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CTR and NPL? Why do these acronyms matter and why should a statistician be aware of European legislation?

Elina Asikanius on behalf of the Biostatistics SIA LT

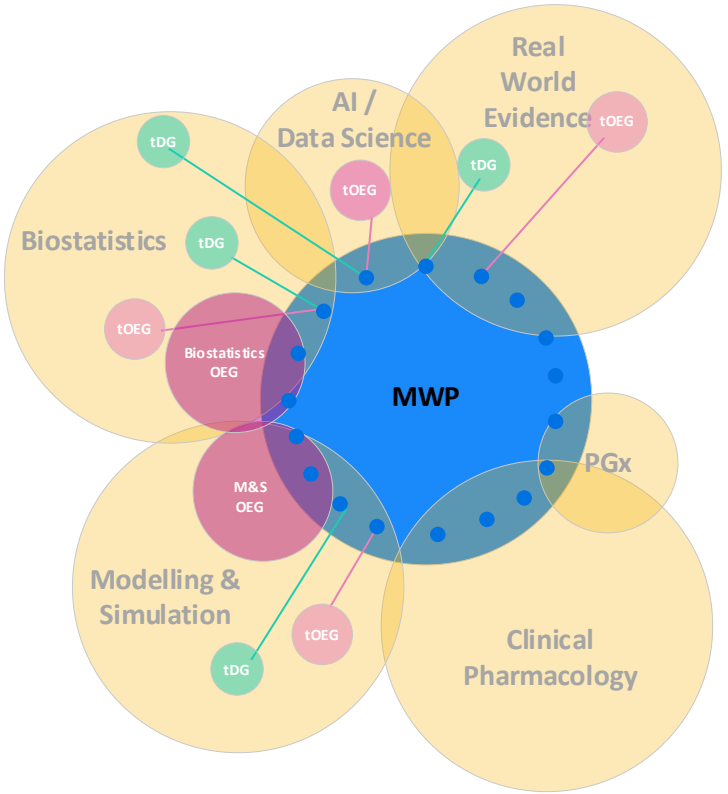
EFSPI workshop, Basel August 2026

Disclaimer

The contents of this presentation are my personal opinion. My remarks do not necessarily reflect the official view of FIMEA, EMA, or any associated working party or committee

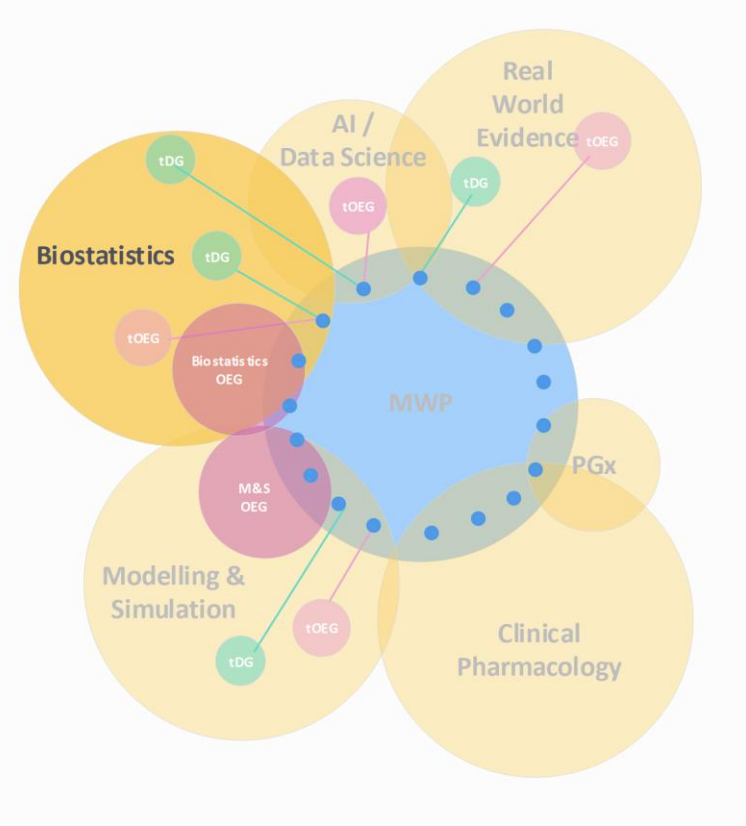
Structure of Methodology Domain

- Methodology Working Party (MWP; Source)
  - Currently consists of 24 members endorsed by CHMP
  - Primary role/mandate:
    - Governance of domain
    - Alignment across disciplines
    - Implementation and oversight of guideline drafting groups
    - Decision making
    - …
- MWP Chairs:
  - Christian (Kit) Roes
  - Kristin Karlsson
- Primary point of contact for overarching topics (concerning whole domain)



Structure of Methodology Domain

- Methodology European Specialised Expert Community (Methodology ESEC; Source) supports MWP (> 250 experts)
  - Divided into 6 (overlapping) domains, so called Specialized Interest Areas (**SIAs**); Composition primarily based on interest (rather than expertise)
  - This is where the actual work is done (in drafting groups etc.)
- Biostatistics SIA consists of > 100 members from 20 countries + EMA
  - Not all are statisticians!
  - Not all are actively engaged in network activities!
  - Each SIA has a dedicated Leadership Team (**SIA LT**).
- Biostats SIA LT:
  - Andreas Brandt (BfArM), Benjamin Hofner (PEI), Elina Asikanius (FIMEA), Florian Klinglmüller (AGES), Frank Pétavy (EMA), Lukas Aguirre Davila (PEI)



Source: List of ESEC member

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What guides a biostatistical assessor´s decision making?

- Science, science, science
- Guidelines ICH, EMA
- Precedence, established practises

The basis for all decision making is outlined in the legislation

Clinical Trials regulation and Pharmaceutical legislation

►B ↓

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)

(OJ L 158 27.5.2014, p. 1)

Amended by:

		Official Journal No	page	date
►M1 ↓	REGULATION (EU) 2022/641 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 12 April 2022	L 118	1	20.4.2022
►M2 ↓	COMMISSION DELEGATED REGULATION (EU) 2022/2239 of 6 September 2022	L 294	5	15.11.2022

Corrected by:

►C1 ↓	Corrigendum, OJ L 311, 17.11.2016, p. 25 (536/2014)	

►B ↓

REGULATION (EC) No 726/2004 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 31 March 2004

laying down ►M7 ↓ Union ◄ procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency

(Text with EEA relevance)

(OJ L 136 30.4.2004, p. 1)

Amended by:

		Official Journal No	page	date
►M1 ↓	REGULATION (EC) No 1901/2006 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 12 December 2006	L 378	1	27.12.2006
►M2 ↓	REGULATION (EC) No 1394/2007 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 13 November 2007	L 324	121	10.12.2007
►M3 ↓	REGULATION (EC) No 219/2009 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 11 March 2009	L 87	109	31.3.2009
►M4 ↓	REGULATION (EC) No 470/2009 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 6 May 2009	L 152	11	16.6.2009
►M5 ↓	REGULATION (EU) No 1235/2010 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 15 December 2010	L 348	1	31.12.2010
►M6 ↓	REGULATION (EU) No 1027/2012 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 25 October 2012	L 316	38	14.11.2012
►M7 ↓	REGULATION (EU) 2019/5 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 11 December 2018	L 4	24	7.1.2019

Corrected by:

►C1 ↓	Corrigendum, OJ L 201, 27.7.2012, p. 138 (1235/2010)	

https://eur-lex.europa.eu/eli/reg/2014/536/2022-12-05
https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:02004R0726-20190128

CTR

Clinical trials regulation

- Key regulation applied in clinical trial application authorisation (CTA)
- In force since 2022
- The main goal was to harmonise clinical trial assessment and supervision across Europe while maintaining high standards of participant protection and data quality
- Key aspects:
  - Single EU submission through Clinical Trials Information System (CTIS)
  - Harmonised assessment
    - Part I: Scientific and technical aspects assessed jointly by Member States.
    - Part II: National and ethical aspects assessed separately by each Member State.
  - Defined timelines
  - Increased transparency
    - CTIS includes a public database containing information about clinical trials, results summaries, and lay summaries for patients and the public

CTR for statisticians

Article 3

General principle

A clinical trial may be conducted only if:

(a) the rights, safety, dignity and well-being of subjects are protected and prevail over all other interests; and

(b) it is designed to generate reliable and robust data.

CTR for statisticians *cont.*

(k) a description of the type of clinical trial to be conducted and a discussion of the trial design (including a schematic diagram of trial design, procedures and stages, if relevant);

(l) a specification of the primary end-points and the secondary end-points, if any, to be measured during the clinical trial;

(m) a description of the measures taken to minimise bias, including, if applicable, randomisation and blinding;

(n) a description of the expected duration of subject participation and a description of the sequence and duration of all clinical trial periods, including follow-up, if relevant;

(o) a clear and unambiguous definition of the end of the clinical trial in question and, if it is not the date of the last visit of the last subject, a specification of the estimated end date and a justification thereof;

(p) a description of the criteria for discontinuing parts of the clinical trial or the entire clinical trial;

(q) arrangements for the maintenance of clinical trial treatment randomisation codes and procedures for breaking codes, if relevant;

(r) a description of procedures for the identification of data to be recorded directly on the Case Report Forms considered as source data;

(u) a description of the statistical methods to be employed, including, if relevant:

- timing of any planned interim analysis and the number of subjects planned to be enrolled;
- reasons for choice of sample size;
- calculations of the power of the clinical trial and clinical relevance;
- the level of significance to be used;
- criteria for the termination of the clinical trial;
- procedures for accounting for missing, unused, and spurious data and for reporting any deviation from the original statistical plan; and
- the selection of subjects to be included in the analyses;

Some personal reflections…

- I refer to the CTR all the time
- Breadth of trials is larger than for Marketing Authorisation Assessment and Scientific Advice due to large number of early phase, academic and post-marketing trials
- What is reliable and robust data?
- The clinical trial should answer to *a* scientific question
  - → A study that is not suitable to form the basis of a MA can be accepted at CTA
- …*if relevant*… in point u is of relevance
  - → We need to know when the *level of significance* does not need to be defined
  - → Internal consistency between design, objectives, sample size, estimand, statistical methods etc is key
- What is *missing, unused and spurious data* and how does that link with estimands?
- Only changes to protocol are submitted as substantial modifications

Homework

- Definition of clinical study, clinical trial, low-intervention clinical trial, non-interventional study

NPL

NPL = new pharmaceutical legislation

- The European Parliament and the Council of the European Union have reached political agreement on the reform of the **EU pharmaceutical legislation** on 11 December 2025
- The text of the new pharmaceutical legislation and the changes it introduces will be fully detailed in 2026.
- The new pharmaceutical legislation represents the most significant overhaul of the regulatory framework in over two decades. It will modernise how medicines are developed, authorised and made available to patients across the EU.

Timeline

December 2025
Political agreement on new pharmaceutical legislation

2026
Adopted acts of the new pharmaceutical legislation enter into force

2026-2028
Transition phase
-EU Member States update their national laws to reflect the new rules
-European Commission adopts implementing and delegated acts to help implement the new rules
-EMA and national competent authorities develop implementation guidance and adapt their procedures and IT systems

2028
New pharmaceutical legislation becomes applicable

https://www.ema.europa.eu/en/about-us/what-we-do/reform-eu-pharmaceutical-legislation
https://health.ec.europa.eu/medicinal-products/reform-eu-pharmaceutical-legislation_en
https://data.consilium.europa.eu/doc/document/ST-6366-2026-INIT/en/pdf
https://data.consilium.europa.eu/doc/document/ST-6367-2026-INIT/en/pdf

NPL for statisticians through non-comprehensive list of examples

Data submissions

(45) Marketing authorisation applications, like any other application submitted to the Agency, should follow the digital by default principle and hence be sent to the Agency in electronic form. Applications should be assessed based on the file submitted by the applicant in accordance with the different legal basis provided by [revised Directive 2001/83/EC]. At the same time, the Agency and the relevant committees may take into account any information that is in its possession. Applicants shall be requested to generally submit raw data, in particular with regard to the clinical trials performed by the applicant in order to ensure a full assessment of the quality, safety and efficacy of the medicinal product. ***However, this obligation to submit raw data should not be construed as obliging the Agency and the relevant committees to examine or make use of all such data during their scientific assessment. They should retain the discretion to determine in which cases such data are relevant and necessary for the purposes of assessing the application.***

Conditional Marketing Authorisation

Current legislation:

A conditional marketing authorisation may be granted where the Committee finds that, although comprehensive clinical data referring to the safety and efficacy of the medicinal product have not been supplied, all the following requirements are met:

a) the risk-benefit balance of the medicinal product, as defined in Article 1(28a) of Directive 2001/83/EC, is positive;

b) it is likely that the applicant will be in a position to provide the comprehensive clinical data;

c) unmet medical needs will be fulfilled;

d) the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required.

https://eur-lex.europa.eu/eli/reg/2006/507/oj

NPL:

In duly justified cases, to meet an unmet medical need of patients a conditional marketing authorisation or a new conditional therapeutic indication to an existing marketing authorisation authorised under this Regulation may be granted by the Commission to a medicinal product that is likely to address the unmet medical need in accordance with Article 83(1), point (b), of [revised Directive 2001/83/EC], prior to the submission of comprehensive clinical data provided that the benefit of the immediate availability on the market of that medicinal product outweighs the risk inherent in the fact that additional data are still required.

a) ...

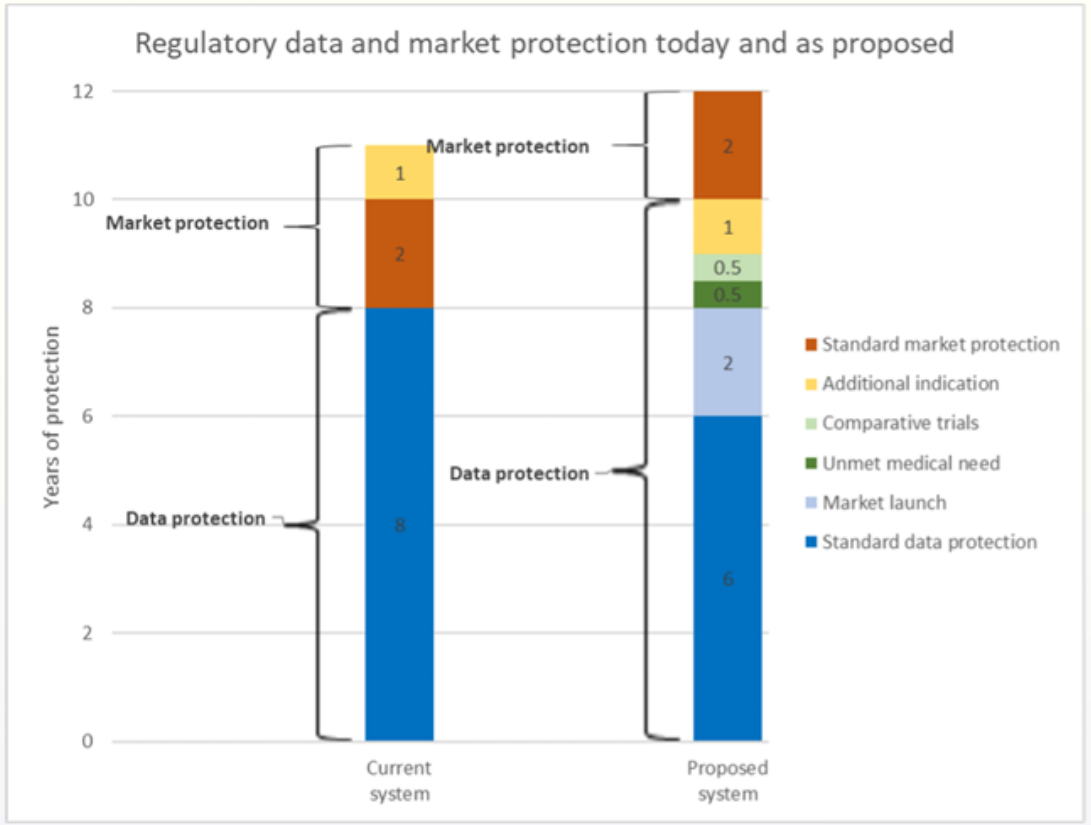
b) ...

...

https://data.consilium.europa.eu/doc/document/ST-6366-2026-INIT/en/pdf

Incentives to encourage innovation

Modulation of incentives for all innovative medicinal products



https://health.ec.europa.eu/document/download/64fdc425-c78d-4f08-aa34-4e6fd1f07bf4_en?filename=factsheet_rdp_en.pdf

Some personal reflections

- There is a lot of text related to data, results and evidence generation
  - This opens strategic opportunities for statisticians within the regulatory network
  - …and also for statisticians in the industry
  - I encourage everyone to familiarize themselves with the NPL even though it feels challenging
- EMRN will be very busy for the years to come
- NPL includes many process changes for us, e.g. changes to the committee structure, changes to MA timelines, changes to roles and responsibilities
- and (more interestingly) it also includes new, different, and modified criteria for decision making that we have to implement

Interesting times ahead!

Cherry on the cake...

Biotech Act

- forms an integral part of the EU's efforts to close the so-called 'innovation gap'
- proposes a comprehensive framework to increase competitiveness by creating the necessary conditions for the health biotechnology sector to thrive
- **strengthens and streamlines the regulatory environment in areas such as clinical trials and cell and gene therapies**
- will be central to strengthening the sector in Europe and ensuring it remains at the forefront of global innovation

https://health.ec.europa.eu/biotechnology/european-biotech-act_en

Biotech Act *cont.*

- The Biotech Act seeks to address these challenges through **substantial amendments to the EU Clinical Trials Regulation**:
  - streamlining and accelerating authorisation procedures, with a voluntary initiative by 23 member States, FAST EU, piloting the new authorisation procedure as early as January;
  - strengthening collaboration among Member States and simplifying multi-country trials;
  - introducing regulatory sandboxes to facilitate atypical clinical trials, while securing safety of patients;
  - introducing a single authorisation process for combined clinical trials and reinforce risk-based approaches.

https://ec.europa.eu/commission/presscorner/detail/en/qanda_25_3079

Take home message:
The basis for all regulatory decision making is outlined in the legislation

Special thanks to the Biostatistics SIA LT for many discussion on the NPL and to Tommi Nurminen and John Aspegren + our clinical colleagues for many discussions on CTR implementation

Kiitos.

Elina Asikanius

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