Federal agency for medicines and health products

Patient centricity: point of view of the Competent Authority

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1: The EU clinical trial regulation : benefits for the patient

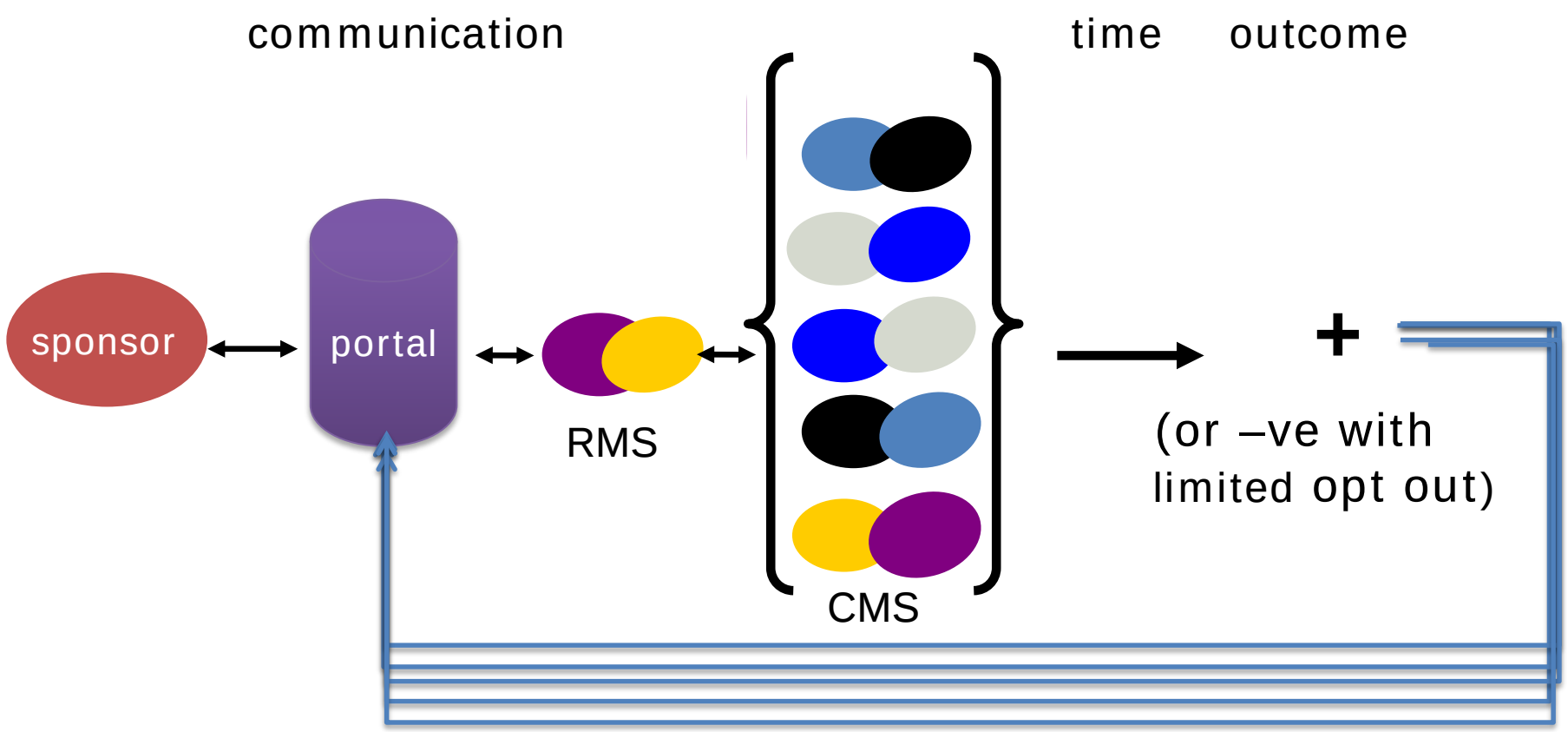
- Increased efficiency avoiding unnecessary duplication or repetition of unsuccesfull trials
  Involvement of patient representatives in the evaluation process: anticipated benefit/risk balance is positive and permanently monitored.

- Highest standards of safety
  - GCP
  - Safety

- Increased Transparancy

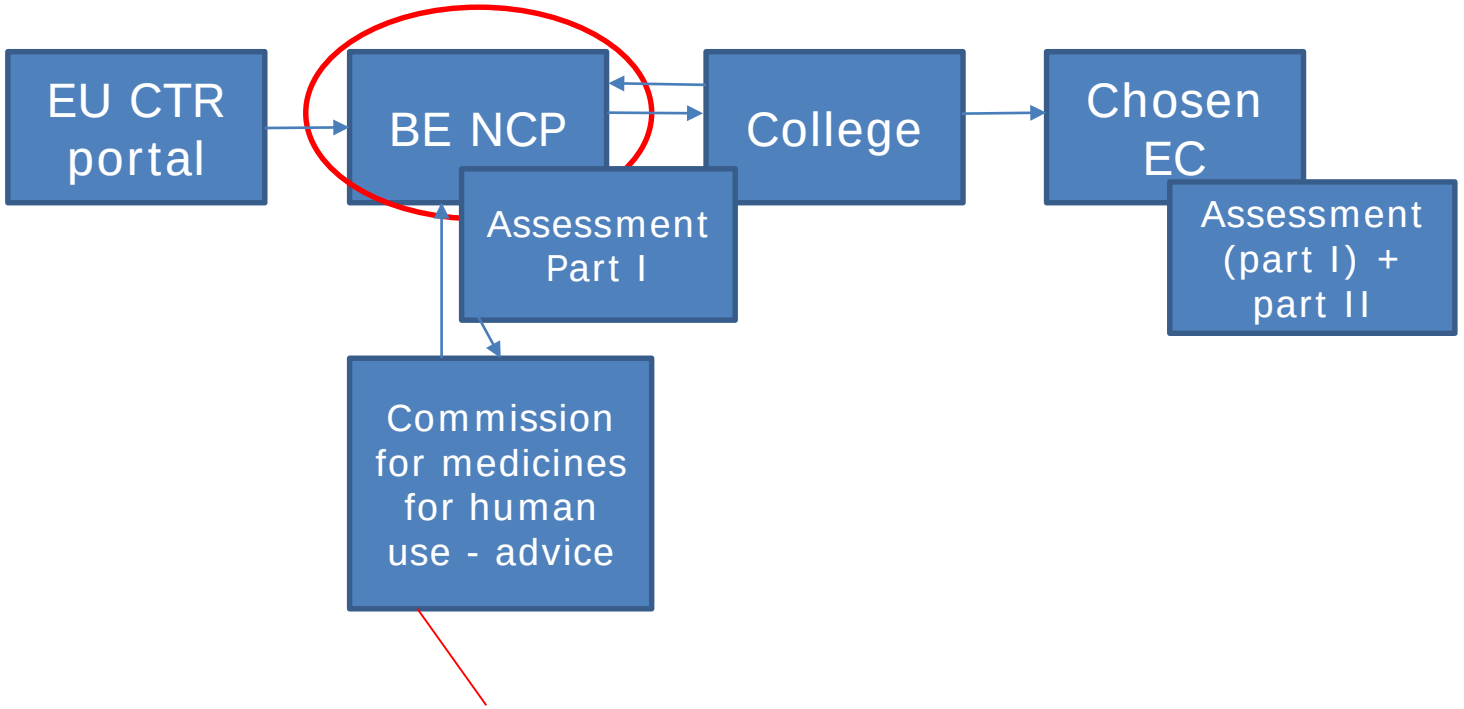
- Specific attention to the protection of participants
  - ICF and subject's rights
  - Damage compensation
  - Vulnerable populations (incapacitated subjects/minors; pregnant /breastfeeding women; emergency situations …)

2.1: New simplified procedure in EU

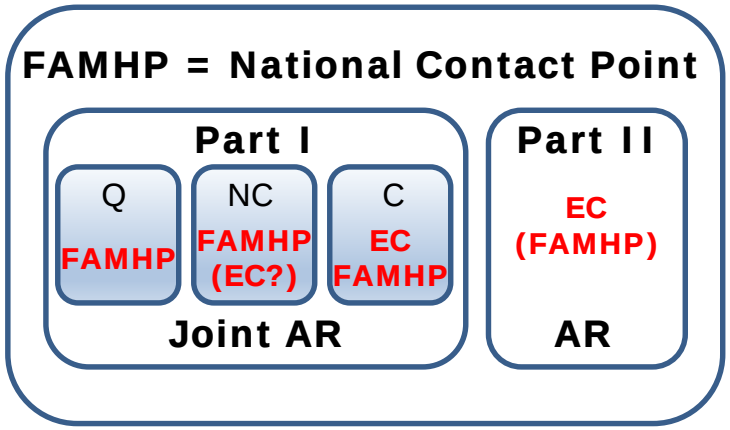


2.2: Belgium: processes and workflow

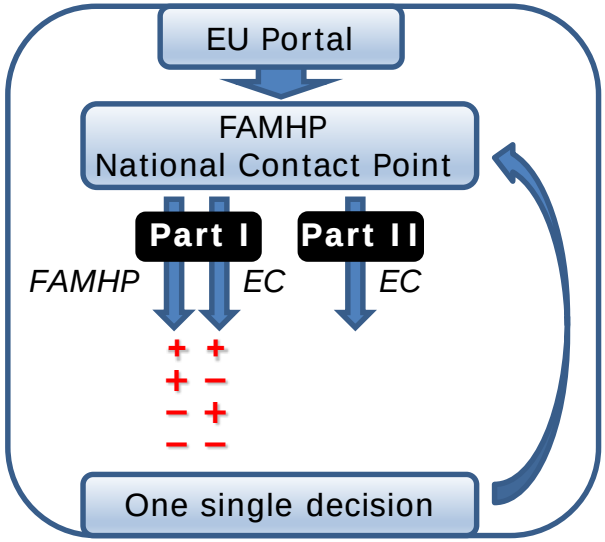
1. The FAMHP as national contact point



AR Part I:	**Quality:**	**FAMHP**
	Non-Clinical:	**FAMHP (EC?)**
	Clinical:	**EC and FAMHP**
AR Part II:		**EC (FAMHP)**



2. The “College” at the FPS of Public Health in a one-to-one relationship with the FAMHP



3. Independent ethical evaluation
4. Representation of lay-men and patients
5. Added value of co-assessment (in touch with medical reality)
6. Short timelines for phase 1 trials will be maintained
7. Pilot joint assessment FAMHP-EC ongoing

2.3: Patient involvement in the Benefit-risk assesment

- Evolution at the level of the Competent Authority:
  from focus on medicinal product towards patient/disease focus.
  Therapeutic Area Coordinators at the FAMHP

- Participation from patient representatives in scientific advice via the National Innovation Office and the SAWP at EMA.
  Ad Hoc consultations

- Representation of the patients at the level of the Commission for medicines for human use.
  Commission on permanent basis

- Finding patients to involve in those procedures:
  - Eligible organisations
  - Pool of patients – individual experts
  - Experience with disease as patient or carer
  - Free of conflict
  - Level of experience with medicines may vary

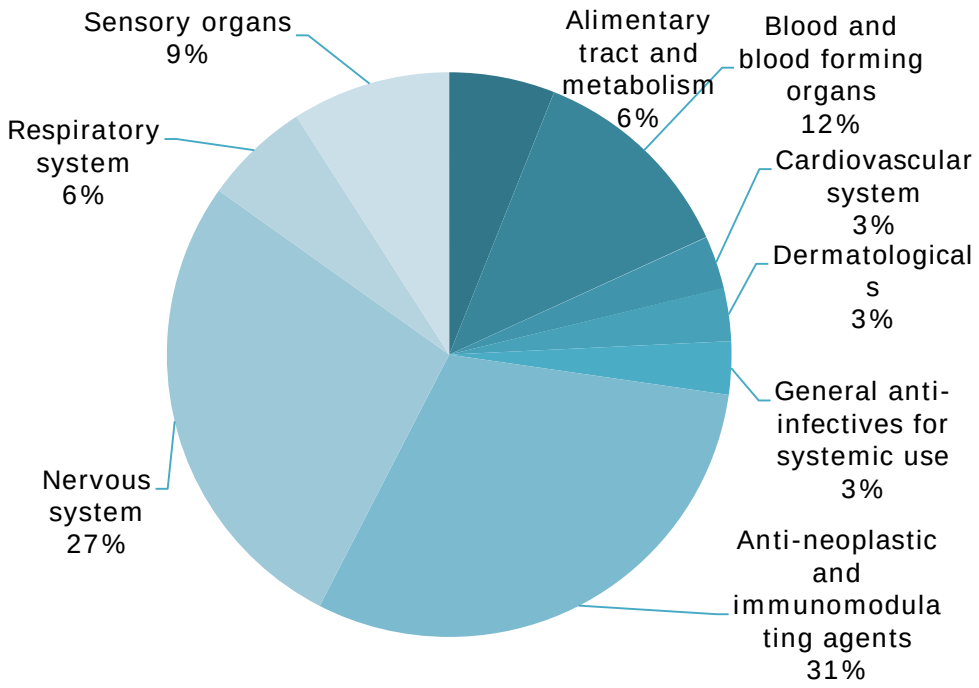
- Paticipating in person, by telecall or by written procedure

- Where patients can contribute:
  - Population, inclusion/exclusion criteria
  - Endpoints, choice of comparator
  - Quality of Life
  - Feasblity of the study

- Expertise on specific questions and/or general information on living with the disease, its manangement and its impact on daily life.

2.4: Scientific advice procedures with patient involvement. Experience from SAWP so far.

Alimentary tract and metabolism	2
Blood and blood forming organs	4
Cardiovascular system	1
Dermatologicals	1
General anti-infectives for systemic use	1
Anti-neoplastic and immuno-modulating agents	10
Nervous system	9
Respiratory system	2
Sensory organs	3
Total	33



3.1: Highest standards of safety: GCP inspections

- Protecting the rights, well-being ,safety of the subjects involved in clinical trials and assuring the reliability of the data.

- ICH E6 explicitely quoted in the new regulation 536/2014.

- Clear mandate of the GCP inspectors at MS level, empowering them to contact trial subjects if justified (Impl.Act 2017/556).

- EU Commission Guidance on:

    - Risk proportionated approach in clinical trials;
    - Serious Breaches;
    - ICF Cluster trials, pregnant/breastfeeding women, emergency trials …

- GCP Inspection reports will become public.

3.2 : Highest standards of safety : Safety reporting

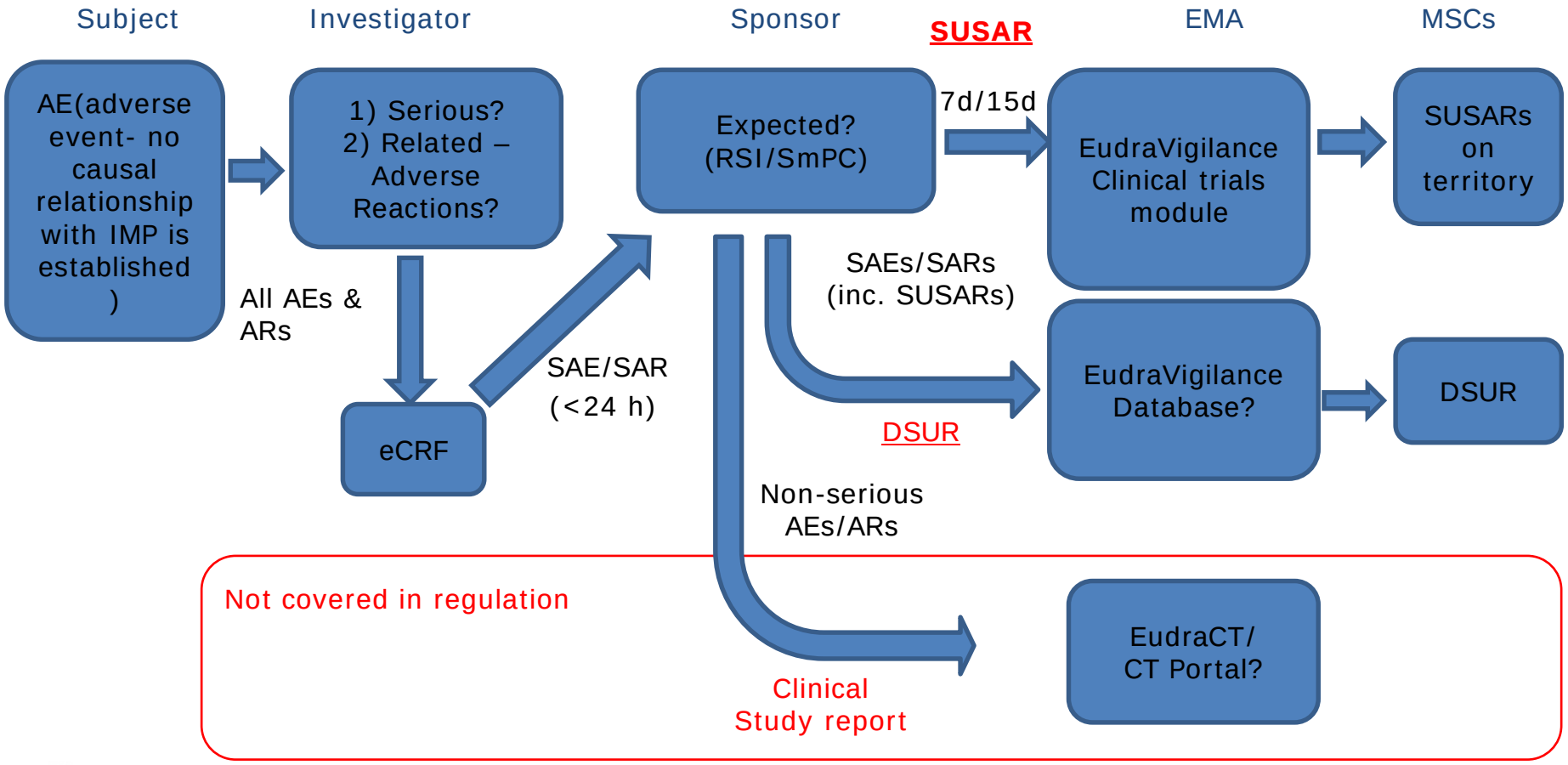
Importance of safety monitoring in clinical trials:

- An IMP under development → limited knowledge on safety profile → serious side-effects (SARs) as well as serious **unexpected** suspected adverse reactions (SUSARs) are possible!

We therefore need :

- To make sure that safety reporting is done correctly (no SUSAR underreporting) → adequate characterization of safety profile of an IMP.
- To make sure that safety of patients taking part in clinical trials is well protected → adequate risk minimization measures including frequent clinical tests, dose modifications and criteria for discontinuation are present in the study protocols.
- In case of safety issues, make sure that they are addressed by a sponsor, an investigator and patients are informed → assessment of urgent safety measures, investigator letter, update of clinical trial documents (investigator's brochure, protocol, ICF ...), taking measures (temporary halt or early termination of a clinical trial)

Clinical Trials Regulation 536/2014: articles 40-43 and CT-3: CT safety reporting routes



4: Transparancy

- Have all clinical trials been publicly registered?
- Is there a trial in which I could participate?
- What was the outcome of the trial I did participate in?
- What is known about the medicine I am taking / prescribing?
- What trials were the basis of the marketing authorisation, what results?
- Can we review the data used to support the marketing authorisation?
- Has the trial we are designing already been conducted? Were there problems with similar trials?

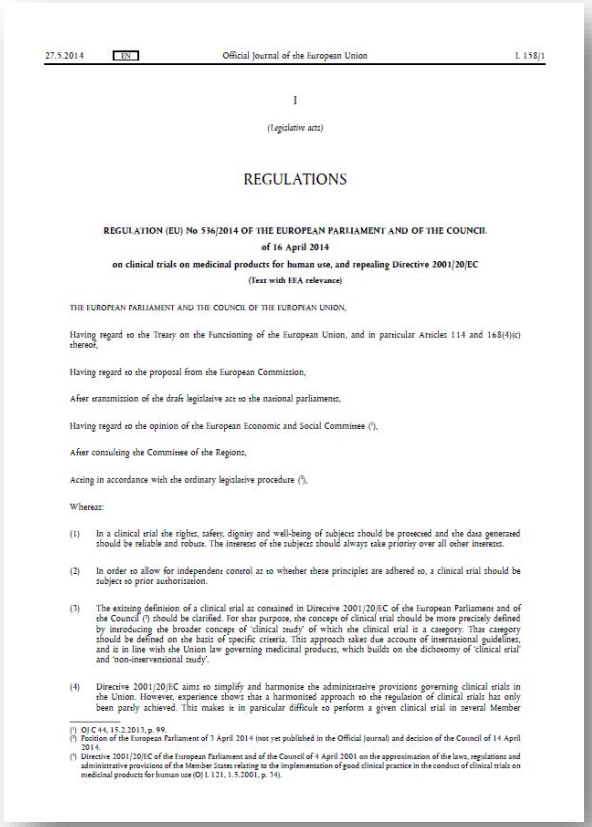
Strike the right balance to inform the public, protect public health and foster the innovation capacity of European medical research.

Clinical Trials Regulation: what about transparency?

- “The EU database should contain all relevant information as regards the clinical trial submitted through the EU portal. The EU database should be publicly accessible”.

Publicly available information contained in the EU database should contribute to:

- protecting public health and
- fostering the innovation capacity of European medical research,
- while recognising the legitimate economic interests of sponsors



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(Legislative acts)

REGULATIONS

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)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on the Functioning of the European Union, and in particular Articles 114 and 168(4)(c) thereof,

Having regard to the proposal from the European Commission,

After transmission of the draft legislative act to the national parliaments,

Having regard to the opinion of the European Economic and Social Committee (1),

After consulting the Committee of the Regions,

Acting in accordance with the ordinary legislative procedure (2),

Whereas:

(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.

(2) In order to allow for independent control as to whether these principles are adhered to, a clinical trial should be subject to prior authorisation.

(3) The existing definition of a clinical trial as contained in Directive 2001/20/EC of the European Parliament and of the Council (3) should be clarified. For that purpose, the concept of clinical trial should be more precisely defined by introducing the broader concept of 'clinical study' of which the clinical trial is a category. That category should be defined on the basis of specific criteria. This approach takes due account of international guidelines, and is in line with the Union law governing medicinal products, which builds on the dichotomy of 'clinical trial' and 'non-interventional study'.

(4) Directive 2001/20/EC aims to simplify and harmonise the administrative provisions governing clinical trials in the Union. However, experience shows that a harmonised approach to the regulation of clinical trials has only been partly achieved. This makes it in particular difficult to perform a given clinical trial in several Member

(1) OJ C 44, 15.2.2013, p. 99.
(2) Position of the European Parliament of 3 April 2014 (not yet published in the Official Journal) and decision of the Council of 14 April 2014.
(3) Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (OJ L 121, 1.5.2001, p. 34).

Article 81(4) of Regulation (EU) No. 536/2014

EU database publically accessible by default, with exceptions justified on any of the following grounds:

- Protection of personal data;
- Protection of commercially confidential information in particular taking into account the MA status of the medicinal product, unless there is an overriding public interest in disclosure;
- Protecting confidential communication between MS in relation to the preparation of the assessment report;
- Ensuring effective supervision of the conduct of a clinical trial MSs.

- A key aim of Clinical Trials Regulation is to provide publicly available information from the EU database, increasing transparency of clinical trials and their results.
- EU database will serve as the source of public information on clinical trial applications assessed, and clinical trials conducted in the EU, from authorisation to finalisation submission of results in the database.
- The **Disclosure Rules** intend to strike the right balance between:
  - respecting patients' and doctors' needs and the public entitlement to extensive and timely information about clinical trials;
  - and developers' and researchers' need to protect their investments;
  - The essential need to protect public health while also fostering the innovation capacity of European medical research.

4.1: Disclosure rules: protecting personal data

Personal data only to be entered into the database to the extent required for application of the Regulation (Article 81(6))

Clinical trial subjects evaluated for or participating in a trial

- No personal data of trial subjects will be publically available from the database.

Clinical trial investigator information to be made public

- Principal Investigators' names, name and addresses of clinical trial sites.
- Principal Investigators' CVs containing only professional information relevant to CT.
- Economic interests, institutional affiliations that might influence impartiality.
- Name of Head of clinic/institution, or responsible person issuing written statement testifying to suitability of facilities.

Sponsor staff

- Personal information identifying sponsor staff will only be public for those persons with legal roles, or where the sponsor is a natural person (e.g. an investigator who is also the sponsor, or where the legal representative is a natural person).

MAH / applicant personnel

- Names of signatories of the clinical study report and the investigator(s) who conducted the trial should be identified and will be made public.
- Personal information identifying other MAH/applicant/sponsor personnel identified in the clinical study report may be redacted or omitted but what is loaded into the database by the MAH/applicant will be made public

Member state experts

- No personal information identifying Member State experts will be made public

4.2: Disclosure rules: protecting commercially confidential information

- Trials defined as belonging to one of three categories, at the time of initial assessment of the clinical trial application:
  - Category One: Pharmaceutical development trials– essentially Phase I trials in healthy or patient volunteers, bio-equivalence and bio-similarity trials.
  - Category Two: Therapeutic exploratory and confirmatory trials - essentially Phase II and III trials of novel products or new indications or formulations of existing products
  - Category Three: Therapeutic use trials – essentially Phase IV and low-intervention trials
- Depending on the category of trial the sponsor can defer publication of certain data and documents up to a maximum time limit, if needed
- The sponsor will set the deferrals when drafting the application, submit with application
- The use of deferrals will be monitored and should not exceed what is really needed.

OPTIONS FOR DEFERRALS				
		CATEGORY 1	**CATEGORY 2**	**CATEGORY 3**
Main Characteristics of the trial		For a subset of information and up to the time the CT Results Summary is posted (Justification)	No deferral	No deferral
Trial related documents	Subject Information sheet	Up to the time of MA using this trial or up to 7 years after the end of the trial, whichever is earlier	Up to the time of MA using this trial or up to 5 years after the end of the trial, whichever is earlier	No deferral
	Protocol	As above	As above	Up to the time the CT Results Summary is posted (usually 12 months after the end of the trial in the EU)
Product related Documents	IB	As above	As above	As above
	IMPD, S&E	As above	As above	As above
Assessors documents /data	Request for information	MS decides but takes into account the exceptions of the legislation and the deferral time proposed by the sponsor		
	AR (I & II)			
	Conditions			

- "**Irrespective of the outcome of a clinical trial**, within one year from the end of a clinical trial in all Member States concerned, the sponsor shall submit to the EU database a summary of the results of the clinical trial."
- Publication of results of all trials
  - **Results summary, layperson summary made public 12 months after the end of each trial**
  - Clinical study report following MAA in EU.
- Possibility of justified deferral for summary results in case of category I trials up to a maximum of 30 months post end of trial (i.e. maximum 18 months deferral).

5: Additional initiatives

- Info to patients and health care providers on running clinical trials in Belgium on the FAMHP website.
- Accreditation of phase 1 centres and national database for healthy volunteers.
- Facilitating recruitment of patients:
  - Cooperation between centres (i.e. paediatric oncology)
  - Enhancing and facilitating the role of the general practicioner
- Fostering the coöperation of all the concerned stakeholders in order to facilitate the access to innovation in the benefit of the patient.

Acknowledgements to the FAMHP collegues from:

- Division R&D (human)
- Medicines GCP Entity
- Legal Affairs Division
- National Innovation Office – Scientific Technical Advice Unit and the SAWP members
- Assessors Division
- Dr. Ana Rodriguez (EMA)

Thank you for listening

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