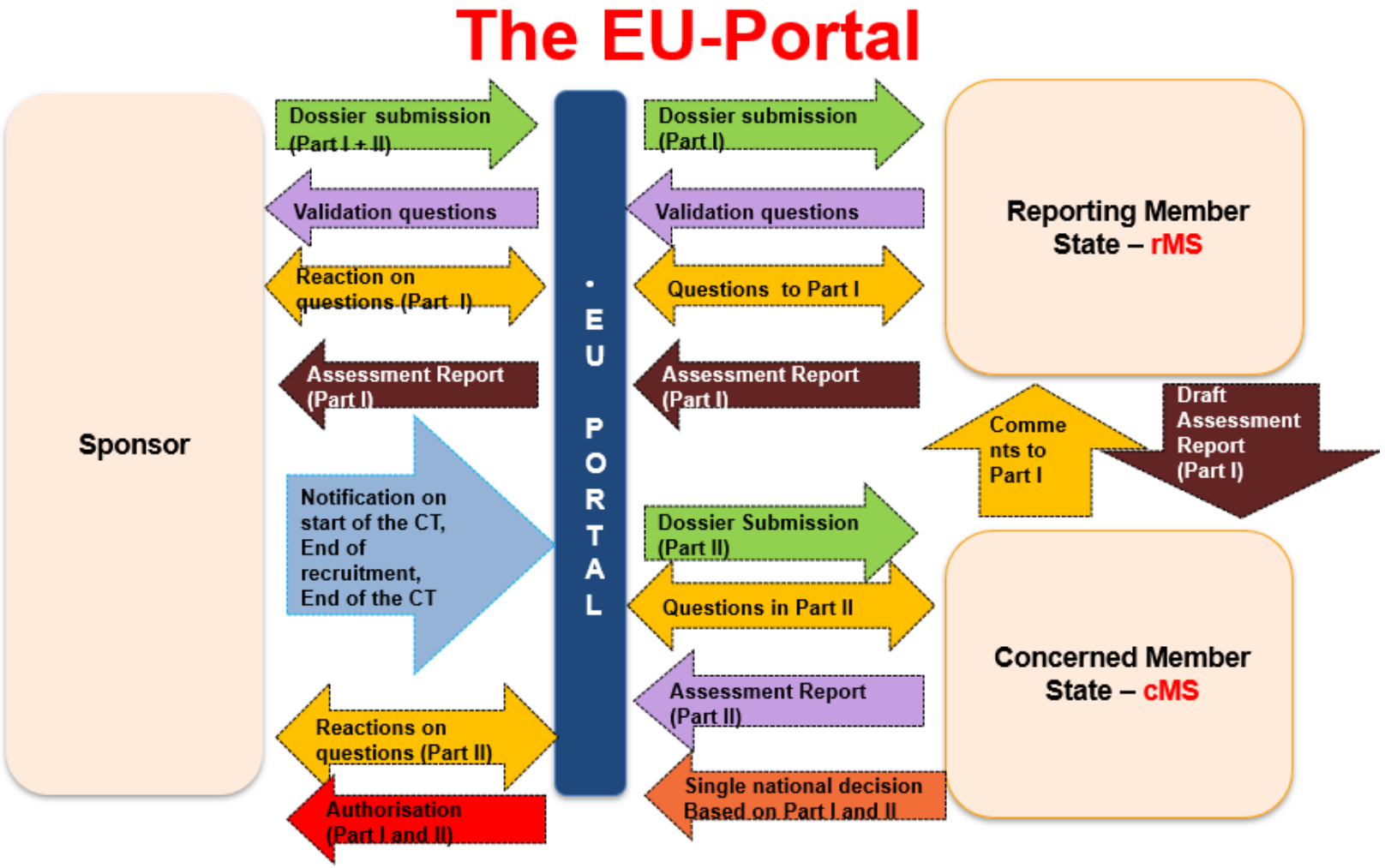

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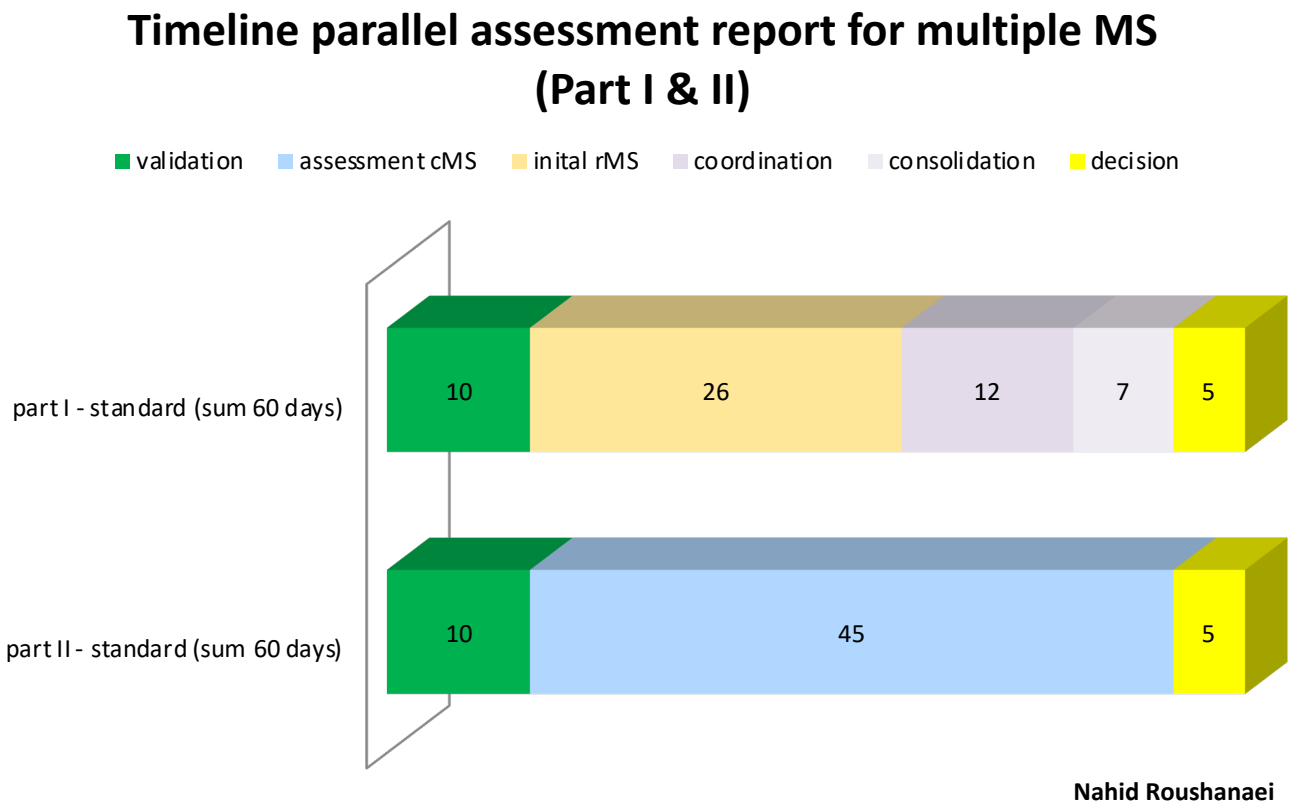
Assessment Timelines PART I + II (Best Case)



rMS can extend the 26 days by 50 days for Advanced Therapy or somatic cell/gene therapy IMPs

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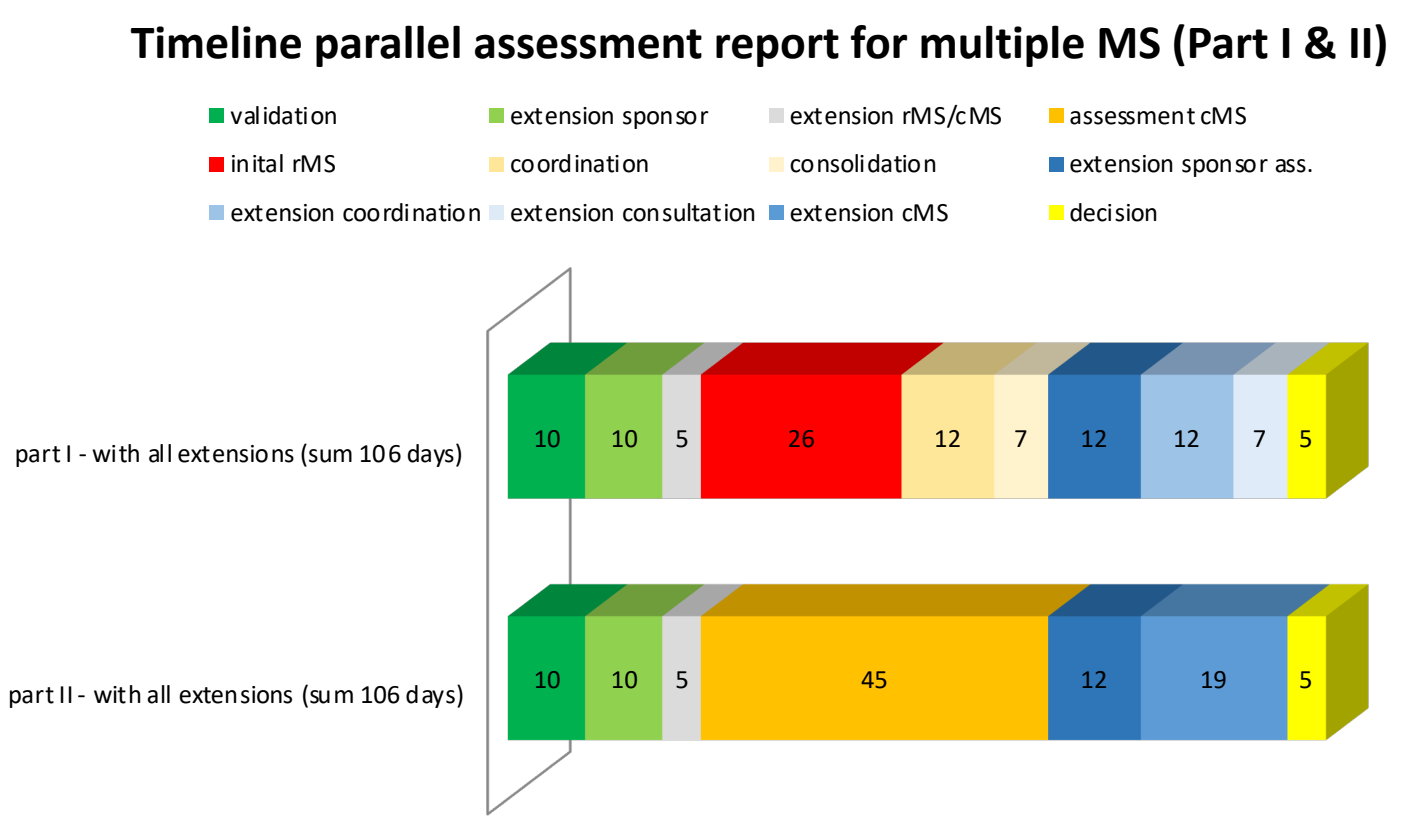
Assessment Timelines PART I + II (Worst Case)



Nahid Roushanaei

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Increased Notification Obligations and their Definitions

- “Start of the clinical trial”: the first act of recruitment of a potential subject in that Member State, unless defined differently in the protocol
- Start of recruitment: First study visit of the first subject in that Member State
- End of recruitment: Last patient enrolled in that Member State
- “End of the clinical trial”: the last visit of the last subject, unless defined differently in the protocol, in that Member State, in the EU, globally
- “Early termination of a clinical trial”: the premature end of a clinical trial due to any reason before the conditions specified in the protocol are complied with
- “Temporary halt of a clinical trial”: an interruption not provided in the protocol for the conduct by the sponsor with the intention of the sponsor to resume it
- “Suspension of a clinical trial”: interruption of the conduct of a trial by a Member State

Changing Aspects for Phase I Trials

Increased Notification Obligations and their Definitions

Serious Breaches

“Start of the clinical trial”: the first act of recruitment of a potential subject in that Member State, unless defined differently in the protocol

13.12.2021

Guideline for the notification of serious breaches of Regulation (EU) No 536/2014 or the clinical trial protocol

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-notification-serious-breaches-regulation-eu-no-536/2014-clinical-trial-protocol_en.pdf

Changing Aspects for Phase I Trials

Changed Definitions

- “Substantial modification”: any change to any aspect of the clinical trial which is made after notification of the authorisation decision and which is likely to have a substantial impact on the safety or rights of the subjects or on the reliability and robustness of the data generated in the clinical trial

- “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

Changing Aspects for Phase I Trials

Regulation EU 536/2014 ('Clinical Trials Regulation')

Art. 4: Prior authorisation

- A clinical trial shall be subject to scientific and ethical review and shall be authorised in accordance with this Regulations.

- The ethical review shall be performed by an ethics committee in accordance with the law of the Member State concerned. The review by the ethics committee may encompass aspects addressed in Part 1 of the assessment report for the authorisation of a clinical trial …… and in Part 2 of that assessment report ….. As appropriate for each Member State concerned.

- Member States shall ensure that the timelines and procedures for the review by the ethics committees are compatible with the timelines and procedures set out in this Regulation for the assessment of the application for authorisation of a clinical trial.

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Regulation EU 536/2014 ('Clinical Trials Regulation')

Art. 9: Persons assessing the application

- Member States have to ensure that the persons validating and assessing the application
  - Do not have a conflict of interest
  - Are independent of the sponsor, the clinical trial site and the investigators involved and of persons financing the CT
  - Are free of any other undue influence
- Member States have to ensure that assessment is done jointly by a reasonable number of persons who collectively have the necessary qualifications and experience
- At least one lay person

Changing Aspects for Phase I Trials

Regulation EU 536/2014 ('Clinical Trials Regulation')

Adaptation of national ethics committee systems

Most Member States have adapted their ethical review system for clinical trials falling under the Clinical Trials Regulation and under the Medical Device Regulation, especially concerning "independence" of the ethics committee, organisational efficiency, only involving a single ethics committee and a defined list of dossier documents to be reviewed

But

Most Member States kept their existing national ethics committee system for all other research in human projects

Changing Aspects for Phase I Trials

Regulation EU 536/2014 ('Clinical Trials Regulation')

EU Commission website "EudraLex Volume 10": Templates

- Compensation of trial participants
- Investigator curriculum vitae template
- Declaration of Interest template
- Site suitability form
- Informed consent and patient recruitment procedure template
- Compliance with applicable rules for biological samples

Changing Aspects for Phase I Trials

Clinical Trial Result Reporting

Definition 35

„Clinical Trial Report“ means a report on the clinical trial presented in an easily searchable format, prepared in accordance with Annex 1, Part I, Module 5 of Directive 2001/83/EC and *accompanying an application for marketing authorisation*

Art. 37.4

Irrespective of the outcome of a clinical trial, within *one year* from the end of the clinical trial in all Member States concerend, the sponsor shall submit to the EU database a *summary of the results* of the clinical trial Art. 37.4

It shall be accompanied by a summary written in a manner that is understandable to laypersons.

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Clinical Trial Result Reporting

Art. 37.4

In addition to the summary of results, where the clinical trial was *intended to be used for obtaining a marketing authorisation* for the IMP, the applicant for MA shall submit to the EU database the *clinical study report within 30 days* after the day the MA has been granted, the procedure for granting the MA has been completed, or the applicant for MA has withdrawn the application.

For cases where the sponsor decides to share raw data on a voluntary basis, the Commission shall produce guidelines for the formatting and sharing of those data.

Summary of results from Phase 1 trials need to be uploaded to CTIS within 30 months after end of the trial.

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Clinical Trial Result Reporting

Annex IV: Content of the summary of the results of the clinical trial

- General clinical trial information
- Subject disposition
- Baseline characteristics
- End points
- Adverse events
- Additional information

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Clinical Trial Result Reporting

Annex V: Content of summary of results of the clinical trial for lay persons

- Clinical trial identification
- Name and contact details of the sponsor
- General information about the trial
- Population of subjects
- IMPs
- Descrption of adverse reactions and their frequency
- Overall results of the clinical trial
- Comments on the outcome of the clinical trial
- Indication if follow-up clinical trials are foreseen
- Indication where additional information could be found

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Clinical Trial Result Reporting

Good Lay Summary Practice Recommendations

EudraLex Volume 10: https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-10/glsp_en.pdf

Generated by the Roadmap Initiative to Good Lay Summary Practice in collaboration with the European Commission‘s DG Santé „Clinical Trial Expert Group (CTEG)“

Including the collaboration and input from the US initiatives:

TransCelerate Biopharma Inc: “Layperson Summaries of Clinical Trials: An Implementation Guide” (2015)

MRCT*: Return of Results Guidance Document (16Jul2016)

*Multi-Regional Clinical Trial Center, Harvard University

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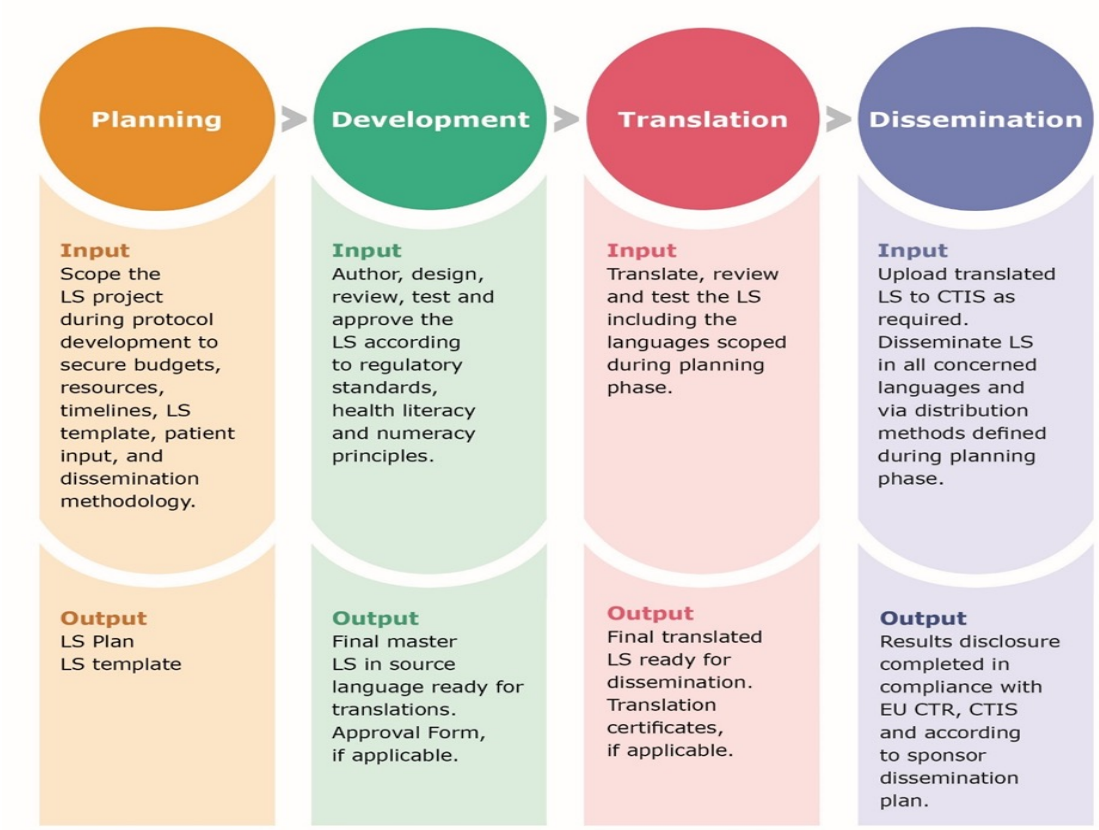
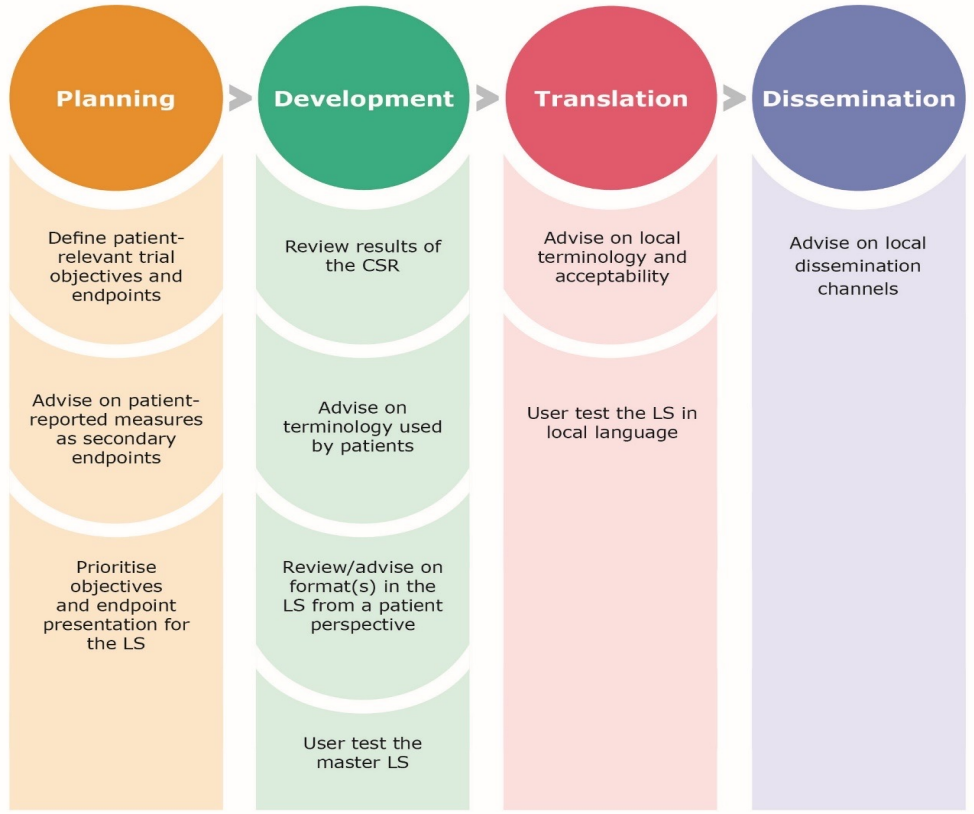
Good Lay Summary Practice Recommendations

Flowchart of the lay summary process



Patient involvement



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Be clear about the applicable EU regulatory framework:

Clinical Trials: Regulation EU 536/2014 “Medicines”

Clinical Investigations: Regulation 2017/745 “Medical Devices”

Clinical Performance Study: Regulation 2017/746 “In-vitro Diagnostics”

Remaining Studies: Current national legislation

UK and Switzerland have their own legislative framework for clinical trials