THE E.U. CLINICAL TRIALS REGULATION IMPLEMENTATION

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BEFORE WE START

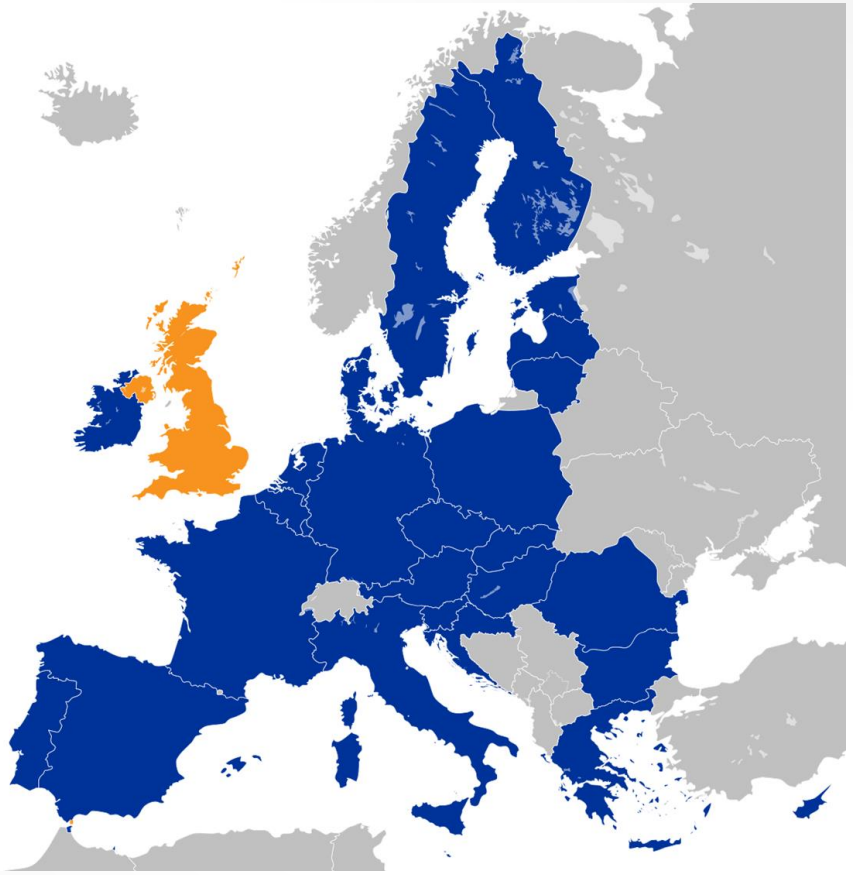
- How many of you are familiar with the E.U. regulatory framework?
- How many of you have been involved with clinical trials under the Directive?
- How many of you are aware of the new Clinical Trials Regulation?
- Has anyone been involved with submissions through CTIS?
- Who attended Claire's table at the roundtable dinner?

THE EUROPEAN UNION (E.U.)

E.U. Countries (27)

Austria, Belgium, Bulgaria, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxemburg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden

(Do not use the EURO as currency)



European Economic Area (E.E.A.)

EU countries + Iceland, Lichtenstein, Norway

THE "THREE BUCKETS" OF E.U. REGULATION

- Clinical trial oversight
- Scientific Advice
- National approval of medicines
- GMP compliance/Import licensure
- Pharmacy formulary, pricing reimbursement

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

- Scientific assessment of medicines
- Scientific Committees
- Opinions on medicines
- Issue Guidance
- EMA Scientific Advice

European Commission

- Right of Initiative – New/amend legislation
- Implement/oversee E.U. law
- Approve medicines (centralized procedure)

THE E.U. MEDICINES REGULATION – BRIEF HISTORY

1957 – Establishment of the European Commission – Treaty of Rome
1964 – Principles for clinical research
1965 – E.U. decides medicines need to be authorized
(Thalidomide – US 1962, but FD&C A 1938)
1975 – First steps to joint E.U. position on market authorizations
1987 – Concentration procedure – opinion of an E.U. level committee
1993 – Formation of the European Union/Agreement on Centralized Procedure
1995 – EMA established
1996 – Launch of international harmonization
2000 – Orphan medicine regulation established (U.S. 1983)
2001 – Clinical Trial Directive 2001/20/EC
2001 – EC Code on human medicines 2001/83/EC
2004 – Regulation (EC) 726/2004 on EC procedures
2006 – Pediatric Regulation (EU) No 1901/2006 (PREA 2003, BPCA 2007)
2007 – Advanced Therapy Regulation (EC) No 1394/2007
2014 – Clinical Trials Regulation: Regulation (EU) 536/2014
2019 – EMA moves to Amsterdam

THE E.U. LEGAL FRAMEWORK

Regulations – binding legal acts to be applied across the E.U.

Directives – legislative acts providing goals for national implementation in E.U. countries

Scientific guidelines – recommendation on the application of legal requirements

THE CLINICAL TRIAL DIRECTIVE

- Aimed to simplify and standardize clinical trial rules throughout Europe and increase participant protection
- E.U. Member States transpose directives into national law fulfil the Directive's requirements
- Requires a separate clinical trial applications to each Member State according to the national requirements

CHALLENGES CREATED BY THE DIRECTIVE

- Patchwork of national requirements
- Fragmented assessment process and timelines across the E.U.
- Challenges for aligned trial initiation
- High bureaucratic burden for application and data submission
- Higher number of trials in only one E.U. country
- Disadvantages for academic sponsors

THE CLINICAL TRIALS REGULATION

- Signed in April 2014, published May 27, 2014
- Application was pending completion of the Clinical Trials Information System
- Became applicable January 31, 2022 and repealed the CTD
- Legally binding in all E.U. Member States

Goals/Benefits:

- Ensure E.U. provides favorable and attractive environment for large trials
- Implement high standards on transparency and patient safety
- Harmonize processes for clinical trial assessment and supervision
- E.U. member states remain responsible for evaluation, approval, supervision – cooperation and collaboration
- One online submission to all E.U. member states through single online platform (CTIS)

CTR

THE CLINICAL TRIALS INFORMATION SYSTEM (CTIS)

- One stop shop for submitting, reviewing and approving a clinical trial application
- One submission for all E.U. countries (one submission for up to 30 countries)
- Collaboration among reviewers from national authorities and ethic committees
- One combined harmonized opinion
- One round of requests for information (ideally)

- Finally got the go ahead to start in August 2021 for a go-live on January 31, 2022

CTIS

IMPLEMENTATION OF THE CTR IS A STEPWISE PROCESS

- Until January 30, 2023 – CTR application voluntary for new application, CTD can still be used

- **From January 31, 2023 – CTR becomes mandatory for all new trial applications**

- From January 31, 2025 – all still ongoing CTD trials must comply with CTR requirements including CTIS information submission

SPONSOR FUNCTIONALITIES OF CTIS

- Manage users and roles
- Compile clinical trial applications, submit them and provide updates for assessments
- Alerts and notification on ongoing trials
- Provide information in response to requests
- Search and access trials
- Notify clinical trial milestones
- Record trial results

Sponsor Functionalities

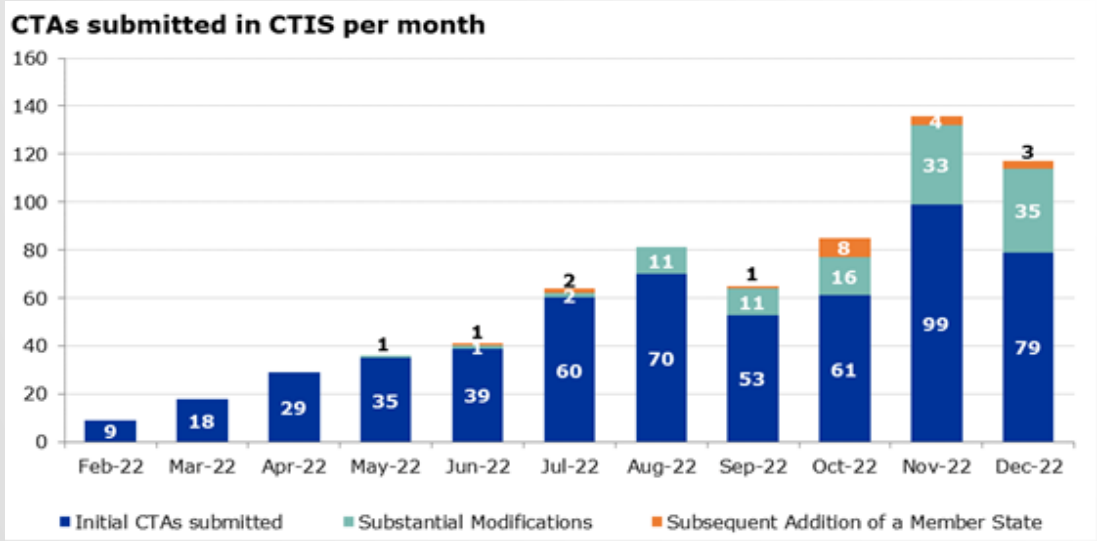
AUTHORITY FUNCTIONALITIES OF CTIS

- Manage users and roles
- View clinical trial applications
- Manage assessment tasks
- Collaborate with Member State authorities
- Alerts and notification on ongoing trials
- Download sponsor documentation
- Record inspection results for sites and clinical trials

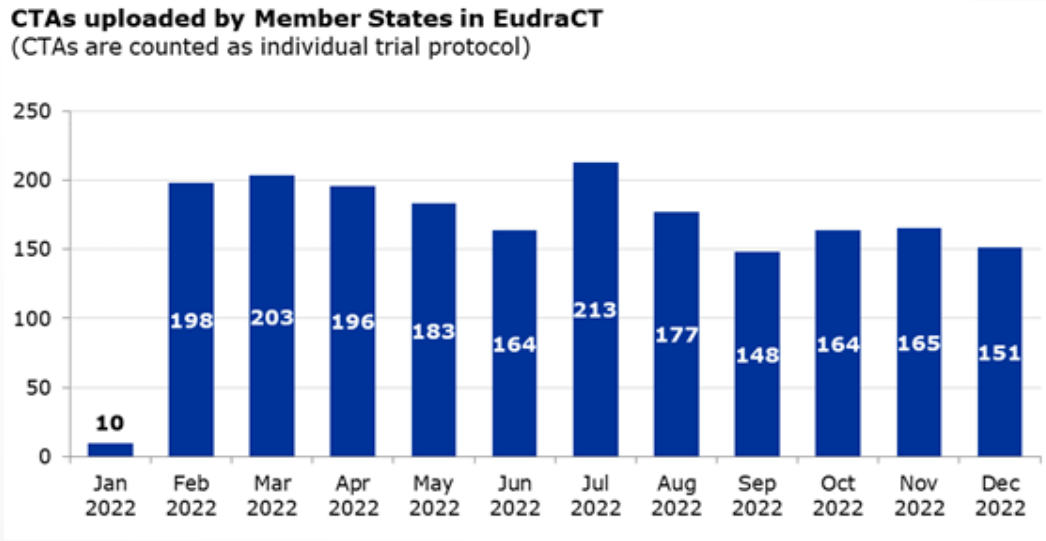
Authority Functionalities

KPI – SUBMISSIONS THROUGH CTIS STEADILY INCREASED

CTIS - CTR



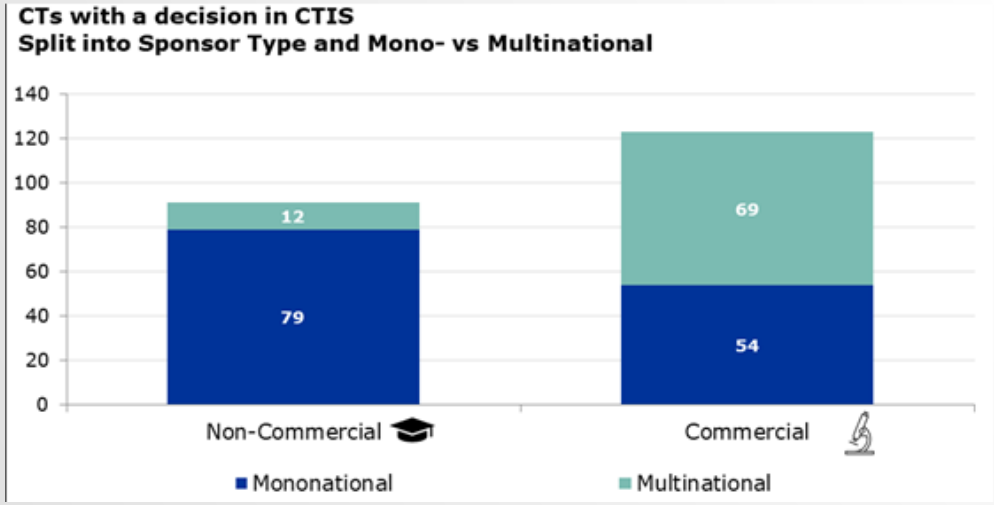
EUDRACT - CTD



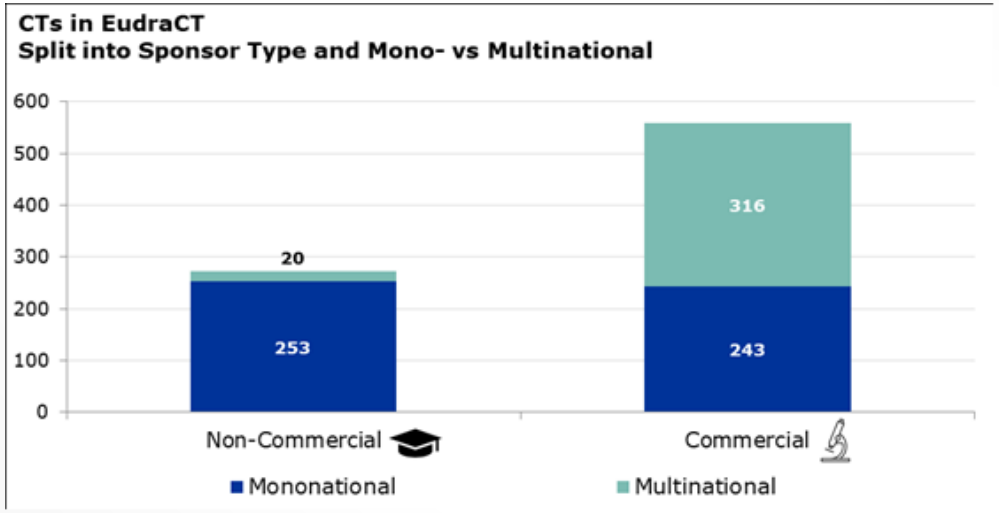
KPI Report

KPI – TRIALS ARE STILL LARGELY MONO-NATIONAL

CTIS - CTR



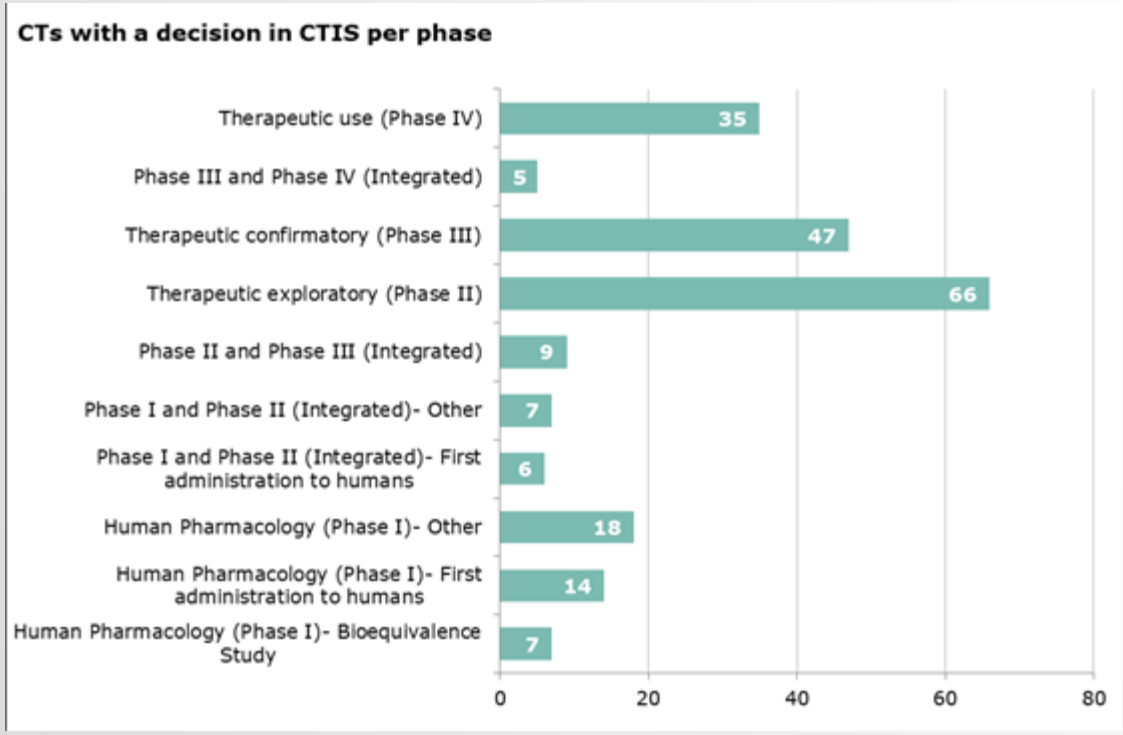
EUDRACT - CTD



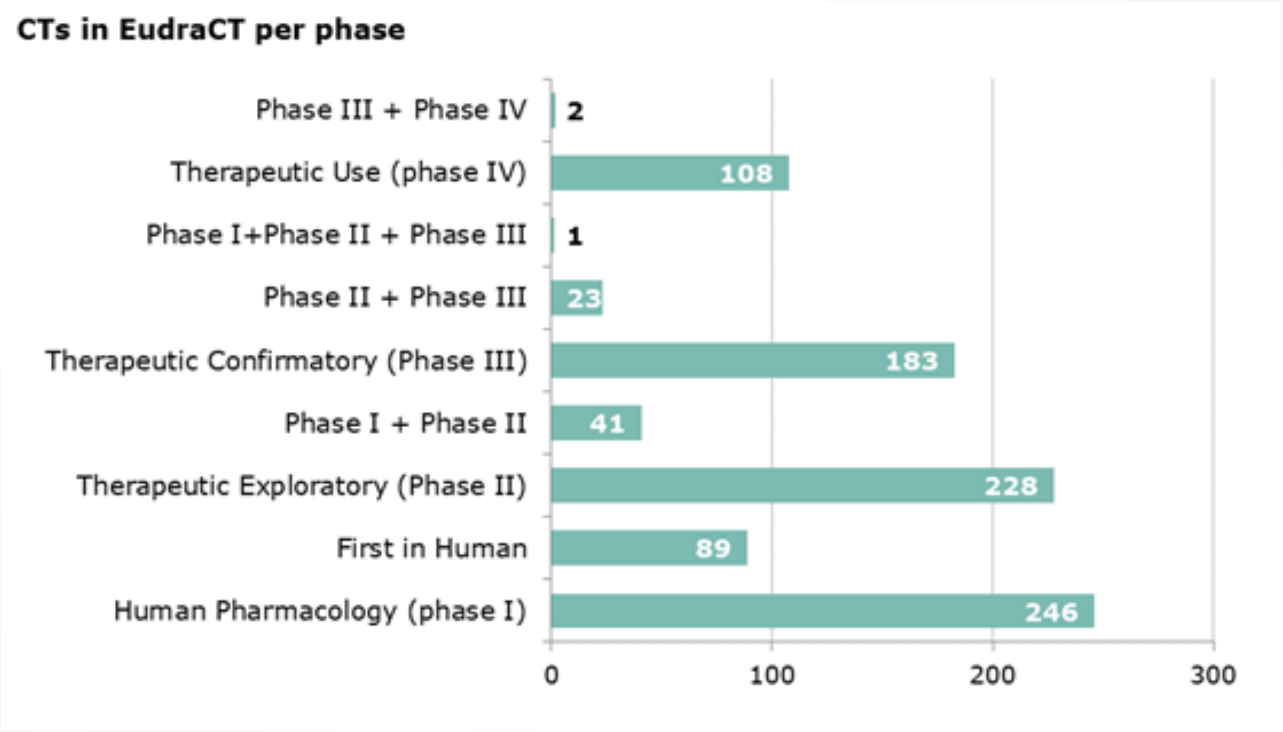
KPI Report

KPI – TRIALS COVER ALL CLINICAL PHASES

CTIS - CTR

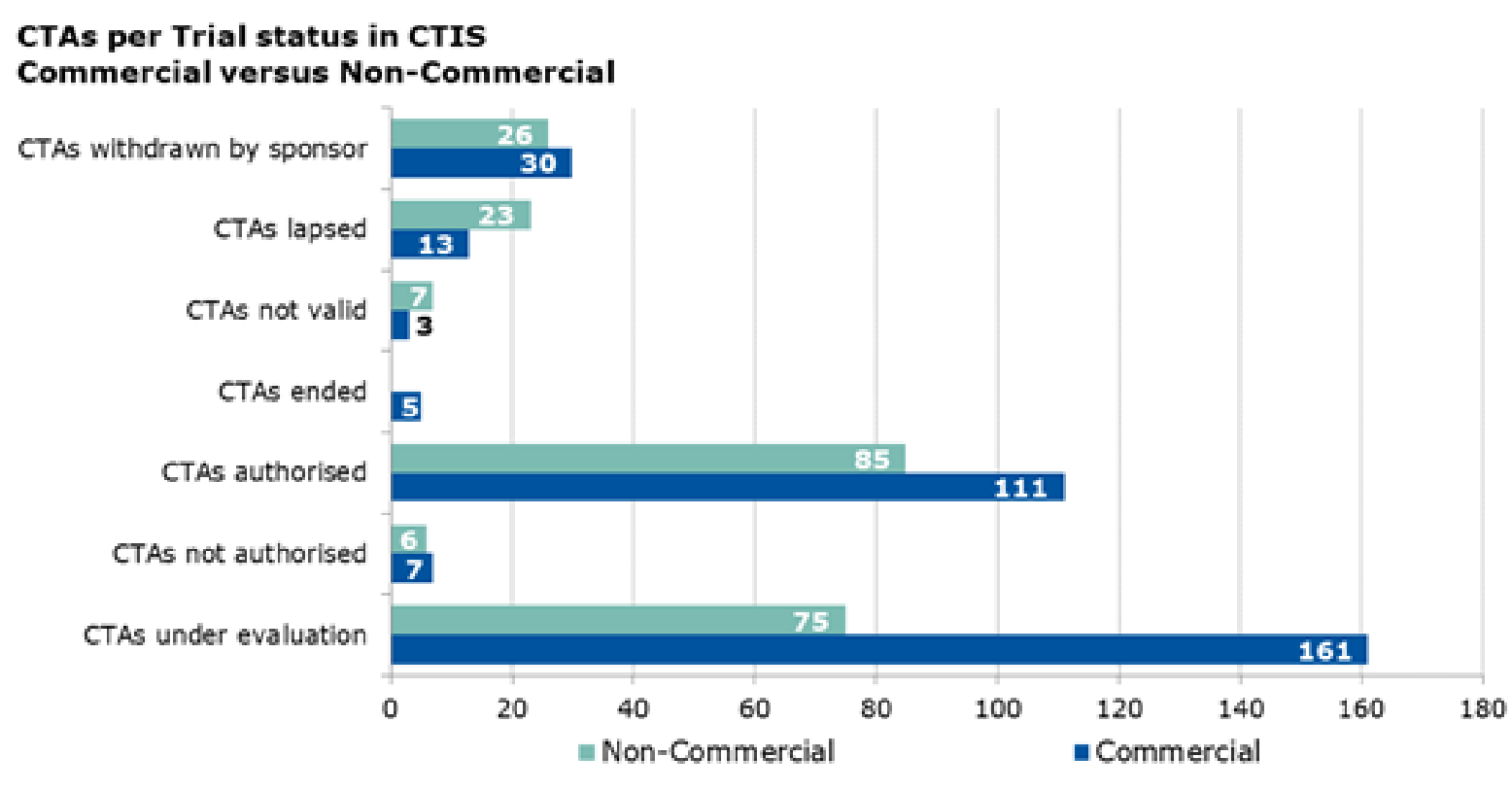


EUDRACT - CTD



KPI Report

KPI – STATUS OF CLINICAL TRIALS IN CTIS



KPI Report

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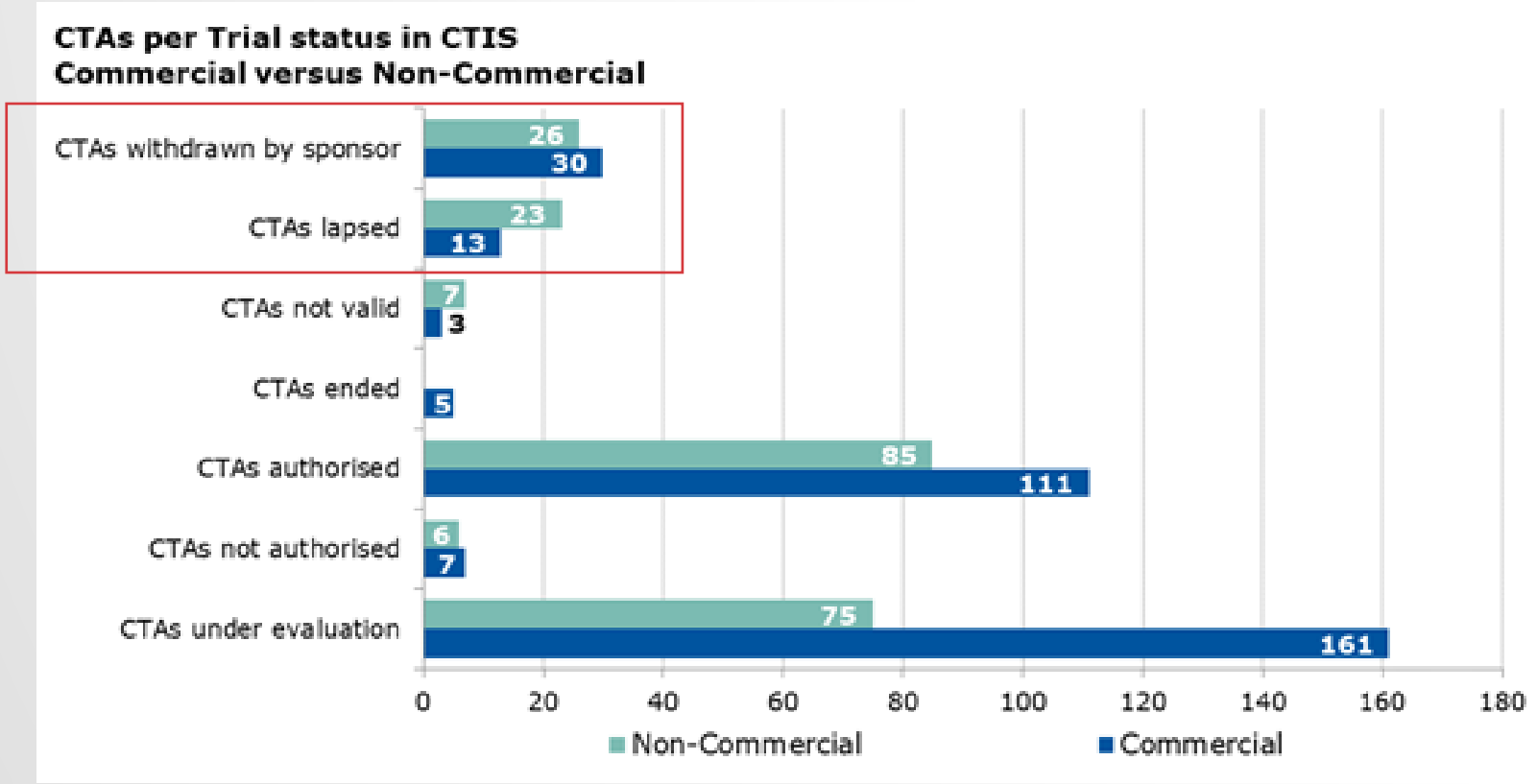

KPI Report

VIEW FROM A REGULATOR

LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

Danish Medicines Agency

- Agency received the first clinical trial application through CTIS
- High number of lapses and withdrawals raises concerns
- One round of requests for information is the ideal world
- More coordination required from the Reporting Member State

Recommendation to sponsors

- Be prepared for requests of information and requested changes
- Monitor CTIS diligently for updates
- Use the cover letter wisely

Stakeholder event on CTIS readiness

INDUSTRY VIEWPOINT

The good:

- Regulatory sandboxes – and they should remain
- Single opinion is beneficial – but timelines are not always adhered to
- Communication with potential Reference Member States before submission could be beneficial

The not so good:

- Redaction of confidential information continues to be a challenge
- Workaround should be published sooner
- The multiple requests for information are challenging
- Inclusion of confidential information in assessment reports needs addressing
- Part II requirements not as harmonized as expected

Stakeholder event on CTIS readiness

ACADEMIA VIEWPOINT

Same timelines, requirements and challenges but different hurdles

- The severity of problems caused by challenges could cause prohibitive consequences
- Limitations of funding, personnel and resources pose limitations
- Lack of harmonization of Part II documents
- Multiple requests for information and unharmonized requests
- Lack of opportunity to consult on requests
- Diversity of fee requirements

OUTSTANDING WORK TO BE DONE

- Fixing issues through workarounds and quick fixes
- Improving user experience and functionality
- Lack of harmonization of Part II documents
- Roundtable assessor discussions and training support will continue
- Transparency rules will be reviewed – Question and answer recently published
- Product owners and users guide continued updates

THERE ARE NEW ISSUES WITH LARGER TRIALS

- Very large Phase III trials covering 15+ countries with multiple sites per country see difficulties with preparing the application

Potential reasons:

- Number of countries
- Number of sites
- Number of documents (2 copies each)

EMA currently does not know what the issue is but Helpdesk working on it.

Companies are concerned about delays of their trials.

Source: Bertrand Fournier
Shionogi Europe

KEY TAKE-AWAYS

- The Clinical Trials Regulation aimed to harmonize application requirements across the E.U. but only partially achieved that goal.
- The Clinical Trials Information System (under development for years) still has issues, and the increased application volume may cause new issues.
- There has not yet been a shift to more multinational trials and academic sponsors still experience significant challenges.
- The regulation was supposed to make the conduct of large multinational trials enticing – which now seems to cause problems.

QUESTIONS?

Feel free to email me:

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