WECAN
Workgroup of European Cancer Patient Advocacy Networks

Patient perspective on the new Clinical Trials Regulation

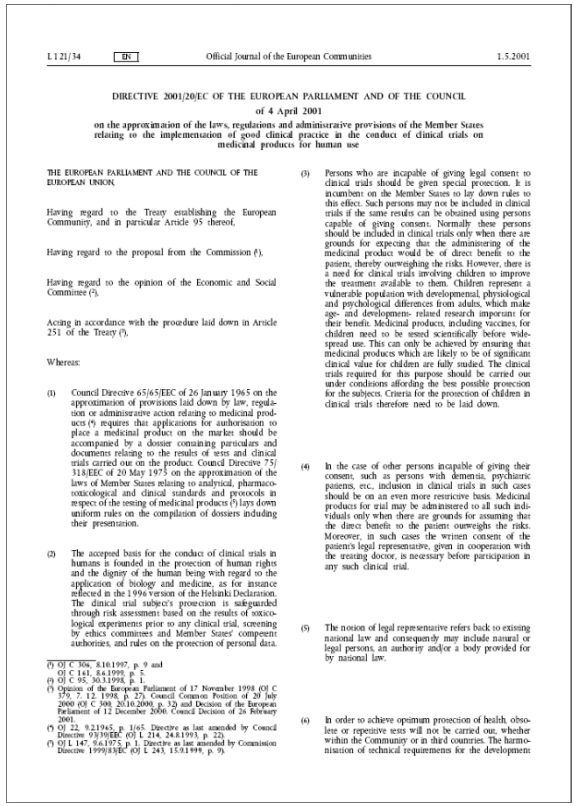
The past, the present and (our hopes for) the future

Jan Geissler, ESMO webinar, 12/10/2021

EU Clinical Trial Directive (2001/2005)

- Clinical Trial Directives 2001/20/EC and 2005/28/EC **introduced in early 2000s to protect us, the patients:**
  - **Ensure safety** of participants
  - **Guarantee rights** of participants
  - ~~Harmonisation of trial procedures across the EU~~
  - ~~Increase reliability and robustness of trial data~~

- Implementation did **not fully serve the interests of patients** (nor research nor industry): false promises of safety through bureaucracy, heterogeneity of implementation on Member State Level



L 121/34 EN Official Journal of the European Communities 1.5.2001

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

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,

Having regard to the proposal from the Commission (1),

Having regard to the opinion of the Economic and Social Committee (2),

Acting in accordance with the procedure laid down in Article 251 of the Treaty (3),

Whereas:

(1) Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products (4) requires that applications for authorisation to place a medicinal product on the market should be accompanied by a dossier containing particulars and documents relating to the results of tests and clinical trials carried out on the product. Council Directive 75/318/EEC of 20 May 1975 on the approximation of the laws of Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of medicinal products (5) lays down uniform rules on the compilation of dossiers including their presentation.

(2) The accepted basis for the conduct of clinical trials in humans is founded in the protection of human rights and the dignity of the human being with regard to the application of biology and medicine, as for instance reflected in the 1996 version of the Helsinki Declaration. The clinical trial subject's protection is safeguarded through risk assessment based on the results of toxicological experiments prior to any clinical trial, screening by ethics committees and Member States' competent authorities, and rules on the protection of personal data.

(3) Persons who are incapable of giving legal consent to clinical trials should be given special protection. It is incumbent on the Member States to lay down rules to this effect. Such persons may not be included in clinical trials if the same results can be obtained using persons capable of giving consent. Normally these persons should be included in clinical trials only when there are grounds for expecting that the administering of the medicinal product would be of direct benefit to the patient, thereby outweighing the risks. However, there is a need for clinical trials involving children to improve the treatment available to them. Children represent a vulnerable population with developmental, physiological and psychological differences from adults, which make age- and development- related research important for their benefit. Medicinal products, including vaccines, for children need to be tested scientifically before widespread use. This can only be achieved by ensuring that medicinal products which are likely to be of significant clinical value for children are fully studied. The clinical trials required for this purpose should be carried out under conditions affording the best possible protection for the subjects. Criteria for the protection of children in clinical trials therefore need to be laid down.

(4) In the case of other persons incapable of giving their consent, such as persons with dementia, psychiatric patients, etc., inclusion in clinical trials in such cases should be on an even more restrictive basis. Medicinal products for trial may be administered to all such individuals only when there are grounds for assuming that the direct benefit to the patient outweighs the risks. Moreover, in such cases the written consent of the patient's legal representative, given in cooperation with the treating doctor, is necessary before participation in any such clinical trial.

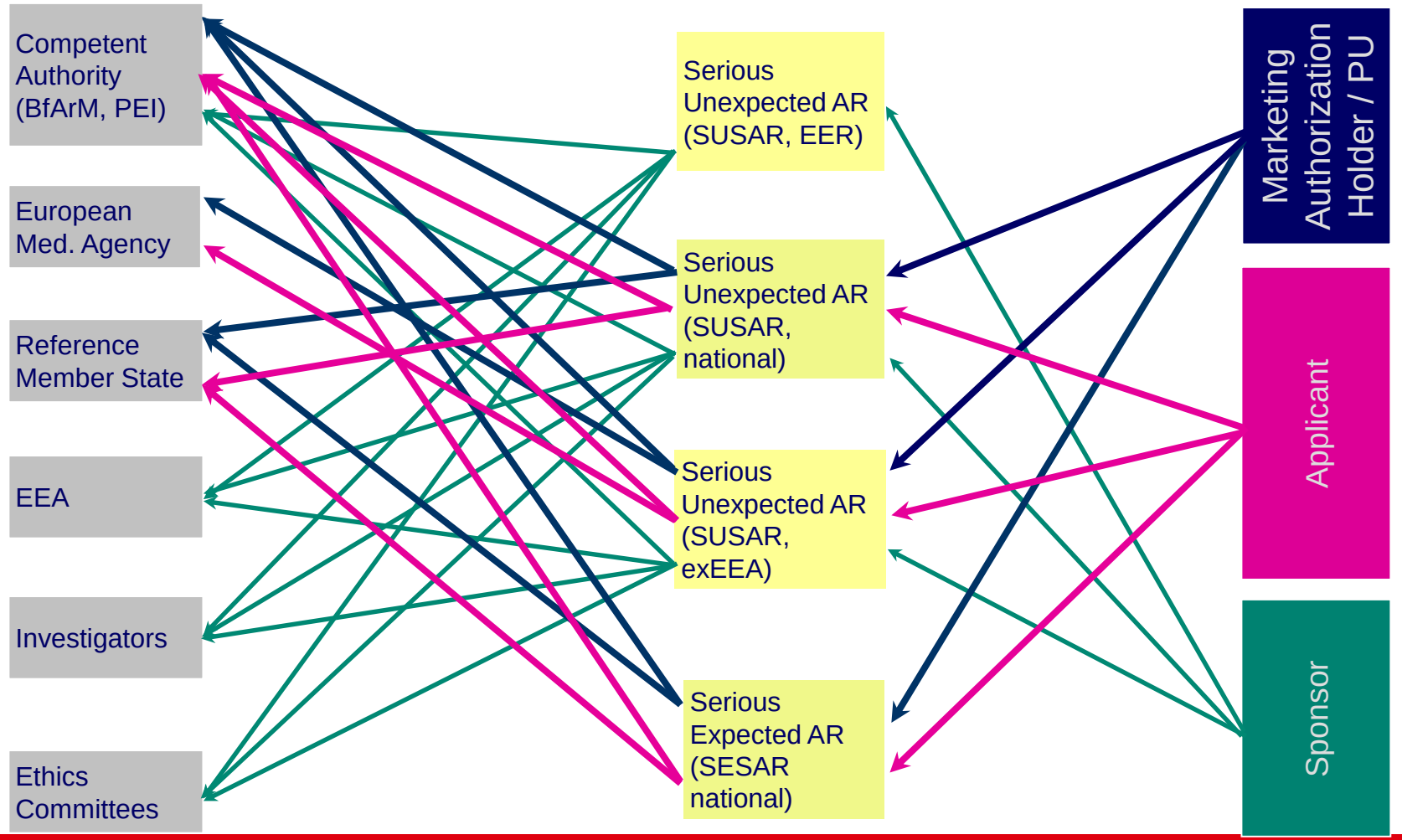
(5) The notion of legal representative refers back to existing national law and consequently may include natural or legal persons, an authority and/or a body provided for by national law.

(6) In order to achieve optimum protection of health, obsolete or repetitive tests will not be carried out, whether within the Community or in third countries. The harmonisation of technical requirements for the development

(1) OJ C 306, 8.10.1997, p. 9 and OJ C 161, 6.6.1998, p. 5.
(2) OJ C 95, 30.3.1998, p. 1.
(3) Opinion of the European Parliament of 17 November 1998 (OJ C 379, 7.12.1998, p. 27), Council Common Position of 20 July 2000 (OJ C 300, 20.10.2000, p. 32) and Decision of the European Parliament of 12 December 2000. Council Decision of 26 February 2001.
(4) OJ 22, 9.2.1965, p. 1/65. Directive as last amended by Council Directive 93/39/EEC (OJ L 214, 24.8.1993, p. 22).
(5) OJ L 147, 9.6.1975, p. 1. Directive as last amended by Commission Directive 1999/83/EC (OJ L 243, 15.9.1999, p. 9).

Example Clinical Trials Directive (2001) Safety Reporting

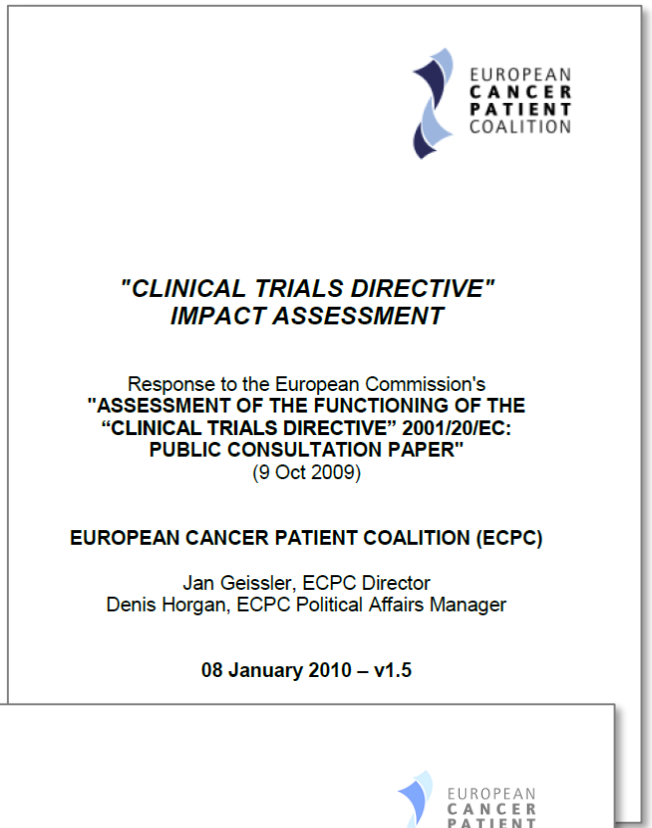
Obligatory reporting of unexpected adverse events, based on German implementation of CTD in medicines law (§63b AMG) and Good Clinical Practice act (§13 GCP)



(Source: Paul-Ehrlich Institute 2009)

Suggestions for modification of CTD (2010-2014): What the patient community said

- **Reverse the trend** from academic to industry-led cancer research
- **Return to a research-friendly, less fragmented framework for trials** in Europe
  - **Consider risk-adapted approaches** (e.g. therapy optimization)
  - **Safety reporting** adjusted to real need
  - Increase transparency of **public information about trials**
  - Re-assessment of cost/benefit of **new insurance requirements,** especially to support long-term observational studies and academic trials in oncology
- **Inclusion of patient groups** when 'needs for protection' are discussed – in policy but also ethics reviews



EUROPEAN CANCER PATIENT COALITION

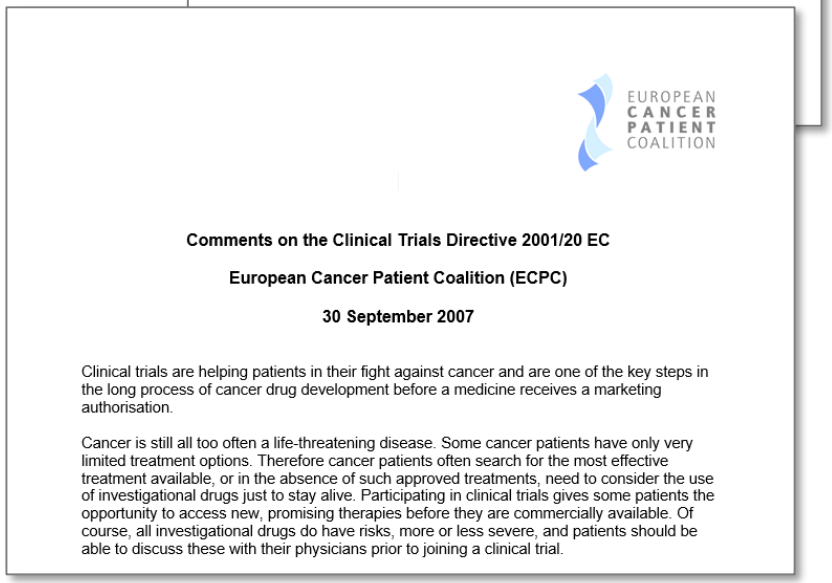
"CLINICAL TRIALS DIRECTIVE" IMPACT ASSESSMENT

Response to the European Commission's
"ASSESSMENT OF THE FUNCTIONING OF THE "CLINICAL TRIALS DIRECTIVE" 2001/20/EC: PUBLIC CONSULTATION PAPER"
(9 Oct 2009)

EUROPEAN CANCER PATIENT COALITION (ECPC)

Jan Geissler, ECPC Director
Denis Horgan, ECPC Political Affairs Manager

08 January 2010 – v1.5



EUROPEAN CANCER PATIENT COALITION

Comments on the Clinical Trials Directive 2001/20 EC

European Cancer Patient Coalition (ECPC)

30 September 2007

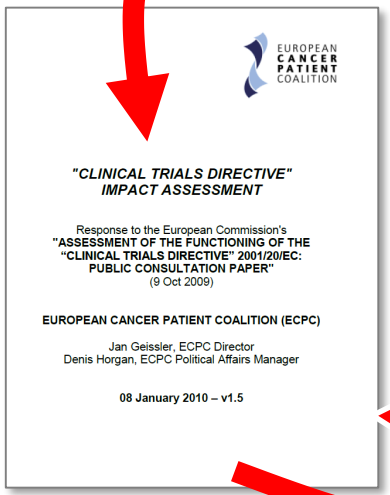
Clinical trials are helping patients in their fight against cancer and are one of the key steps in the long process of cancer drug development before a medicine receives a marketing authorisation.

Cancer is still all too often a life-threatening disease. Some cancer patients have only very limited treatment options. Therefore cancer patients often search for the most effective treatment available, or in the absence of such approved treatments, need to consider the use of investigational drugs just to stay alive. Participating in clinical trials gives some patients the opportunity to access new, promising therapies before they are commercially available. Of course, all investigational drugs do have risks, more or less severe, and patients should be able to discuss these with their physicians prior to joining a clinical trial.

What we patients had done about the revision of the directive: Nothing about us without us…

- **Worked with clinicans to understand CTD's impact on investigator-led research** (ELN, Kompetenznetze)
- **Shared positions** with professional associations & working groups (EHA, EFGCP, ELN, etc)
- **Supported the EU Commission and EU Parliament** with patient perspective and evidence
- **Increased public pressure for change** by addressing the need for patient-centered revision at conferences (DIA, EFGCP)

„[…] The **German Hodgkin Study group** was required to provide 100.000 copied pages of documents to Ethics reviews and authorities for a single study with 280 participating clinics and 65 ethics committees. Furthermore, the **GMALL study group** had to provide 35 folders and 12.000 pages for a study conducted in 13 centres. […]"


EUROPEAN CANCER PATIENT COALITION

"CLINICAL TRIALS DIRECTIVE" IMPACT ASSESSMENT

Response to the European Commission's "ASSESSMENT OF THE FUNCTIONING OF THE "CLINICAL TRIALS DIRECTIVE" 2001/20/EC: PUBLIC CONSULTATION PAPER" (9 Oct 2009)

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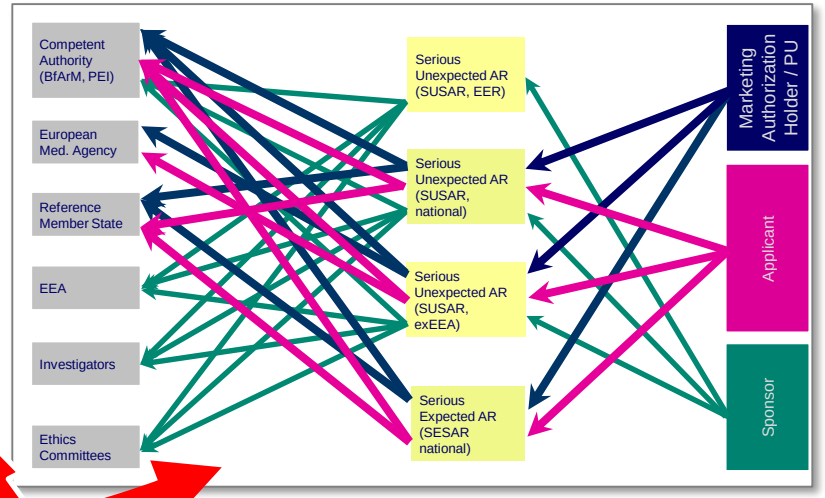
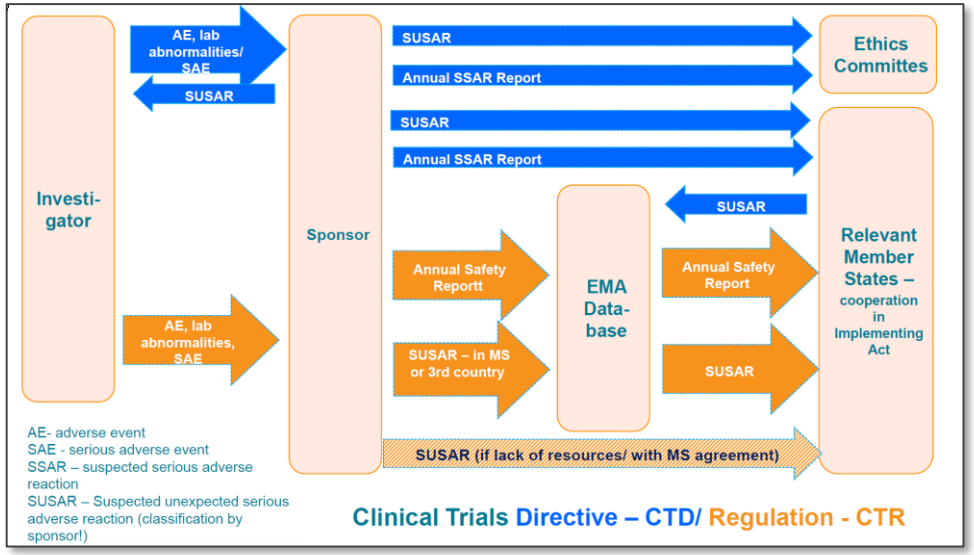
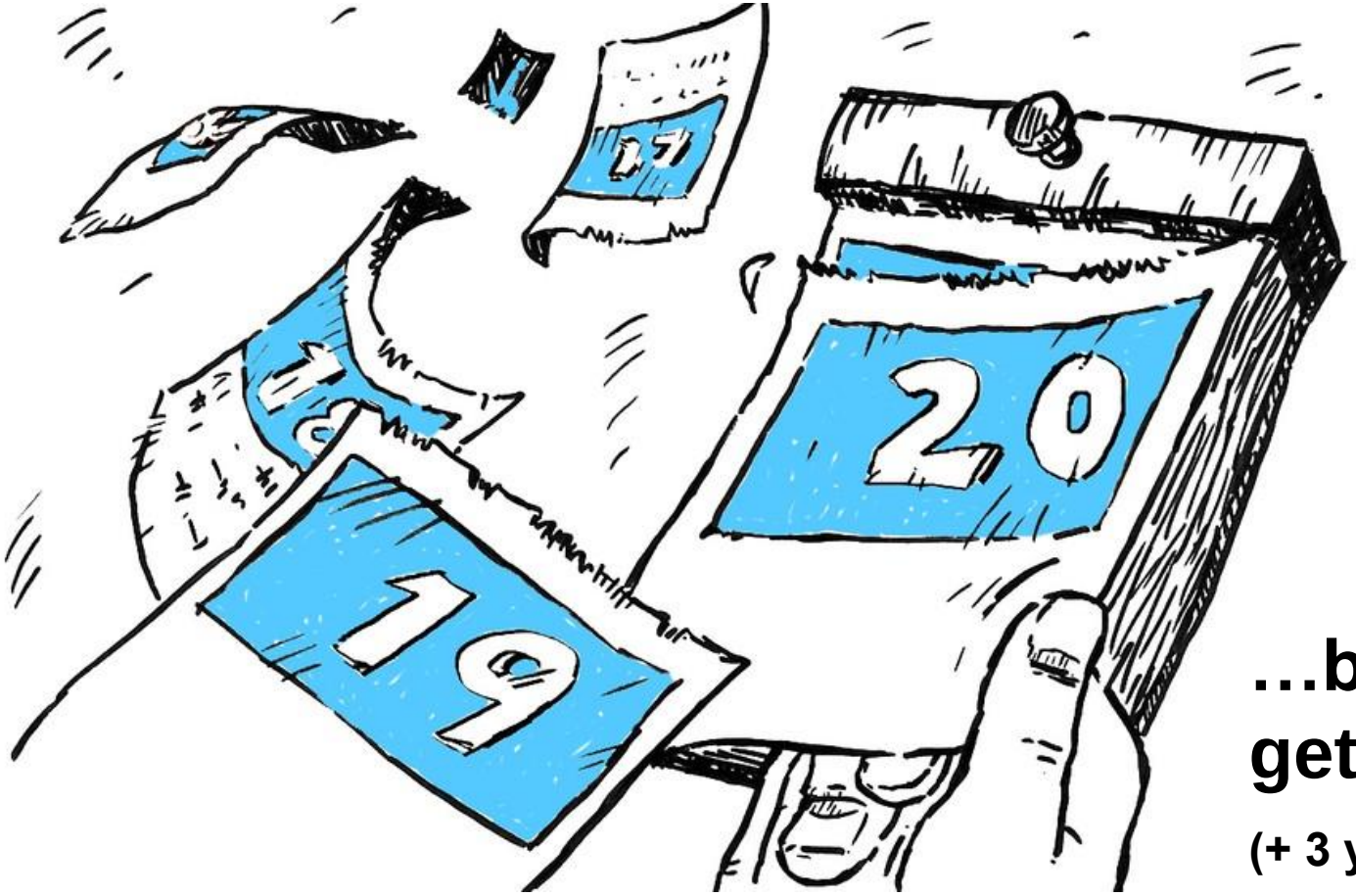


Clinical Trials Regulation (536/2014): High expectations (not only) from the patient community

- One dossier, one portal, one database
- More efficient safety reporting
- Risk-adapted safety reporting
- Coordinated assessment procedure
- One decision per EU Member State
- Tighter timelines, accelerated research
- Better public information on clinical trials (& data) through CTIS



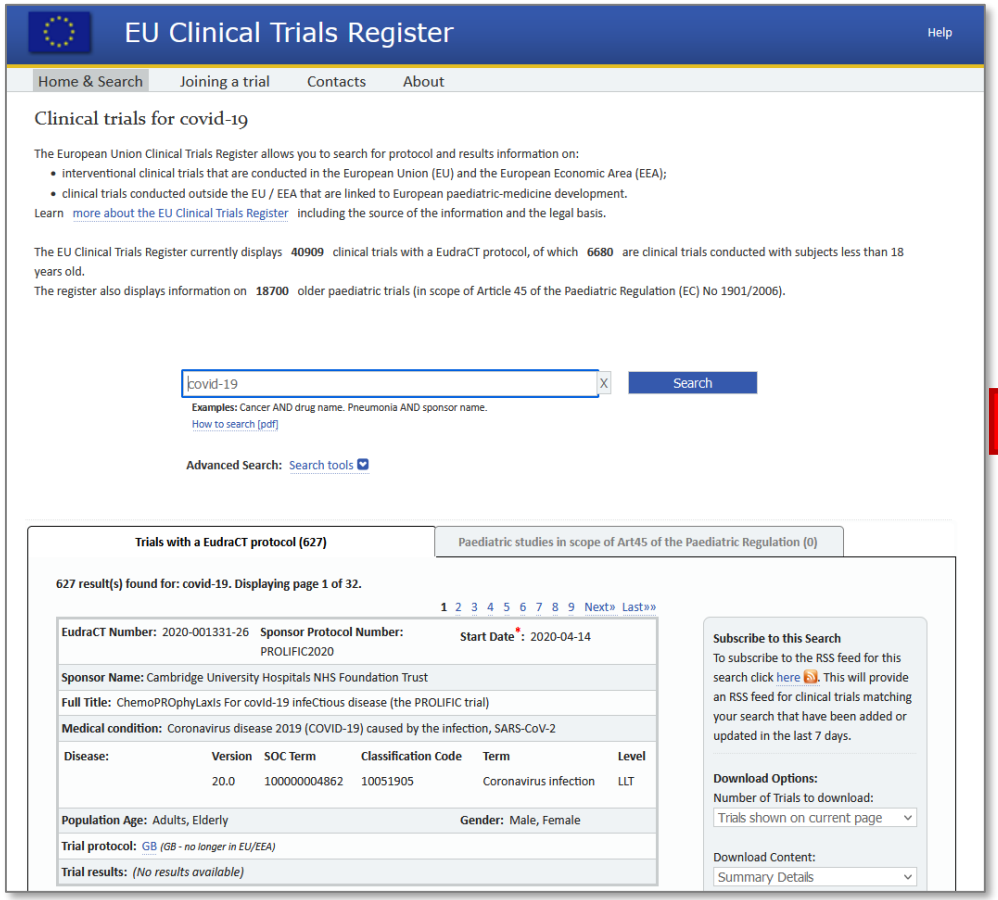
Policy implementation has been unable to catch up with needs of patients and science: Clinical Trial Regulation 536/2014

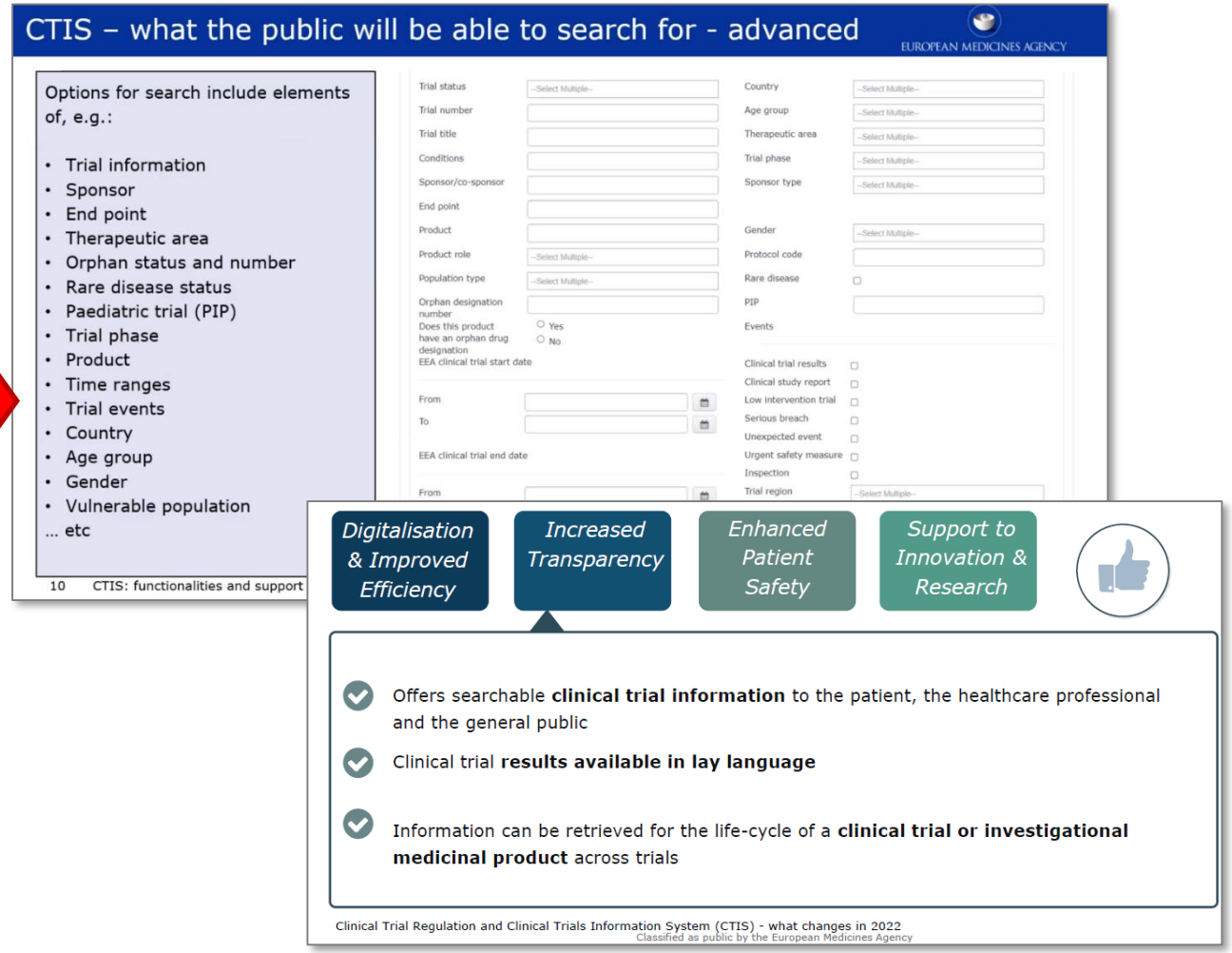


…but we're finally getting there on 31/1/2022

(+ 3 years until it's mandatory)

EudraCT's public interface clinicaltrialsregister.eu has been a mess. Will CTIS be any better for us patients?





Patient involvement in trial applications, trial design and ethics committees – established by law in 536/2014

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Preamble (18)

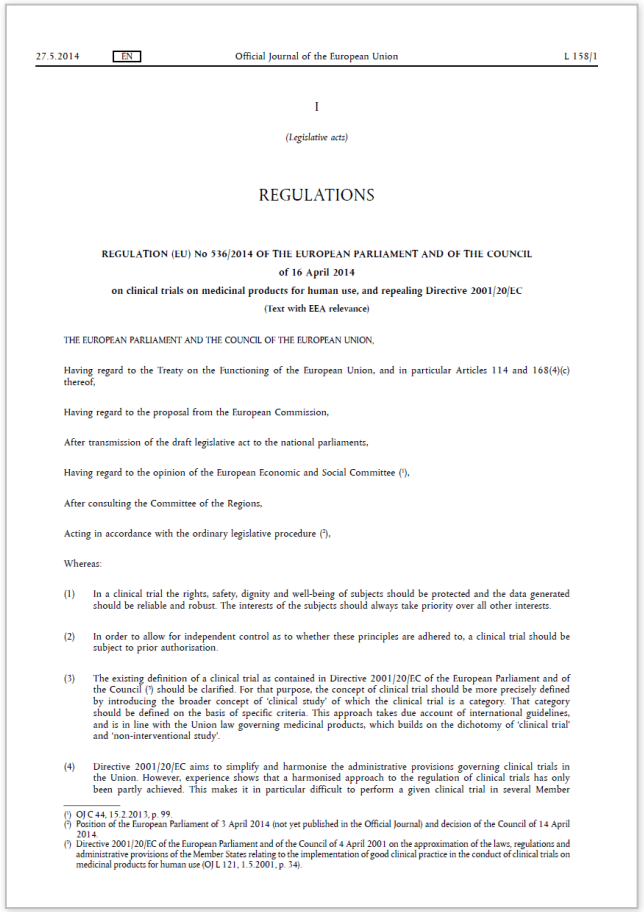
- *In the **assessment of the application** to conduct a clinical trial and to organise the involvement of ethics committees […] Member States should ensure the **involvement of laypersons, in particular patients or patients' organisations**.*

Article 2 (11)

- ***'Ethics committee'** means an independent body established in a Member State in accordance with the law of that Member State and empowered to give opinions for the purposes of this Regulation, **taking into account the views of laypersons, in particular patients or patients' organisations.***

Annex I, D. PROTOCOL (17)

- ***The protocol** shall at least include: […]*
  *(e**) where patients were involved in the design** of the clinical trial, a description of their involvement*



27.5.2014 EN Official Journal of the European Union L 158/1

I

(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).

Conclusions

- The clinical trials directive of 2001 was NOT in patients' best interests and did NOT achieve its objectives

- We welcome the new regulation finally to come into effect.
  Let's now catch up on the past 8 years (2014 → 2022)

- It suggests patient involvement in protocol design, assessment of trial applications, and ethics committees. Let's make this a reality this time.