Historical overview on the ethical approaches to clinical trials

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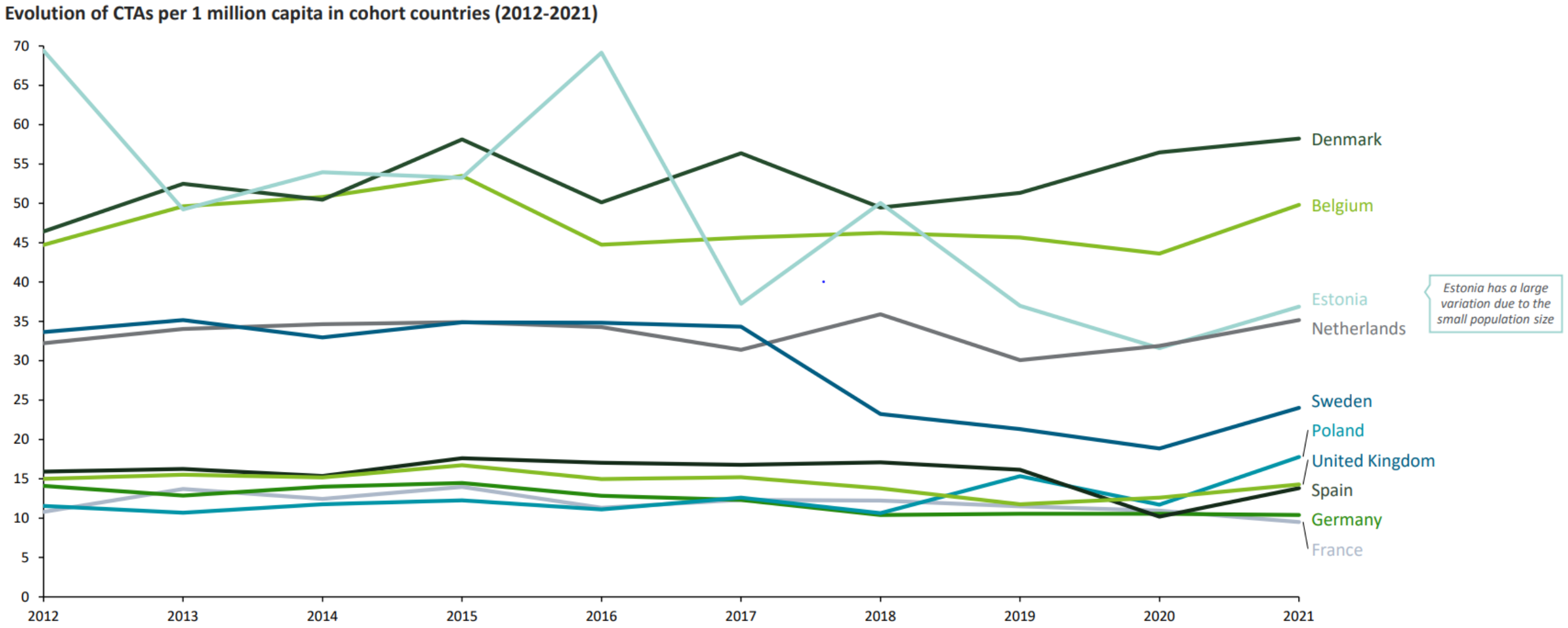
Evolution of clinical trial authorizations in EU



Source: Monitor Deloitte analyses based on National Medicines Agencies' reports, FAMHP data, and Eurostat; MHRA (2022). MHRA Update, March 2022

Countries conducting the most clinical trials

	Country	Total number of studies
1	United States	148,736
2	France	30,080
3	Canada	24,581
4	China	23,509
5	Germany	22,215
6	United Kingdom	21,163
7	Spain	16,492
8	Italy	16,140
9	South Korea	12,693
10	Belgium	11,345

Source: Top five countries running the most clinical trials (pharma-iq.com)

Approach taken for this presentation:

Looking at the past from the present

- **Tomorrow:** transition towards a digital and biological society
  - Proteomics; genetic genomic research
  - In vitro clinical trials
  - In-silico trials or virtual trials
  - Synthetic clinical trials
  - AI
  - …

Neurotechnology/Digital extended reality

Funded by
the European Union

- **Today:** focus on privacy due to digitalization and GDPR (data transfer)
- **Past:** primarily focus on Informed consent (since late 1970’)

The Tuskegee study of the natural history of syphilis

Source: Jones JH. *Bad Blood: The Tuskegee Syphilis Experiment, expanded edn.* New York: The Free Press; 1993 [1981]

Medical Experiments Second WW

- **Process/ Code of Nürnberg** (1947) – 24 MDs:

  Standard practice experiments

  No legal basis, no laws

  Rights of the participant

Article 1:

The voluntary consent of the human subject is absolutely essential.

Source: The Nuremberg Code. Trials of war criminals before the Nuremberg military tribunals under control council law. 1949. [14/10/13]. http://nuremberg.law.harvard.edu/php/docs_swi.php?%20DI=1&text=medical

Important documents in the aftermath of WWII

- **Declaration of Geneva** (WMA – 1948/ …)

  Oath of Hippocrates

- **Declaration of Helsinki** , WMA – 1964/ 1975,…

  Duties of the Investigator

- **Belmont Report** ,1979 published by National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

  Interest of individual is above society

Source; World Medical Association. Declaration of Helsinki, 6th revision. 2008 (14/10/13) http://www.wma.net/en/30publications/10policies/b3/

Increased Patient Protection: Drug disasters, fraud, abuse of rights

- Sulphanilamide incident (1937)

➲1938 Drug laws introduced to regulate safe manufacturing of drugs

- Nuremberg War Crimes Trial

➲1949 Nuremberg Code: required voluntary “informed consent”

- Tuskegee study (syphilis) (1932 – 1972)

➲1979 Belmont report: interest of individual is above interest of society

- Thalidomide (birth defects)

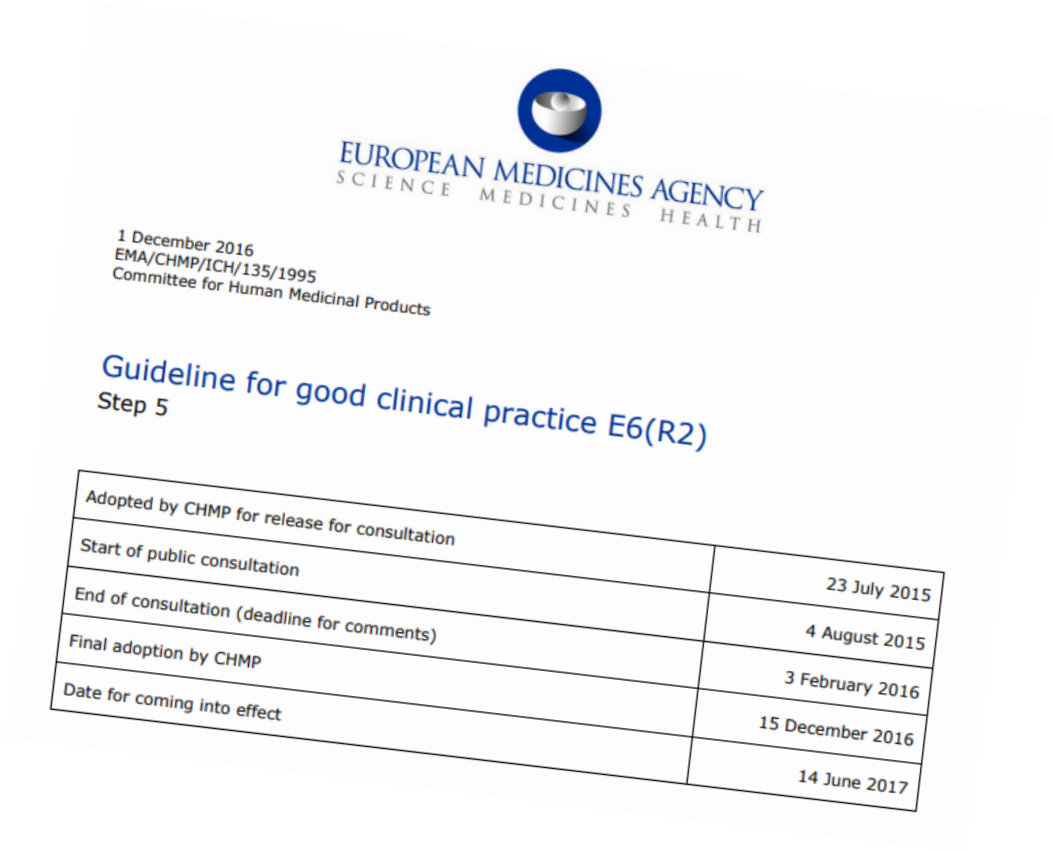
➲1962 Kefauver Amendments: prove drugs are both safe and effective

CORE ETHICAL PRINCIPLES

Three core ethical principles are relevant to research involving human subjects: respect for persons, beneficence, and justice.

Additional principles include voluntary participation, informed consent, anonymity, confidentiality, potential for harm, and results communication.

ICH-GCP (2016)



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 December 2016
EMA/CHMP/ICH/135/1995
Committee for Human Medicinal Products

Guideline for good clinical practice E6(R2)
Step 5

Adopted by CHMP for release for consultation	23 July 2015
Start of public consultation	4 August 2015
End of consultation (deadline for comments)	3 February 2016
Final adoption by CHMP	15 December 2016
Date for coming into effect	14 June 2017

- A statement that the study involves research
- An explanation of the purposes of the research
- The expected duration of the subject's participation
- A description of the procedures to be followed
- Identification of any experimental procedures
- A description of any reasonably foreseeable risks or discomforts to the subject
- A description of any benefits to the subject or to others that may reasonably be expected from the research
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained
- For research that involves more than minimal risk, an explanation as to whether any compensation will be paid and whether any medical treatments are available if injury occurs, and if so, what the treatments consist of or where further information may be obtained
- **Research, Rights or Injury**: An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights and whom to contact in the event of a research-related injury to the subject
- A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled

[ICH: E 6 (R2): Guideline for good clinical practice - Step 5 (europa.eu)]

Source: From Office for Human Research Protections (OHRP). (2014). U.S. Department of Health & Human Services. Retrieved from http://www. hhs.gov/ohrp/policy/consentckls.html

EU Directive on GCP (2004)

- # MECs in Belgium?
- MECs came under law of the MS (no private ECs anymore)
- Timelines: 60 days!
    - Consequences: SOP, minutes of meetings, administration, structure.

EU CTR No 536/2014

European Union pharmaceutical legislation known as the Clinical Trials Regulation, aims to ensure the EU offers an attractive and favorable environment for carrying out clinical research on a large scale, with high standards of public transparency and safety for clinical trial participants.

- Single decision
- Competition US-EU-Asia Pacific
- Speed becomes important
- Part I and part II
- MECs became part of regulatory authorities , no longer under an institution (CCMO NL, France (Loi Huriet), Belgium (College))

Conclusion / Challenges

- Increased protection of subjects throughout the years.
- Shift towards a digital and biological society!
- Today: huge focus on privacy, GDPR (data transfer). Majority of ethical issues deal with GDPR?
- Be prepared to deal with **Personalized CTs – Patient centricity – Decentralized trials – Hybrid trials – Home visit nursing – Direct to patient medication delivery(?)**
- What about monitoring remotely EMRs?
- Ethics committees (15) are now under the umbrella of the FAGG
- Finally: Think about the patient

Coming soon:

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DE IMPACT VAN DE EU-VERORDENING INZAKE KLINISCHE PROEVEN OP STUDIE START-UP TEAMS EN ETHISCHE COMMISSIES IN BELGIË

Yousra El Gazari

Thesis ingediend met het oog op het behalen van de graad van Master in de Biomedische Wetenschappen

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