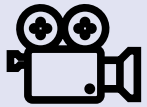
ACT EU Clinical Trials Analytics Workshop

25-26 January 2024

Etiquette for
ACT EU Clinical Trials Analytics Workshop

Chat is disabled



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Welcome & opening remarks

Emer Cooke, Executive Director, EMA

Lars Bo Nielsen, Director General, DKMA/HMA

Session 1: From data to decisions

Co-chairs

Peter Arlett – Head of TDA, EMA

Lars Bo Nielsen – Director General, DKMA, and member of the HMA Management Group

Delivering a research agenda and Identifying relevant data sources

Presented by

IJsbrand den Rooijen – Health Data Scientist, ACT EU Analytics co-lead, EMA

Frederik Grell Nørgaard - Head of Unit, Danish Medicines Agency

Outline

- What is clinical trials analytics?
- Research agenda on clinical trials analytics
- Identifying relevant data sources

What is clinical trials analytics?

Launched in 2022: Accelerating Clinical Trials in the EU

ACT EU was partly a response to COVID
to get **bigger** trials off the ground **faster**

As the programme formed there were natural categories:

- GCP
- Methodologies
- Clinical trials regulation

Where should we discuss data about clinical trials?

Defining clinical trials analytics as a topic

The *data about clinical trials* is important, but what should the analytics be about?

We knew there was interest in the data for:

- Informing clinical guidelines
- Tracking uptake of innovation
- Designs associated with marketing approval
- Benchmarking development pipelines
- Finding and joining ongoing trials
- …

Objective of CT analytics

"Analyse data about clinical trials leveraging academic, non-profit, European, and international initiatives, improving the impact of policymaking and funding on research outputs to support evidence-based decision making."

But where should we be focusing our efforts specifically?

The benefits of the Clinical Trials Regulation (CTR)

- CTIS is the register of the **Clinical Trials Regulation**

- CTIS generates substantially **higher quality data** than EudraCT previously

- Opportunity to capitalise on **technological developments** in *advanced analytics* (i.e., machine learning, AI, NLP)

Image 1.
Since 31 January 2023, sponsors submit all new clinical trial applications in the EU/EEA via CTIS.

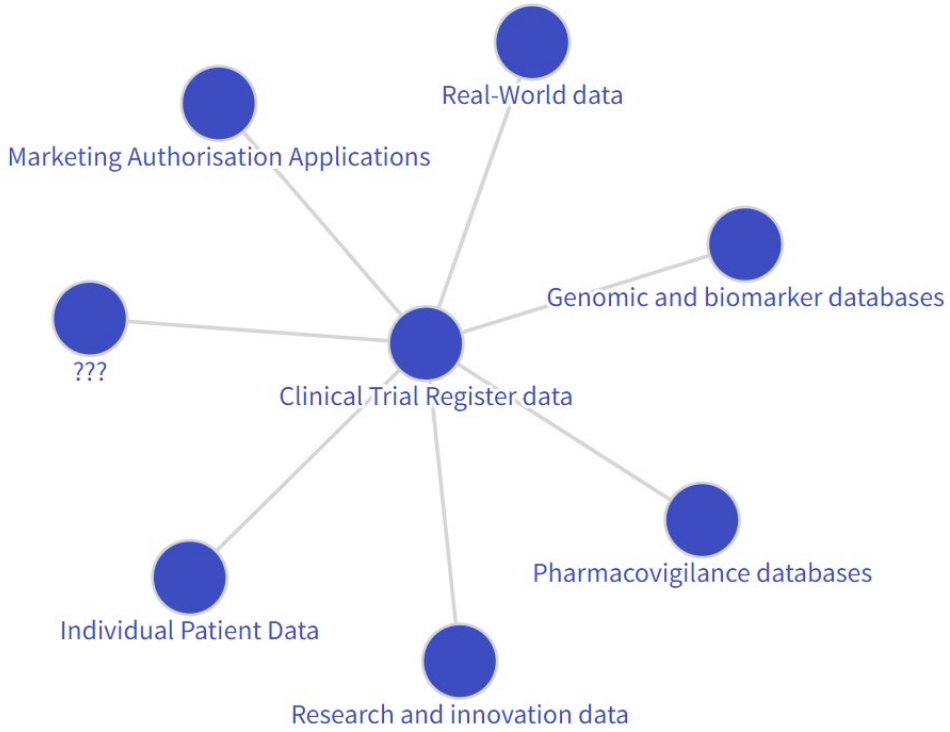
Where should we focus to make better use of the data we collect about clinical trials?

What is data about clinical trials?

Data about clinical trials are held in **CT registers** and contain summary-level information

Data from clinical trials are **CT Individual Patient Data** and are not kept in the CT registers

When using CT data, CT register data **play a bridging role**, facilitating the link between data sources



Collecting use cases for data about clinical trials

Use cases highlight where there is a need to focus

We will collect detailed, actionable use cases as concrete examples of how the data is being used

Day 2 is geared to towards collecting use cases

Definition of use case

"A use case for the data refers to a description of how an individual or organisation intends to use the data to accomplish a specific objective, these could include steps they will take, expected outcomes, and the benefits of using the data in that way."

Research agenda on clinical trials analytics

Research agenda on clinical trials analytics

Use cases will be analysed for **common themes** across stakeholders

Themes will be distilled into **research questions**

Questions gathered into a **research agenda** on clinical trials analytics

Delivering the research agenda

Planning to **publish agenda** in Q2

Empower stakeholders to deliver different parts of the agenda:

- Foster funding opportunities for research projects under the agenda
- Enhancing data access and utility

Supporting a clinical trials analytics ecosystem equipped to deal with the challenges and opportunities of the digital world

Identifying relevant data sources

High level perspectives

National Competent Authorities

- Are the curators of CTIS data
- Ensures that data in CTIS has high validity
- Data quality improved significantly compared to EudraCT

As previously stated; the ‘how’ is not the focus of this workshop.

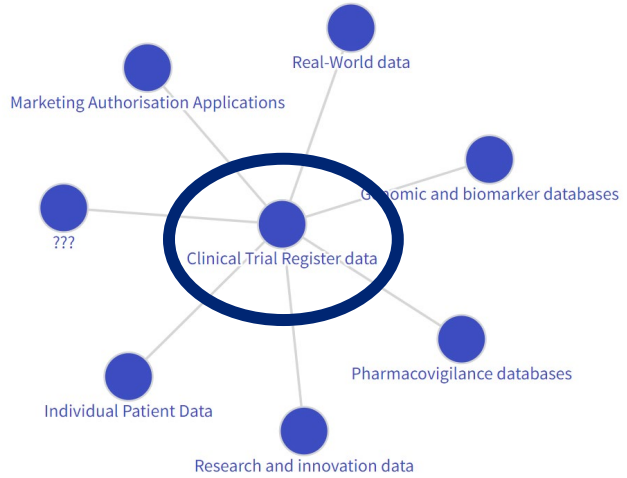
Primary goals

- Use data to optimise regulatory decision making
- Enabling the research agenda. This may eventually include to enable stakeholders to conduct analyses with data from different sources within their own systems

The central clinical trial hub of intelligence

The Clinical Trials Information System (CTIS) is central for the use-cases and the research agenda

- Provides important characteristics of clinical trials, e.g.
  - Which
  - Where
  - Why



Hence, CTIS provides the overarching descriptors

- Descriptors which can be easily linked to other available data

The development of a research agenda will help us to identify relevant data sources and motivate such data linkage and motivate future improvements

Challenge

How to support collaboration and awareness of the existing scientific knowledge for more impactful clinical trials - benefitting patients and healthcare in EU

Question: Is my research question/hypothesis currently being investigated or has it been in previous trials?

- Facilitating multi-site and multi-national clinical trials
- Ensuring that we build on existing knowledge

In addition, assessment of relevance in compliance with the Clinical Trial Regulation (Article 6)

The anticipated therapeutic and public health benefits taking account…
- the relevance of the clinical trial, including whether the groups of subjects participating in the clinical trial represent the population to be treated…

Use-case: Is my research question/hypothesis currently being investigated or has it been in previous trials?

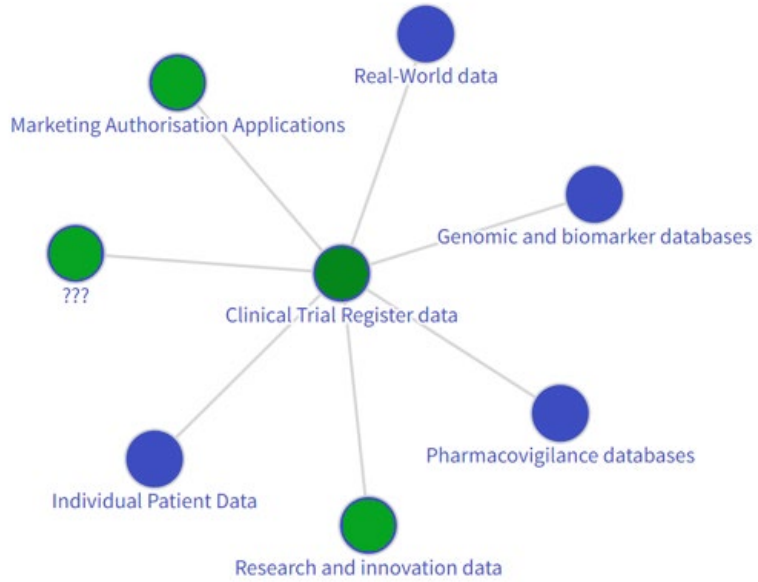
Types of data

CTIS data captures similar clinical trials in EU. Linked data capture a global overview from WHO's International Clinical Trials Registry Platform

→*Facilitate collaboration*

Results data from CTIS together with additional post-authorisation product data and academic publications

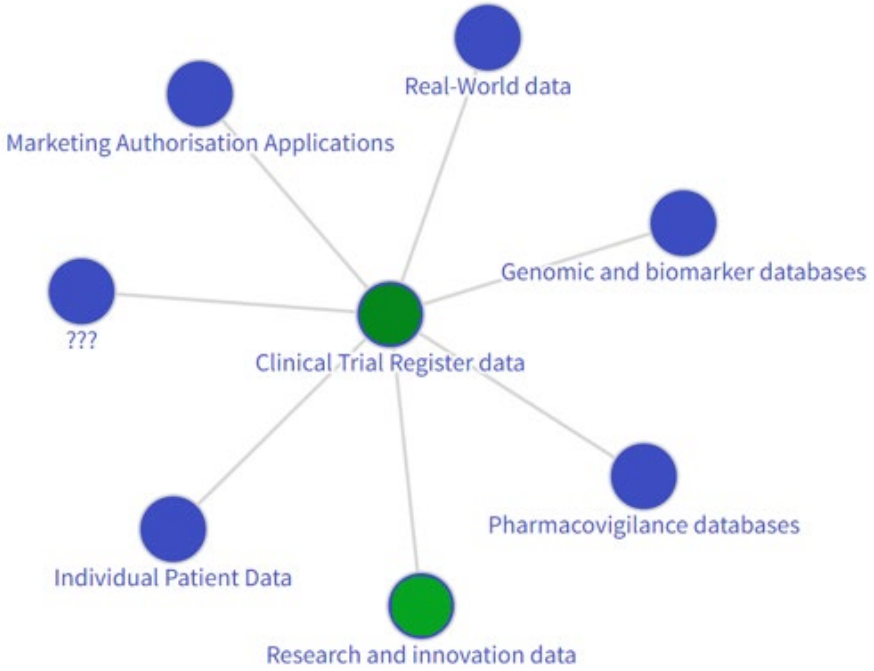
→*Enhanced capabilities for high quality assessments*



Use-case: How can register data combined with funding records identify research gaps and areas needing increased investment?

Significance: Helping stakeholders identify under-researched areas and allocate resources more effectively
→ steering public and private funding towards areas with the greatest potential for health impact

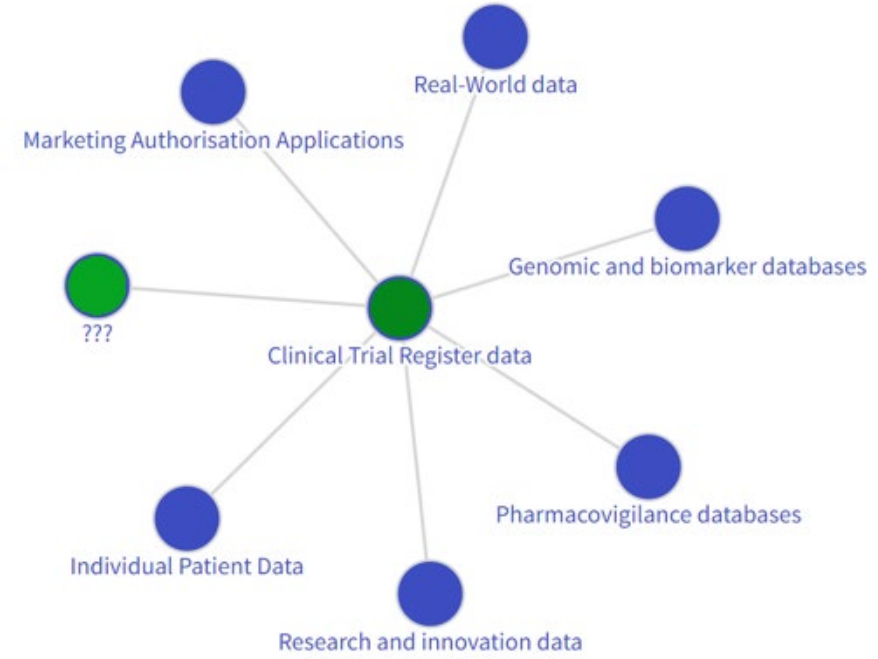
Types of data: Clinical trial register data, Research and innovation data (funding allocation records)



Use-case: How are clinical trials progressing that are part of paediatric medicine development and/or agreed paediatric investigation plans?

Significance: Understanding the impact of policy decisions and healthcare practices regarding child-specific treatments

Types of data: Clinical trial register data, paediatric investigation plans (PIP)



Data sources, non-exhaustive

CTIS: Investigational medicinal product being used, study designs, methodologies, endpoints, results and much more.

Marketing Authorisation Applications: Data from regulatory processes including their assessments and outcomes.

Pharmacovigilance databases: Adverse events and adverse drug reactions and repositories of established medicines safety information.

Real-World Data (RWD) sources: Encompasses EHRs, patient registries, health surveys, data from wearables, mobile health apps, insurance claims, etc.

Genomic and biomarker databases: Genetic, proteomic, metabolomic and other biomarker data relevant to drug responses and diseases.

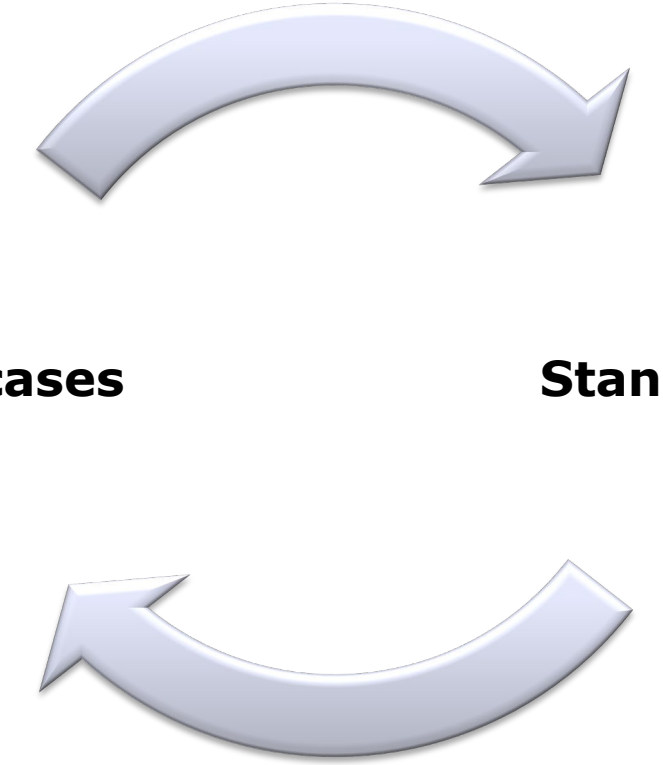
Individual Patient Data (IPD): Detailed data from clinical trial participants for in-depth analysis of treatment effects.

Research and innovation data: Academic research, proprietary datasets and joint research projects.

And many more to be specified from the use-cases identified at this workshop

The use cases require data standardisation

Establish requirements for structuring information



Enable use cases by making data more accessible

Data standardisation

The process of creating a common language by establishing consistent rules for organising and formatting data. These rules facilitates interoperability and data integration.

- Making data easily shareable and understandable across various platforms

Use-cases may rely on the work in ICH M11 (Clinical Electronic Structured Harmonised Protocol Template)

- Provides a comprehensive clinical protocol organisation with standardised content

Identifying the use-cases from all the different stakeholders in the clinical trial ecosystem

Describe specific use-cases from your area of work where data on clinical trials play, or could play, a crucial role?

- What is the significance?
- What is the needed data sources?

→ Focusing our efforts

→ Most importantly, using data to benefit patients by ensuring high quality, safe and effective medicines

Patient perspective on the value of clinical trials data

Presented by

Nikos Dedes – European AIDS Treatment Group

Session 1- Panel discussion

Nikos Dedes
European AIDS Treatment Group

Elmar Nimmesgern
Sr Policy Officer, European Commission

Denise Umuhire
Pharmacoepidemiologist & RWE specialist, EMA

Anton Ussi
CEO, European Advanced Translational Research Infrastructure in Medicine (EATRIS)

Nathalie Seigneuret
Senior Scientific Project Manager at Innovative Health Initiative (IHI)

Any Questions?
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Coffee break

Next up

15:15 Session 2: Clinical trials data: present and future

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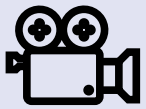

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Session 2: Clinical trials data: present and future

Co-chairs

Christophe Lahorte – Head of National Innovation Office & Scientific-Technical Advice Unit, Federal Agency for Medicines and Health Products

Michael Berntgen - Head of Scientific Evidence Generation Department, Human Medicines Division, EMA

We need a sandbox

Presented by

Julian Isla - Chief Scientific Officer, European Dravet Syndrome Federation

We need a sandbox

Julian Isla
Dravet Syndrome European Federation
COMP member

2 main ideas

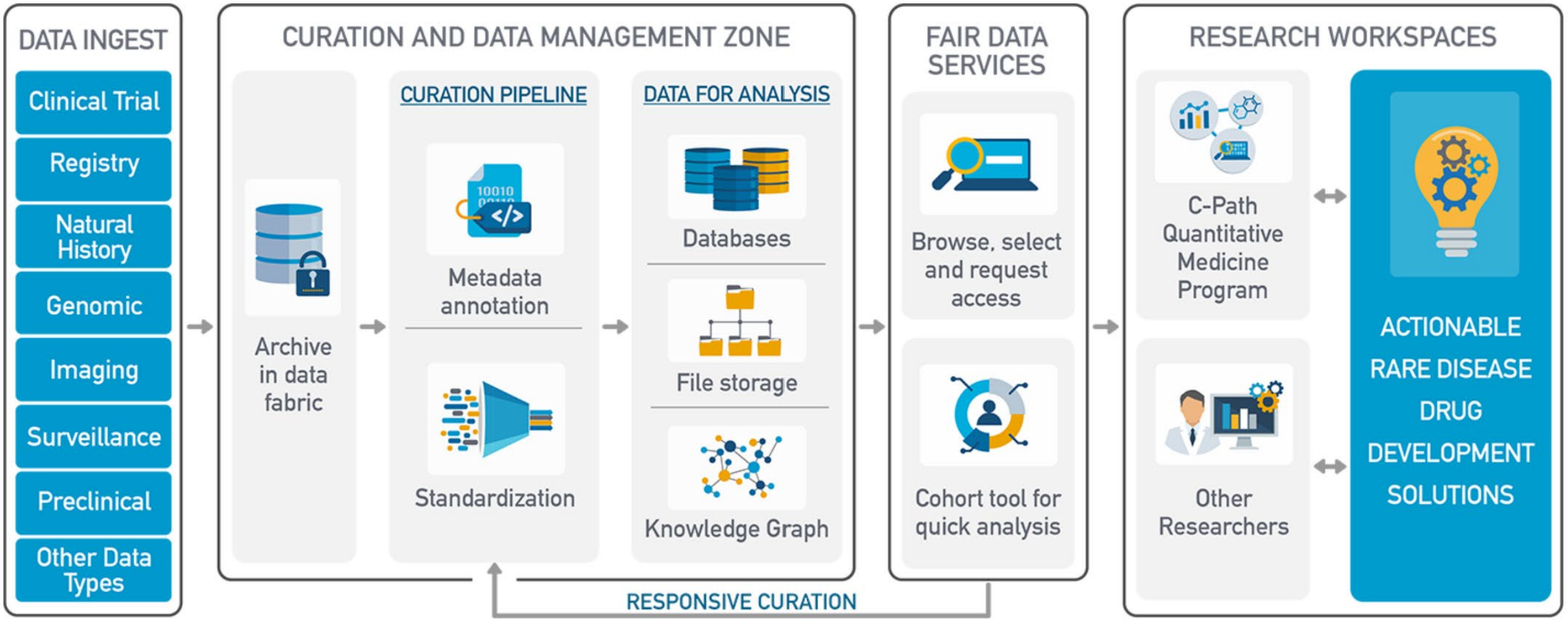
A sandbox with data from clinical trials

Create real-world data datasets by linking and analyzing patient registry data with clinical trials data

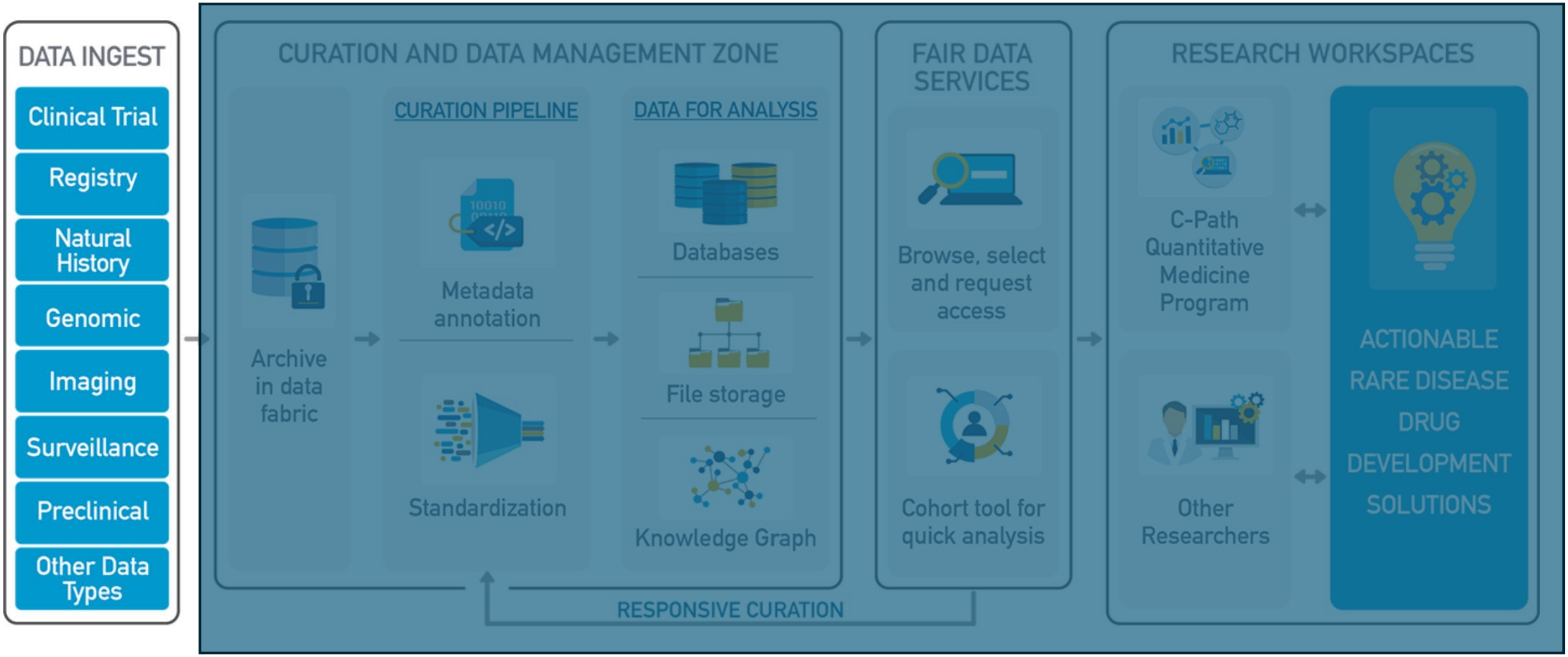
A sandbox with data from clinical trials

- The idea is to provide the data we already have from clinical trials in a research sandbox as an open analytics platform.
- Don’t reinvent the wheel. Just copy one RDCA-DAP | Critical Path Institute (c-path.org)
- RDCA-DAP is an FDA-funded initiative that provides infrastructure to support rare disease characterization and accelerate therapy development. It facilitates data sharing and analysis to better understand disease progression, biomarkers, and support innovative trial designs.

Sandbox architecture



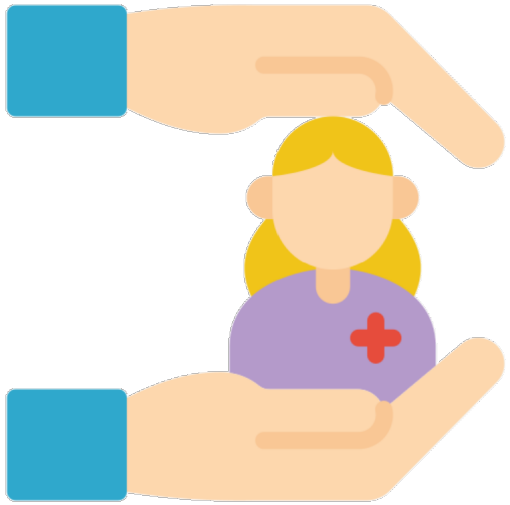
Where is the problem?



Asking patients organization to build their own registries is not fair







EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 May 2016
EMA/327846/2016
Executive Director

Letter of support for Patient Data Platform for capturing patient-reported outcome measures for Dravet syndrome

On 09 December 2015 the applicant Dravet Syndrome Foundation Spain requested qualification opinion for Patient Data Platform as an electronic tool for capturing patient reported outcomes in paediatric epilepsies, pursuant to article 57(1)(n) of regulation (EC) 726/2004 of the European Parliament and of the Council.

During its meeting held on 11-14 April 2016, the SAWP agreed on the qualification advice to be given to the applicant. During its meeting held on 25-28 April 2016, the CHMP adopted the advice to be given to the Applicant.

The sponsor seeks qualification opinion for their proposed "Patient Data Platform" (PDP) as a patient-reported outcome measure (PROM) to be used within drug development for paediatric epilepsies.


Thank you!

Clinical trial data on CTIS: Potential and challenges

Presented by

Till Bruckner - founder of TranspariMED

TranspariMED
Working to end evidence distortion in medicine

Till Bruckner
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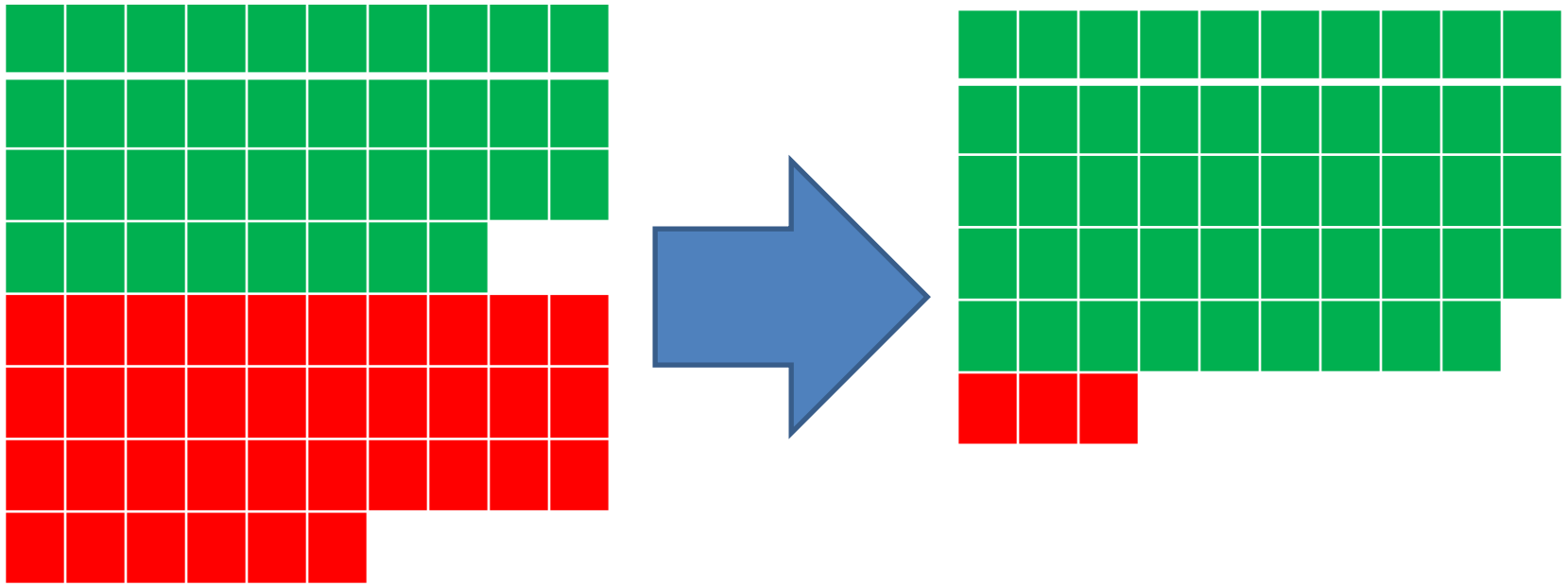
www.TranspariMED.org

25 January 2024

Potential: Full picture

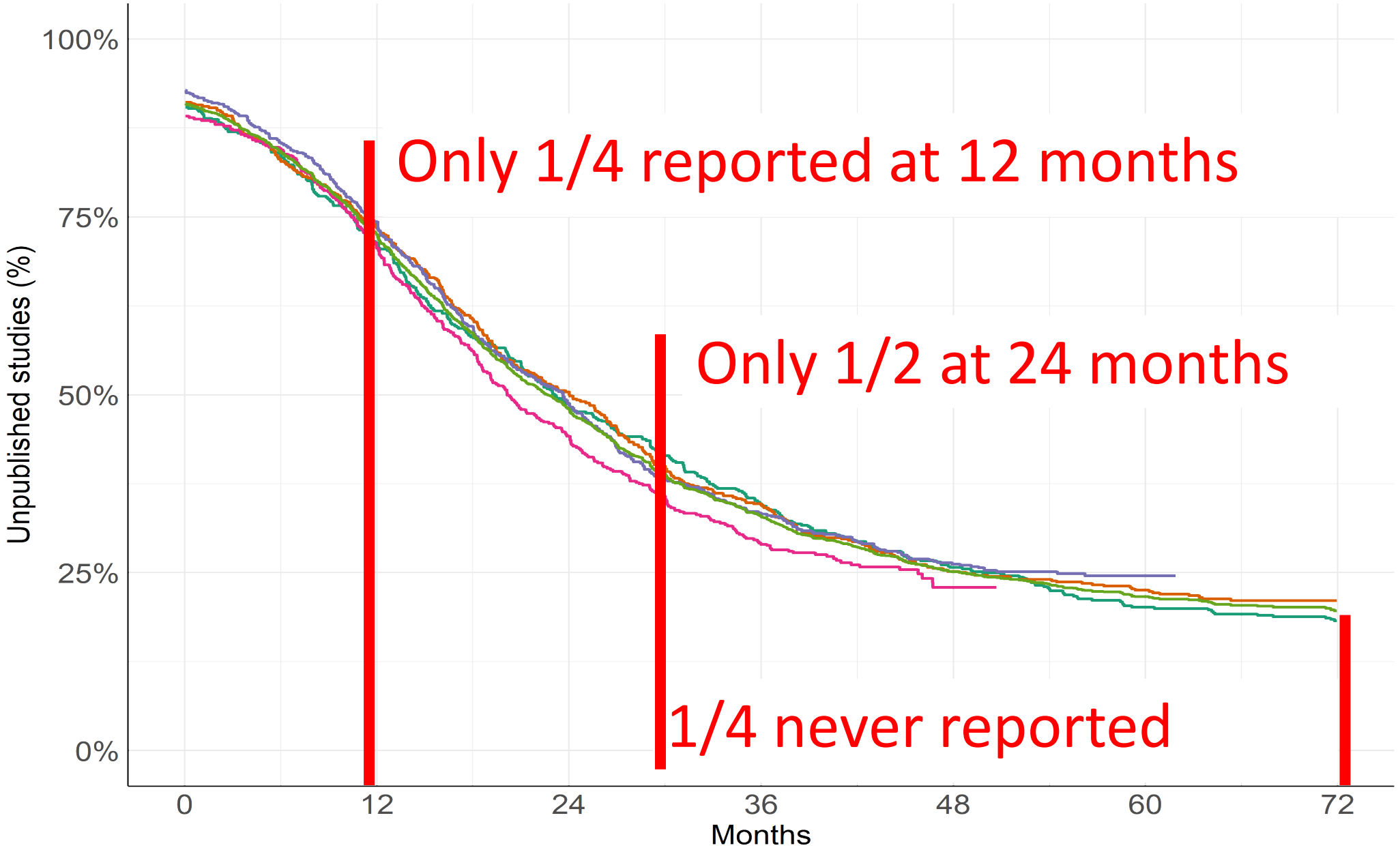
Trials completed: 74

Medical journals: 52



Source: Turner at al. "Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy" NEJM, 2008

Potential: Speed

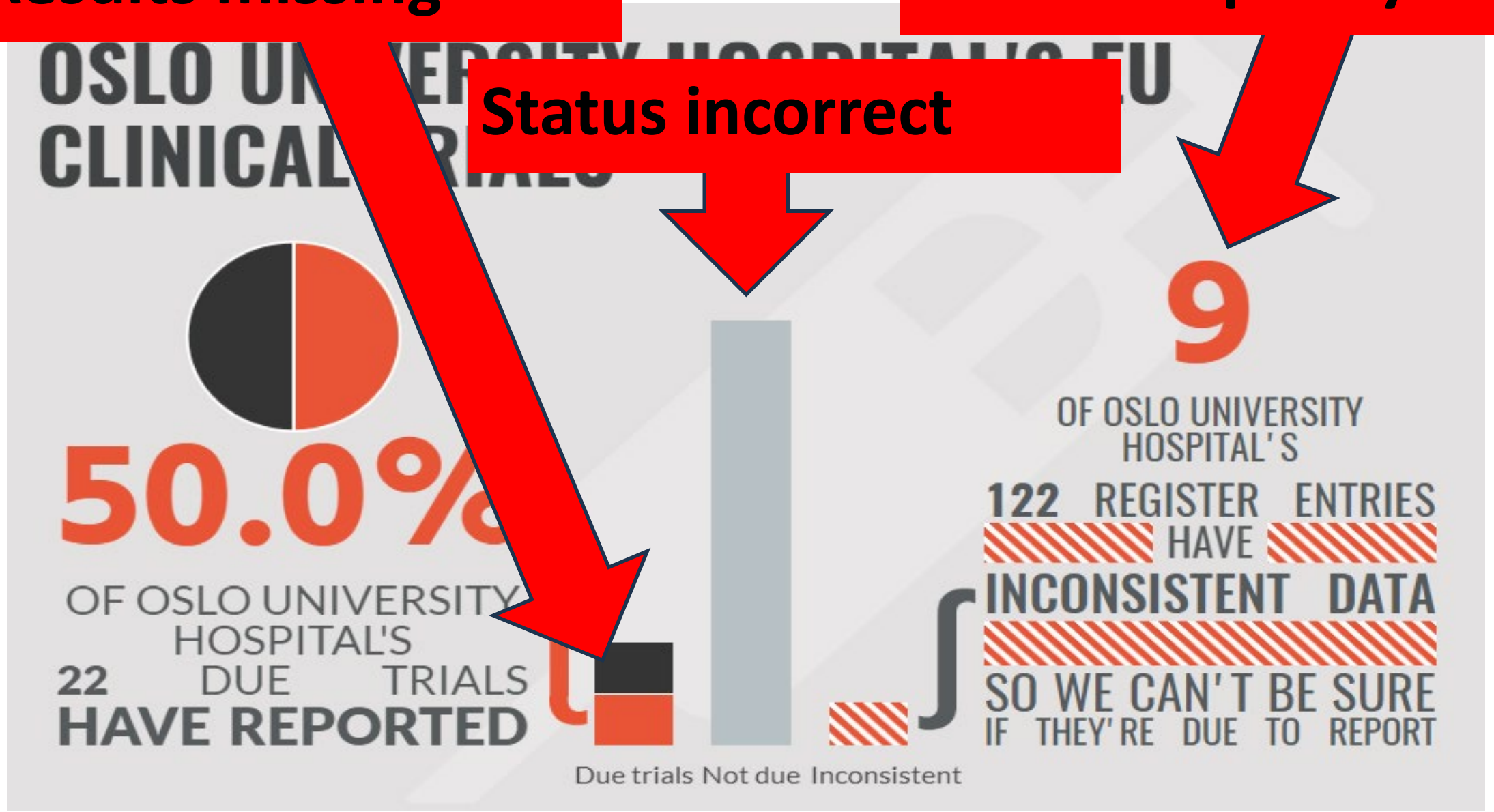


Challenges: EudraCT

Results missing

Status incorrect

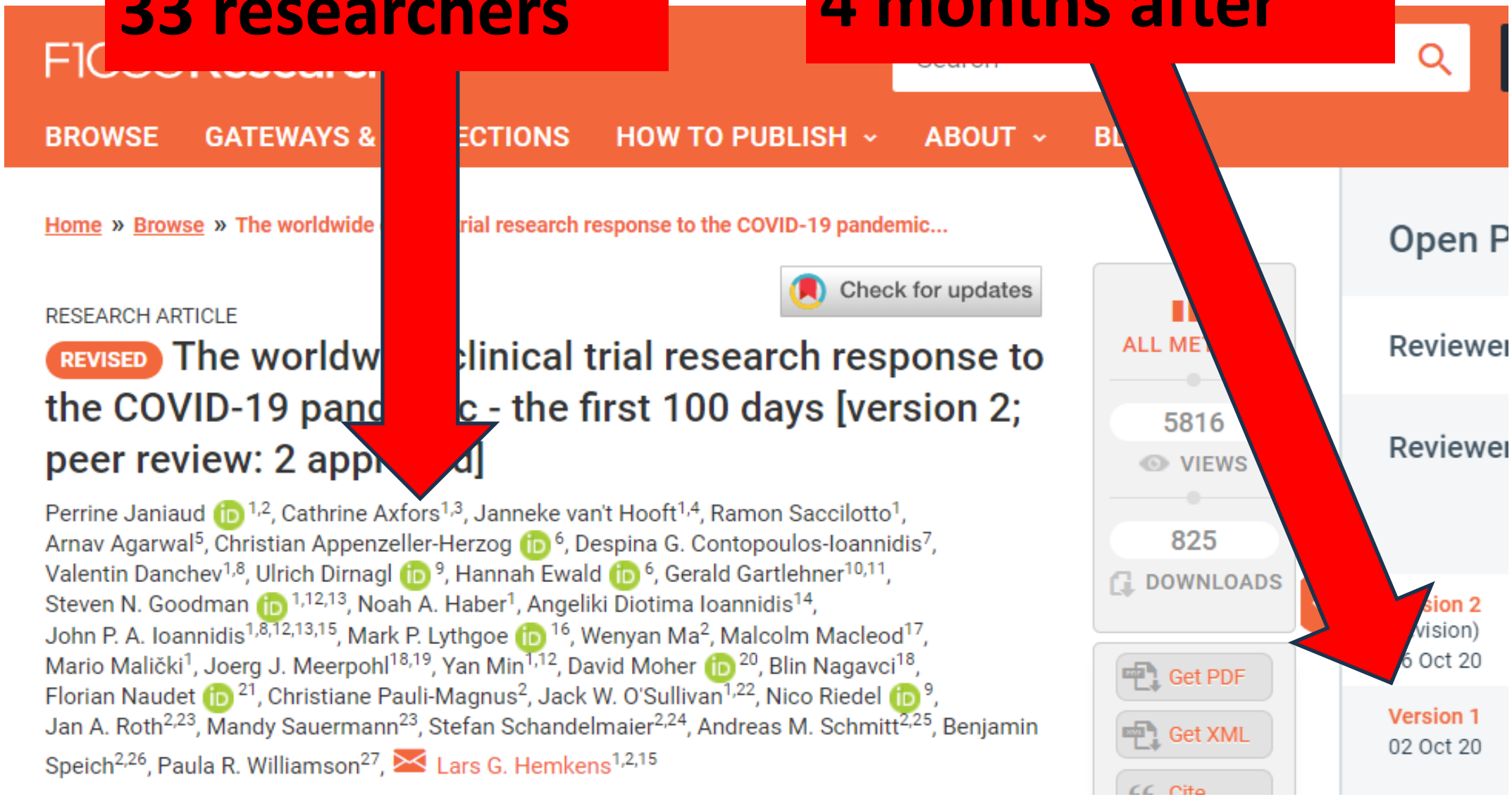
Data quality



Challenges: Global network

33 researchers

4 months after



Example use cases

Patient groups:

- Recruitment support
- Outcome measures
- Equality of access

Policy actors:

- Industrial policy
- Research policy

Overcoming CTIS challenges

TECHNICAL

- ***User friendly***
- ***API enabled***
  - *Scrapable*
  - *Downloadable*
  - *Structured*
  - *Machine readable*
- ***Globally aligned (ICTRP)***

EUROPEAN MEDICINES AGENCY
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POLITICAL

- **Complete**
- **Accurate**
- **Up to date**

Many sponsors are <u>not</u> prepared

National Competent Authorities

TranspariMED

Working to end evidence distortion in medicine

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25 January 2024

Representation in Clinical Trials
- data use-case from REPACT project at DKMA

Presented by

Jakob Wested - Industrial postdoc, DKMA

Representation in Clinical Trials

- data use-case from REPACT project at DKMA

Jakob Wested, Industrial postdoc

Danish Medicines Agency's Dataanalytics Center (DAC) &

Center for Advanced Studies in Biomedical Innovation Law (CeBIL), University of Copenhagen

Context: EU Regulatory basis for representation

EU

”Unless otherwise justified in the protocol, the subjects participating in a clinical trial should represent the population groups, for example gender and age groups, that are **likely to use** the medicinal product investigated in the clinical trial.”

EU Clinical Trial Regulation, recital 14

ICH General considerations & GCP guidelines

“involve participants who are representative of the diverse **populations which will receive** the intervention in clinical practice.

EMA

“Clinical trials need to involve **neglected populations** including the elderly and pregnant women so they too can benefit more directly from research.”

Regulatory science towards 2025 (March 2020)

Neglected populations in clinical trials

A pilot study of asthma medication use, comparing registered Real Word populations with Phase III clinical trial populations

AUTHORS

Wested J[(1)(2)], Ala TS[(1)], Bräuner EV[(1)], Hallum S[(1)], Handest M[(1)], Mogensen S[(1)]

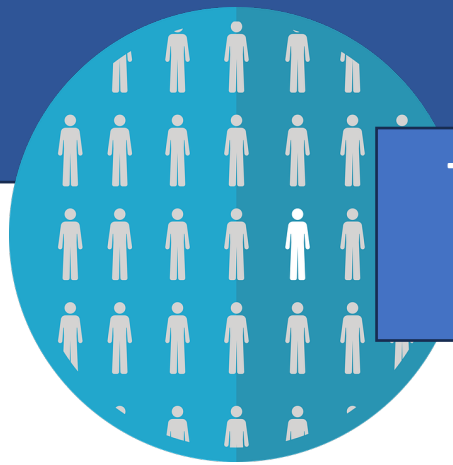
[1]Danish Medicines Agency, Data Analytics Centre (DAC)

[2]University of Copenhagen, Center for advanced studies in biomedical innovation law (CeBIL)

Objectives

Assess representation of sexes and age groups and prevalence of co-morbidities in clinical trials for asthma medciation

Use population
RWD from DK LPR & LSR



Trial population
Phase III CT in EUDRACT

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Use Population

- The National Patient Register (Landspatientregisteret-LPR)
- The Register of Pharmaceutical sales (Lægemiddelstatistikregisteret-LSR)

- All Danish citizens
- 2 years of age or more
- At least 1 prescription of asthma medication (defined by ATC code)
- From 1. jan. 2015 to 31. dec 2022

Characteristics	Entire cohort (n = 1,057,418) n (%)	Females (n = 575,346) n (%)	Males (n = 482,072) n (%)
Age (years)			
2-11 (childhood)	129,445 (12.2%)	54,990 (9.6%)	74,455 (15.4%)
12-17 (adolescence	58,330 (5.5%)	30,199 (5.2%)	28,131 (5.8%)
18-64 (adulthood)	551,403 (52.1%)	311,645 (54.2%)	239,758 (49.7%)
≥65 (middle-aged)	318,240 (30.1%)	178,512 (31.0%)	139,728 (29.0%)
Comorbidties			
Cardiovascular diseases	112,931 (9.8%)	53,974 (9.4%)	58,957 (12.2%)
Diabetes (Type 1 and Type 2)	39,862 (3.5%)	19,339 (3.4 %)	20,524 (4.3%)
Cancer	62,498 (5.4%)	41,956 (7.3%)	20,542 (4.3 %)

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Trial Population

- EUDRACT
- Completed Phase IIII,
- Before 1. january 2015
- Selected with list of ATC codes for asthma medication

Table 1 Population characteristics of the persons enrolled in the 40* phase III clinical trial on asthma medication

Characteristics	Entire cohort (n=98.846)	Females (n=26.537)	Males (n=35.025)
Age (years)			
2-11 (childhood)	3354 (3,39%)		
12-17 (adolescence	5432 (5,49%)	**43%**	**57%**
18-64 (adulthood)	64421 (65,17%)		
≥65a (middle-aged)	25639 (25,93%)		

*only 30 trial reported representation of Sex.

Comorbidities

"Exclusion criteria (…) 7. Any **significant disease** or disorder (eg, **cardiovascular**, pulmonary other than asthma, gastrointestinal, hepatic, renal, neurological, musculoskeletal, endocrine, metabolic, malignant, psychiatric, major physical impairment) which, **in the opinion of the investigator**, either put the **patient at risk** because of participating in the study or may **influence the results of the study**, or the **patient's ability to participate** in the study."

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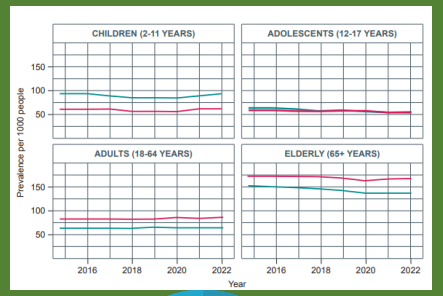
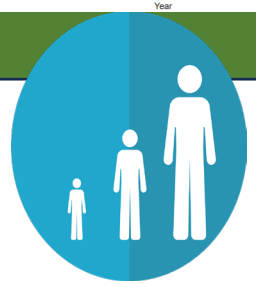
Observations

Representation of SEX relative to AGE in EUDRACT





Reporting of SEX representation

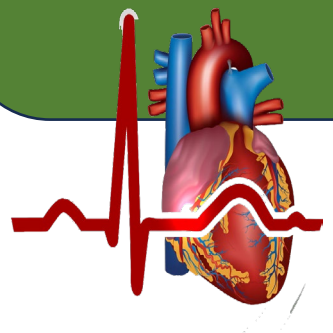
- Are we good?

CO-MORBIDITIES

Transparency & Accountability

FDA criticism

Methods – NLP?

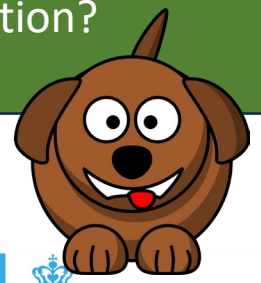


The Dog that didn't Bark….

Pregnant women
=> No ICD10 code

Ethnic minorities
=> Data & standards

=> the right use population?



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Thank you
Jakob.wested@jur.ku.dk
/
JKWE@DKMA.DK

Clinical trial data: present & future
An academic perspective

Presented by

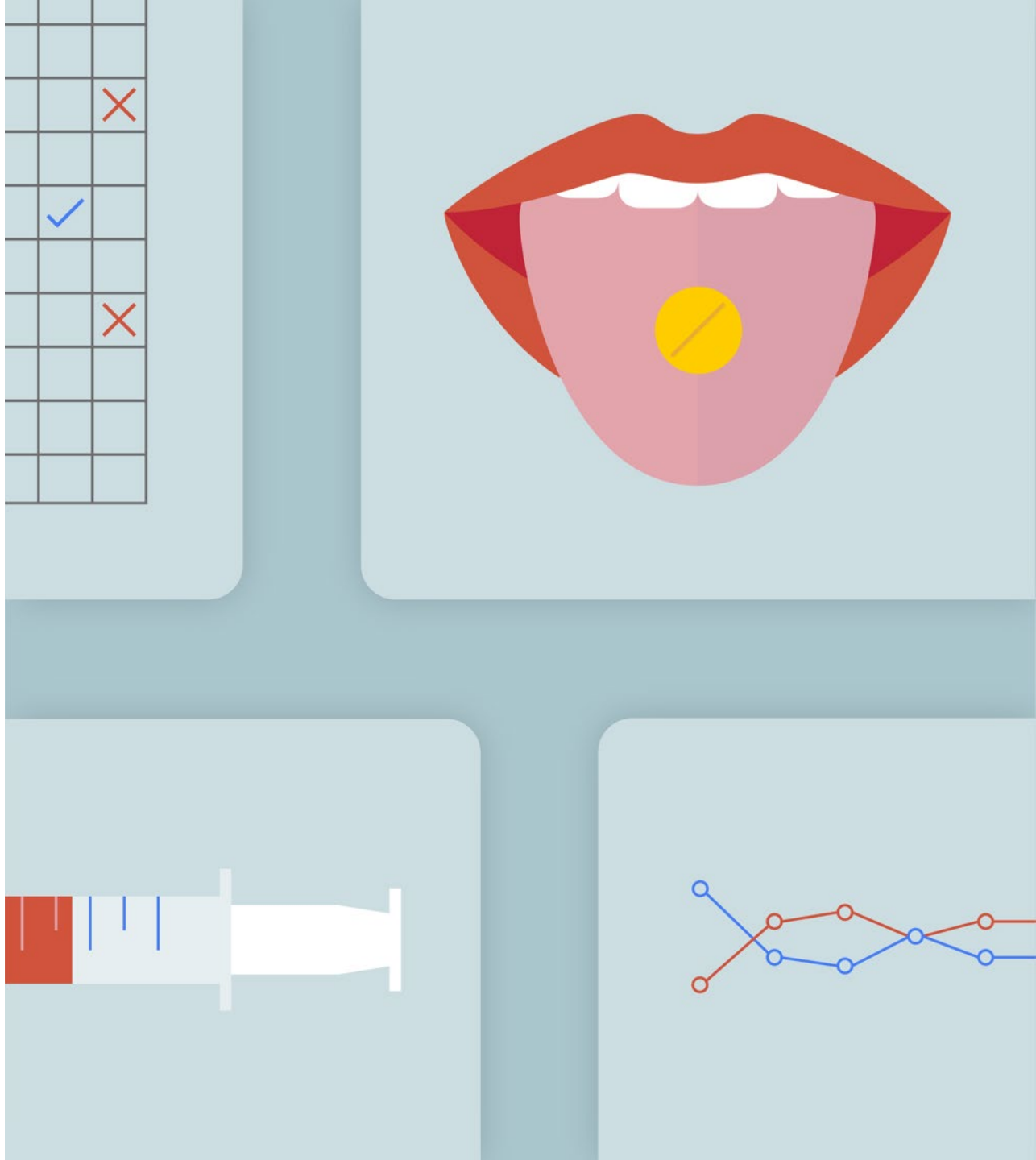
Helga Gardarsdottir - Associate professor, Division Pharmacoepidemiology & Clinical Pharmacology, Utrecht University

Clinical trial data: present & future

An academic perspective

Helga Gardarsdottir, PharmD, PhD
Associate professor

ACT EU Clinical Trials Analytics Workshop:
Amsterdam, 25 January 2024



Utrecht University

Pharmacoepidemiology
and Clinical Pharmacology

Clinical trial data

Research Article

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Regenerative Medicine

Publication rates and reported results in a cohort of gene- and cell-based therapy trials

Delphi GM Coppens[1], Helga Gardarsdottir[1,2], Cornelis A van den Bogert[1], Marie L De Bruin[1,3], Hubert GM Leufkens[1] & Jarno Hoekman*[,1,4]

Non-Publication Is Common among Phase 1, Single-Center, Not Prospectively Registered, or Early Terminated Clinical Drug Trials

Cornelis A. van den Bogert, Patrick C. Souverein, Cecile T. M. Brekelmans, Susan W. J. Janssen, Gerard H. Koëter, Hubert G. M. Leufkens, Lex M. Bouter

Published: December 14, 2016 • https://doi.org/10.1371/journal.pone.0167709

PlosOne 2013

Registries (e.g., EudraCT, clinicaltrials.gov) broadly used by academics

Mainly focusing on knowledge sharing & transparency – sharing of clinical trial results

Clinical trial data

Research Article

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Regenerative Medicine

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Delphi GM Coppens[1], Helga Gardarsdottir[1,2], Cornelis A van den Bogert[1], Marie L De Bruin[1,3], Hubert GM Leufkens[1] & Jarno Hoekman*[,1,4]

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Published: December 14, 2016 • https://doi.org/10.1371/journal.pone.0167709

PlosOne 2013

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RESEARCH ARTICLE

Number of Patients Studied Prior to Approval of New Medicines: A Database Analysis

Ruben G. Duijnhoven, Sabine M. J. M. Straus, June M. Raine, Anthonius de Boer, Arno W. Hoes, Marie L. De Bruin

Published: March 19, 2013 • https://doi.org/10.1371/journal.pmed.1001407

Registries (e.g., EudraCT, clinicaltrials.gov) broadly used by academics

Mainly focusing on knowledge sharing & transparency – sharing of clinical trial results

But also very useful for:

- Information on regulatory decision making in relation to evidence from clinical trials

Clinical trial data

Research Article

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Regenerative Medicine

Publication rates and reported results in a cohort of gene- and cell-based therapy trials

Delphi GM Coppens[1], Helga Gardarsdottir[1,2], Cornelis A van den Bogert[1], Marie L De Bruin[1,3], Hubert GM Leufkens[1] & Jarno Hoekman*[,1,4]

Non-Publication Is Common among Phase 1, Single-Center, Not Prospectively Registered, or Early Terminated Clinical Drug Trials

Cornelis A. van den Bogert, Patrick C. Souverein, Cecile T. M. Brekelmans, Susan W. J. Janssen, Gerard H. Koëter, Hubert G. M. Leufkens, Lex M. Bouter

Published: December 14, 2016 • https://doi.org/10.1371/journal.pone.0167709

PlosOne 2013

BROWSE PUBLISH ABC

PLOS MEDICINE

OPEN ACCESS PEER-REVIEWED

RESEARCH ARTICLE

Number of Patients Studied Prior to Approval of New Medicines: A Database Analysis

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Utrecht University

Pharmacoepidemiology and Clinical Pharmacology

Registries (e.g., EudraCT, clinicaltrials.gov) broadly used by academics

Mainly focusing on knowledge sharing & transparency – sharing of clinical trial results

But also very useful for:

- Information on regulatory decision making in relation to evidence from clinical trials
- Clinical endpoints

ORIGINAL ARTICLE | VOLUME 89, P199-208, SEPTEMBER 2017 Download Full Issue

Primary endpoint discrepancies were found in one in ten clinical drug trials. Results of an inception cohort study

Cornelis A. van den Bogert • Patrick C. Souverein • Cecile T.M. Brekelmans • ... Gerard H. Koëter • Hubert G.M. Leufkens • Lex M. Bouter • Show all authors

Published: May 20, 2017 • DOI: https://doi.org/10.1016/j.jclinepi.2017.05.012 • Check for updates

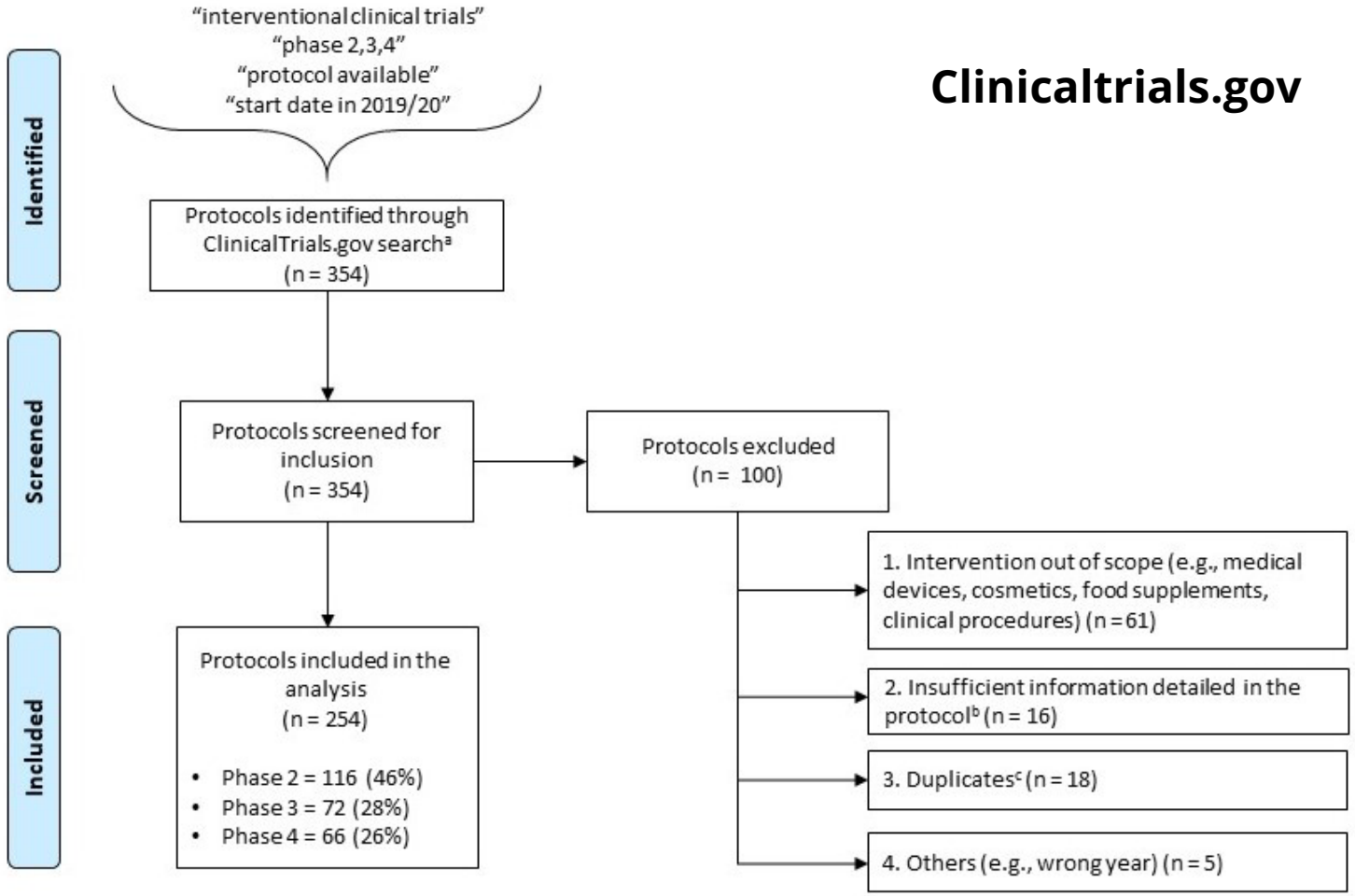
Remote Trial Elements Reported in Publicly Available Clinical Trial Protocols

Methodology

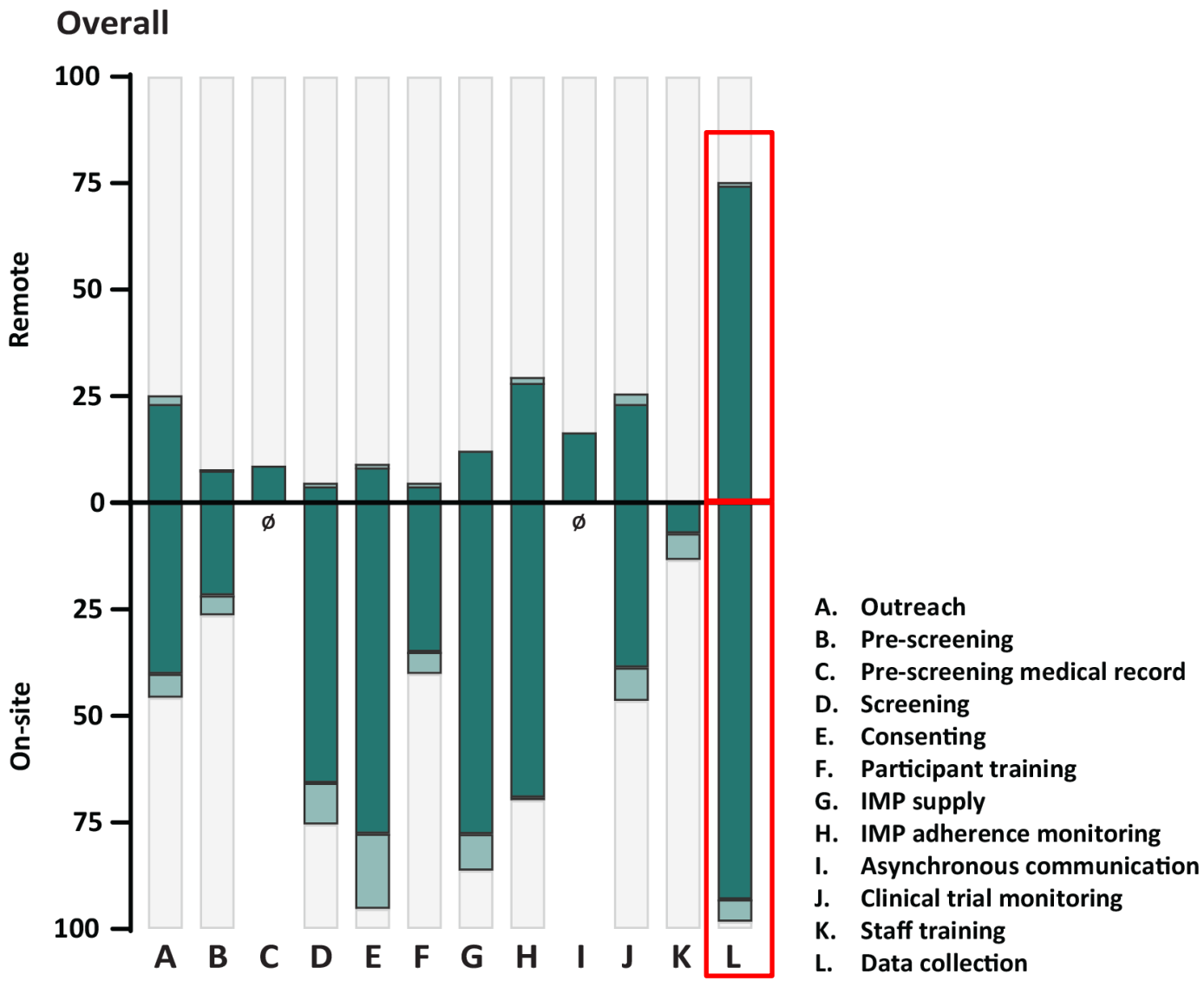
Remote element

'Operational trial activities that take place outside the investigator site'

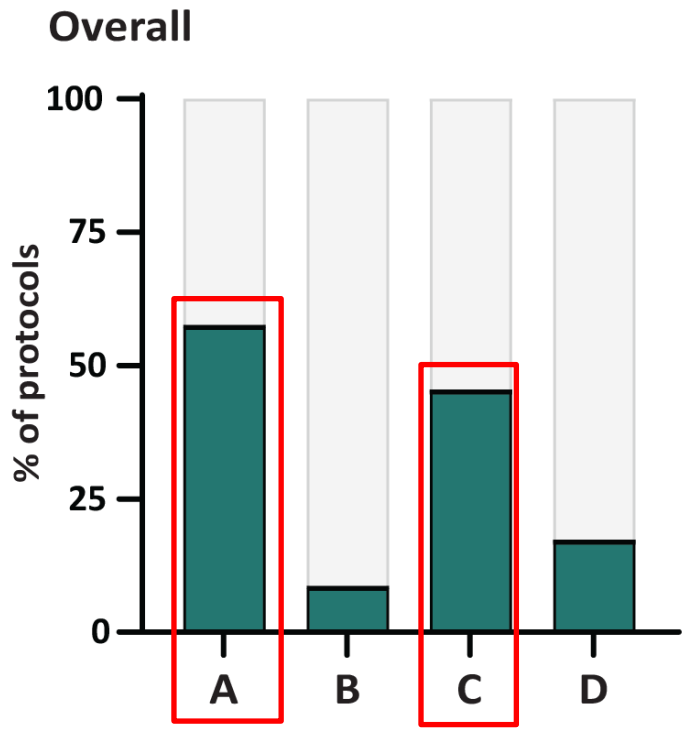
Clinicaltrials.gov



de Jong et al. BMJ Open 2022:12:e063236. doi:10.1136/



A. Outreach
B. Pre-screening
C. Pre-screening medical record
D. Screening
E. Consenting
F. Participant training
G. IMP supply
H. IMP adherence monitoring
I. Asynchronous communication
J. Clinical trial monitoring
K. Staff training
L. Data collection



A. Telemedicine visit
B. Home health visit
C. Remote PRO
D. (wearable) devices and biomarker kits

de Jong et al. BMJ Open 2022:12:e063236. doi:10.1136/

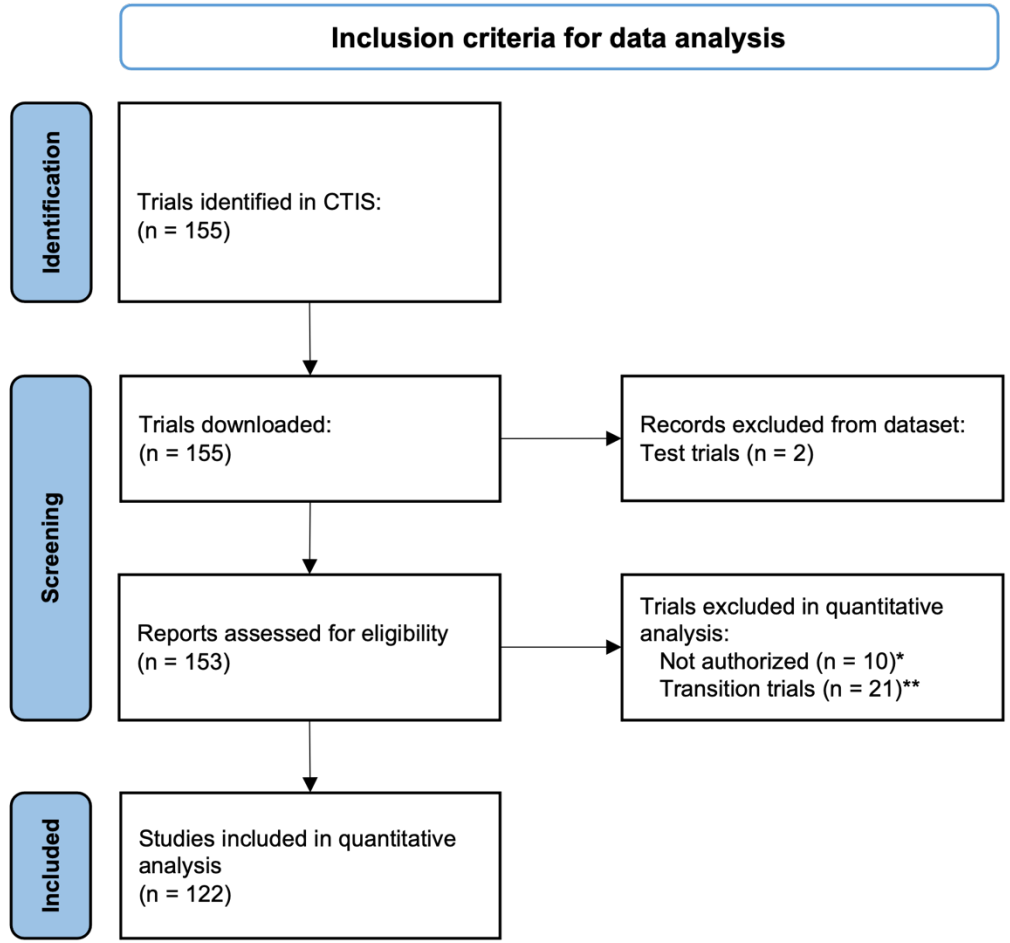
Low-intervention clinical trials in Europe: investigating the characteristics and sponsor experiences

Utrecht University

Pharmacoepidemiology
and Clinical Pharmacology

Methodology

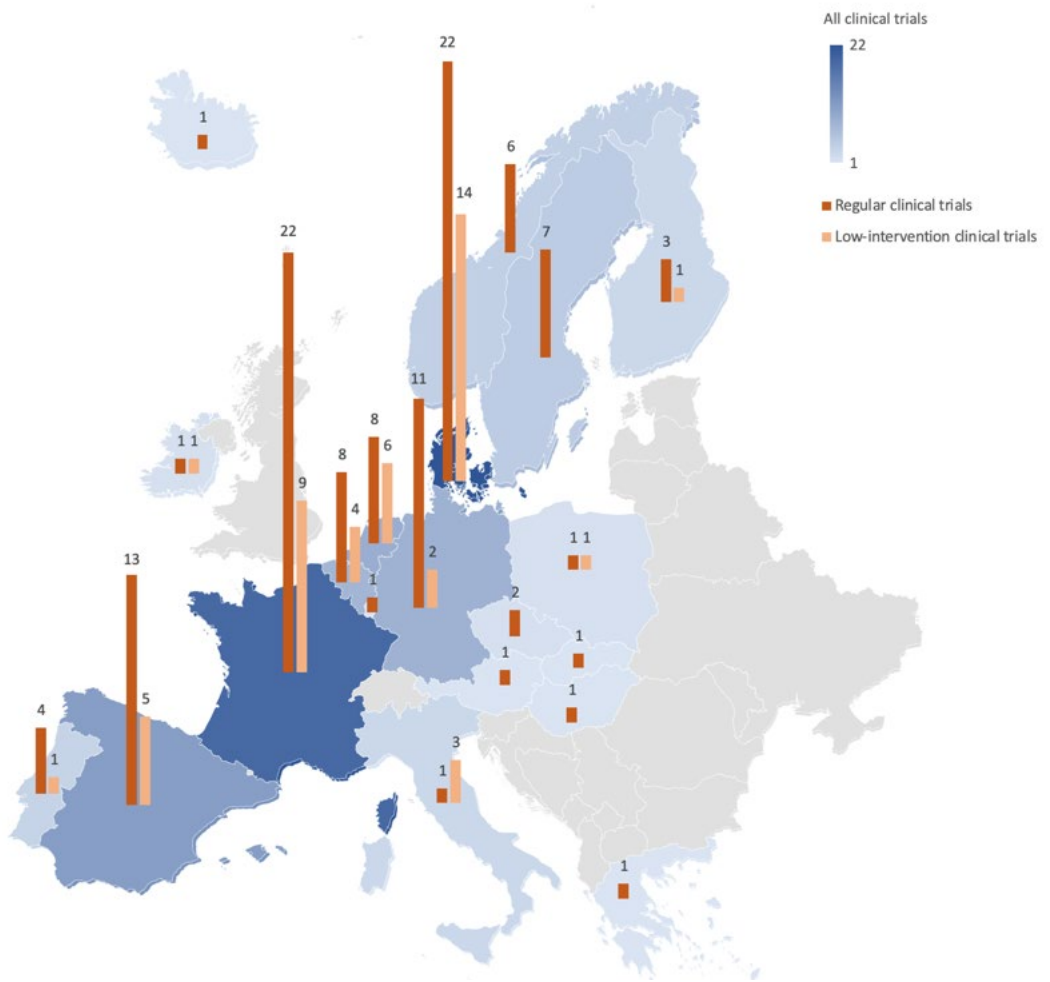
- **Low interventional clinical trials** (article 2.2 of CTR EU 536/2014 CTR)
- Clinical Trial Information System (CTIS)
- Data extraction on 21 April 2023



*Trials authorized in at least one country are included.
**Transition trials: trials that were submitted under the CTD as well.

de Jong & Hertog et al. unpublished data

Distribution of identified clinical trials in Europe (CTIS, April 2023)



	Clinical trials		LIMC
	Investigator (N=66)	**Industry (N=18)**	**Investigator (N=38)**
Participants			
Number of participants	80 (40-260)	96 (66-200)	320 (180-880)
Follow up (weeks)	29 (12-55)	40 (11-89)	48 (12-100)
Therapeutic area			
Cancer (C04)	10 (15.2%)	4 (22.2%)	3 (7.9%)
Cardiovascular (C14)	8 (12.1)	1 (5.6%)	8 (21.1%)
Clinical trial characteristics			
Study phase IV	12 (18.2%)	0 (0.0%)	31 (81.6%)
Multi-site trials	33 (50.0%)	11 (61.1%)	26 (68.4%)
Multi-country	7 (10.6%)	8 (44.4%)	3 (9%)

LIMC: Low interventional clinical trials

Thank you!

h.gardarsdottir@uu.nl

Finding Clinical Trials on DMD/BMD (demo)

Presented by

George Paliouras - Chairman of the Board (voluntary), Duchenne Data Foundation and Research Director, National Centre for Scientific Research "Demokritos"

USE CASE: FINDING CLINICAL TRIALS ON DMD/BMD

GEORGE PALIOURAS
Chair of DDF board of directors (voluntary)
Head of the AI Lab SKEL, NCSR “Demokritos”
Email: paliourg@iit.demokritos.gr

Our vision

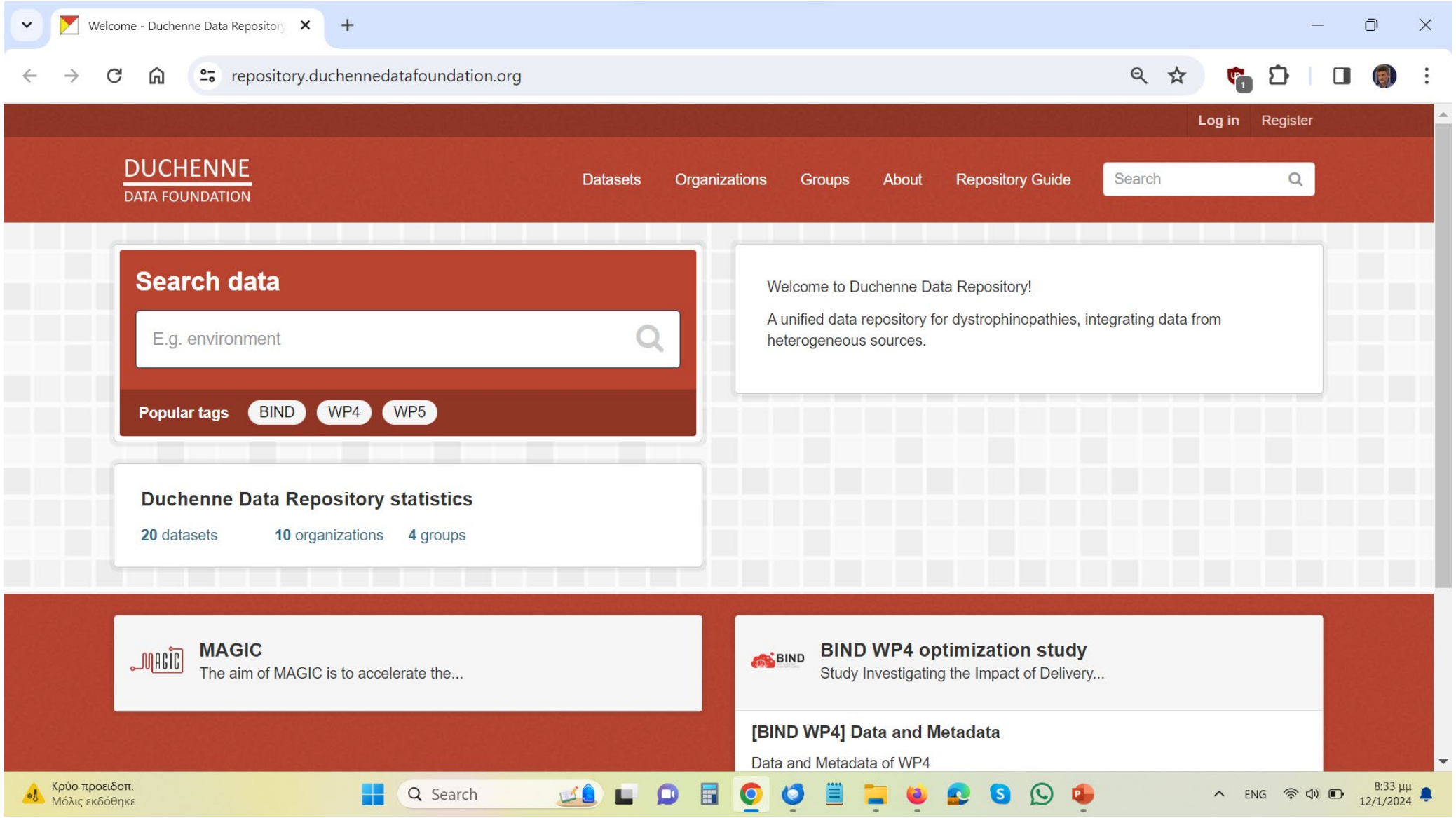
To bring data to life for the benefit of DMD and BMD patients

Our Principles

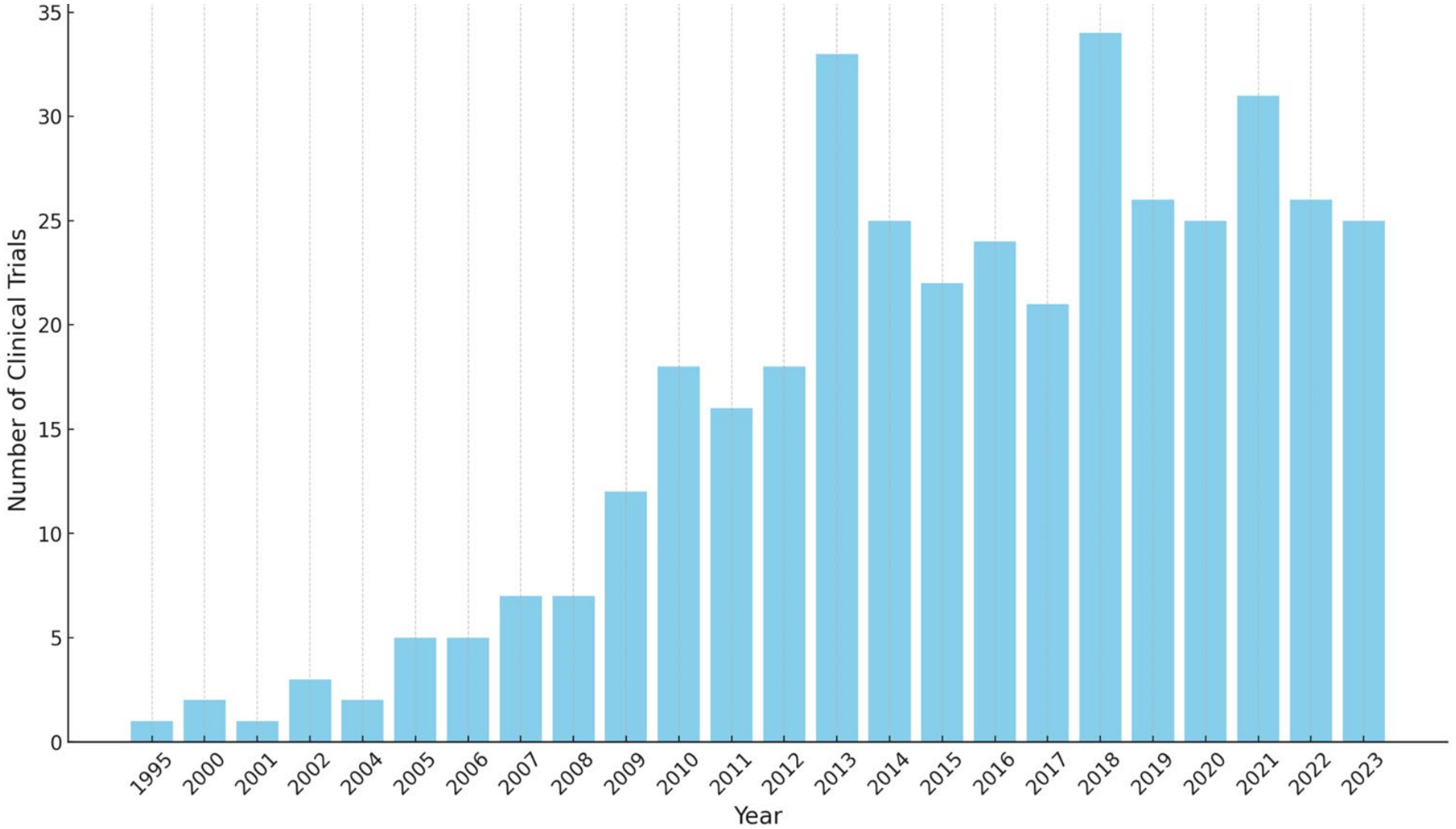
- Equal and easy access to data for all
- Open access to data analysis results
- Data use and re-use to advance research and drug development
- Open source tools for research
- Patient data ownership

DUCHENNE
DATA FOUNDATION

Duchenne Data Repository

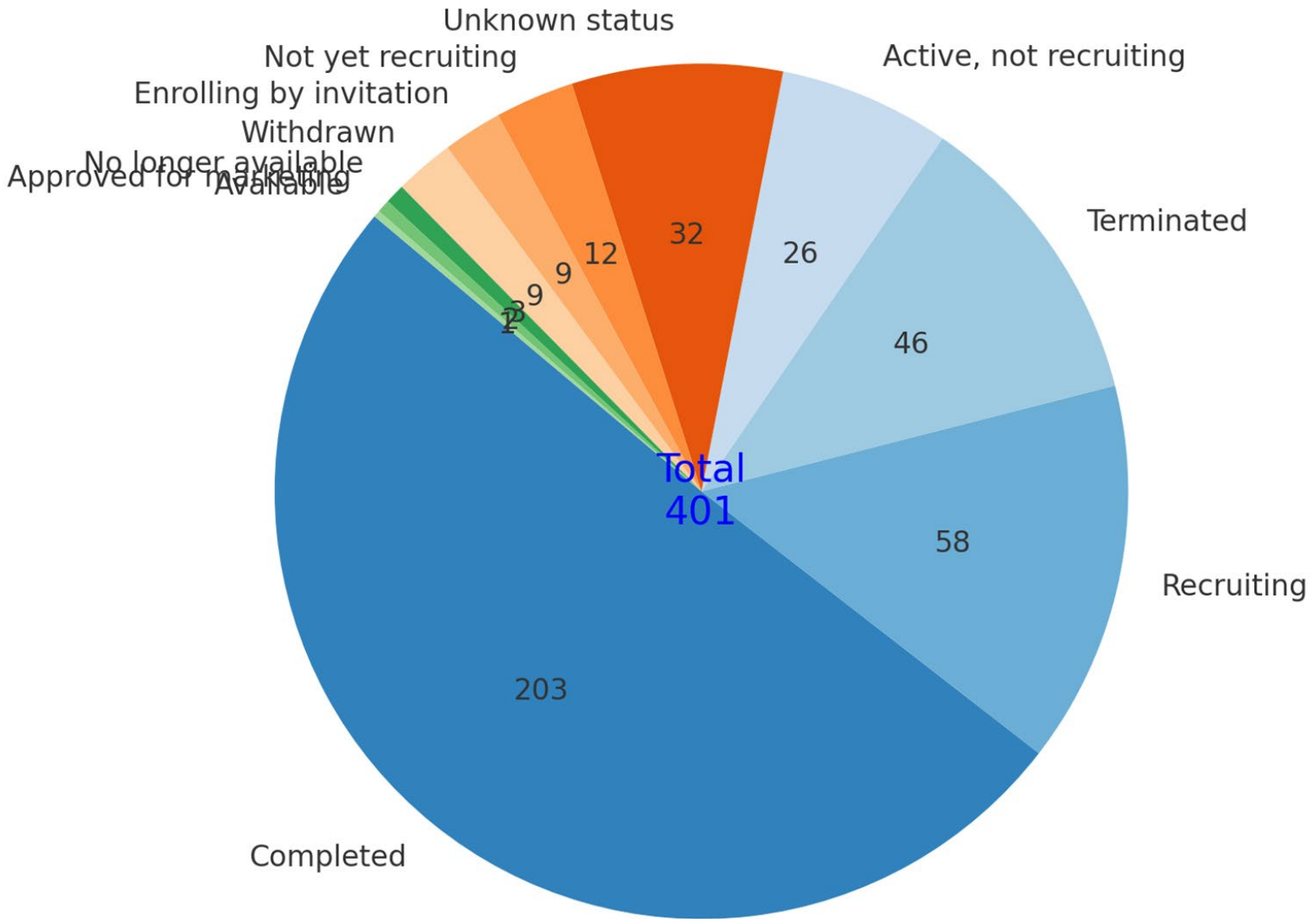


Clinical Trials started in DMD/BMD per year

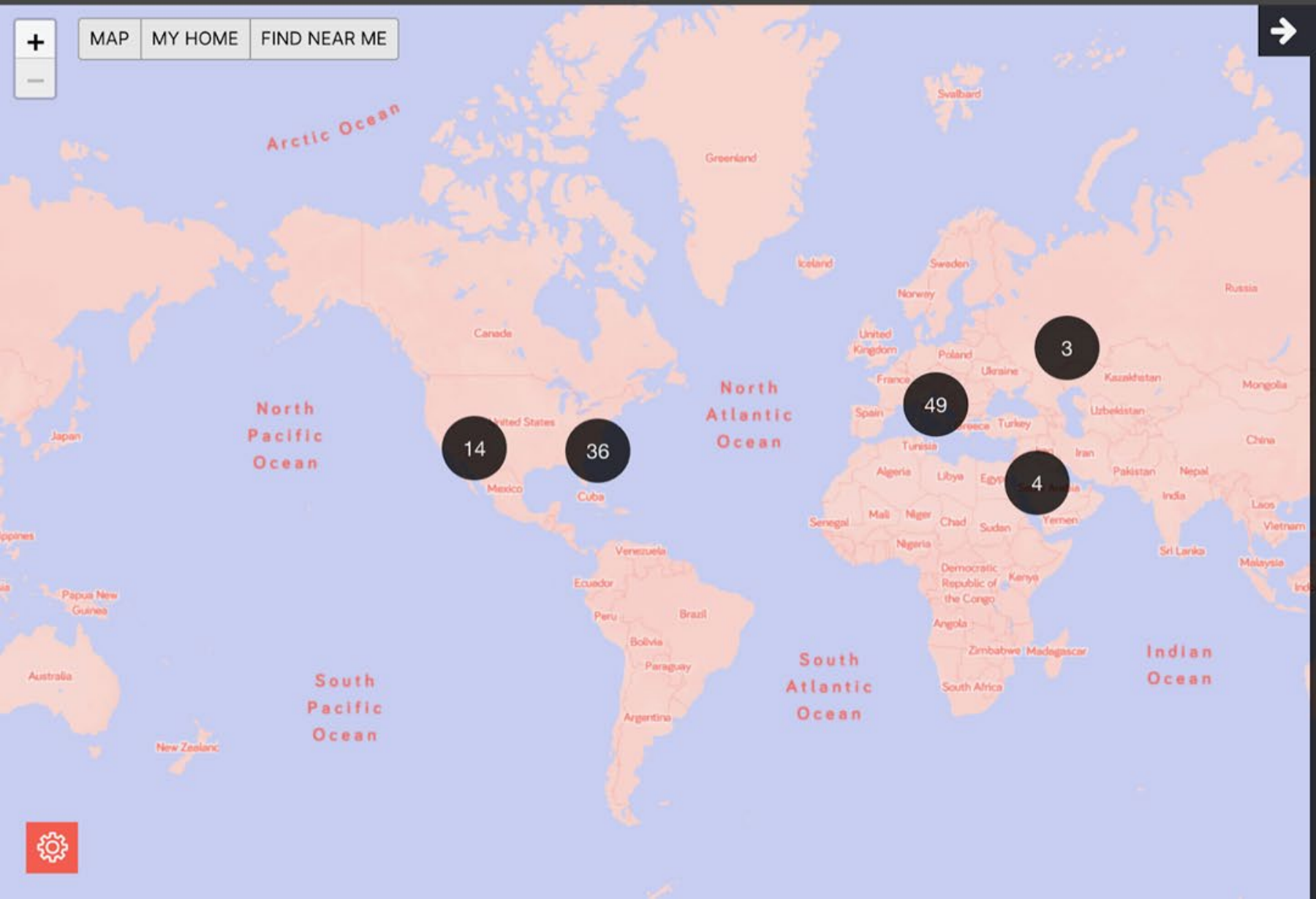


Source: clinicaltrials.gov

Clinical Trials in DMD/BMD - Status



Source: clinical trials.gov



I am looking for

Organizations & Companies

Clinical Trials

Able to join if ambulatory

Able to join with corticosteroids

Within age range

3 years - 15 years

SHOW RECRUITING TRIALS

Clear all

Publications [coming soon]

Care Centers [coming soon]

I am looking for

Organizations & Companies

Clinical Trials

Able to join if ambulatory

Able to join with corticosteroids

Within age range

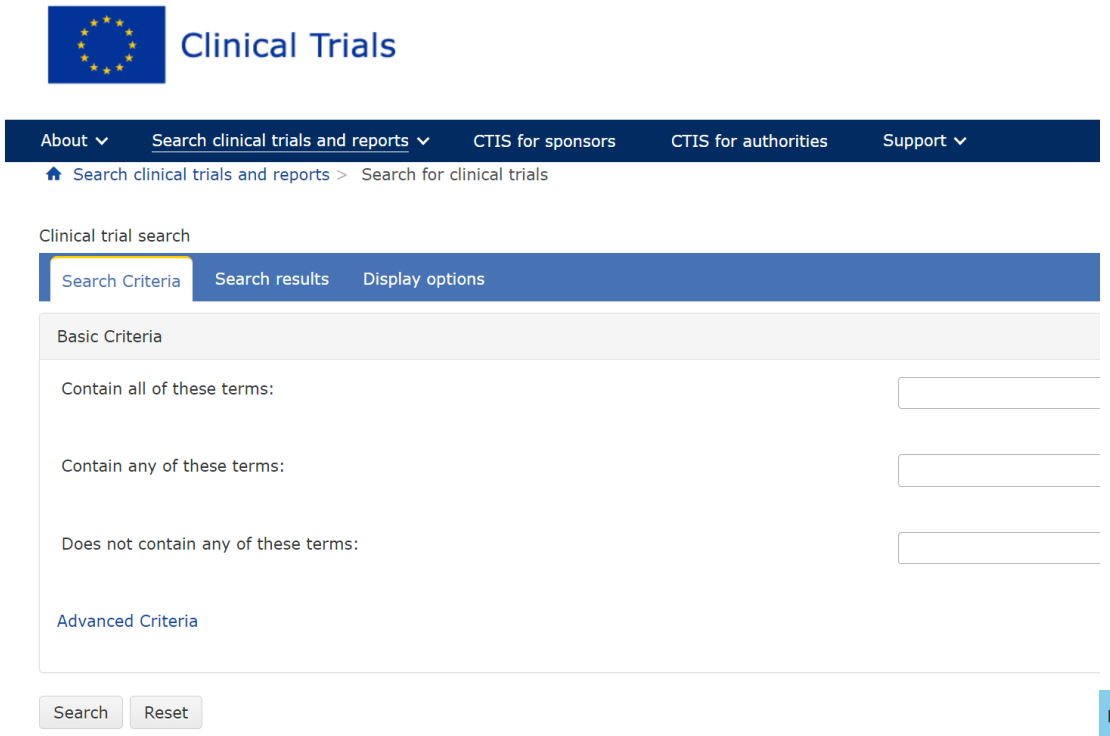
3 years - 15 years

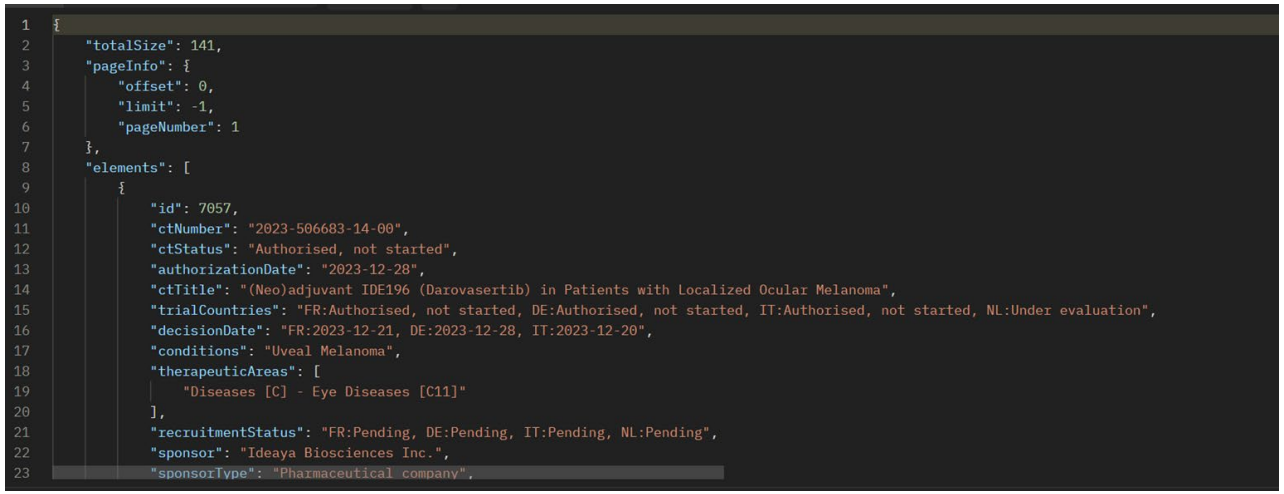
SHOW RECRUITING TRIALS

Publications

Care Centers

euclinicaltrials.eu



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            "sponsorType": "Pharmaceutical company",
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7057	2023-506683-14-00	Authorised, not started	FR:2023-12-21, DE:2023-12-28, IT:2023-12-20	Uveal Melanoma	Diseases [C] - Eye Diseases [C11]	FR:Pending, DE:Pending, IT:Pending, NL:Pending	Ideaya Biosciences Inc.
2010	2022-501874-21-00	Ongoing, recruiting	SE:2023-12-20, DK:2023-09-13, NO:2023-09-06	Takotsubo syndrome	Diseases [C] - Cardiovascular Diseases [C14]	SE:Ongoing, DK:Pending, NO:Pending	Vastra Gotalandsregionen
9568	2023-508993-27-00	Ongoing, recruitment ended	ES:2023-12-21	Chronic myelogenous leukemia	Diseases [C] - Neoplasms [C04]	ES:Ended	Fundacion Cris De Investigacion Par Vencer El Cancer
8780	2023-508266-15-00	Authorised, not started	DE:2023-12-19	type 2 diabetes mellitus	Diseases [C] - Nutritional and Metabolic Diseases [C18]	DE:Pending	Universitaetsklinikum Erlangen AöR
5687	2023-505356-22-00	Authorised, not started	IT:2023-12-18	Liver limited unresectable colorectal cancer	Diseases [C] - Neoplasms [C04]	IT:Pending	Gruppo Oncologico Del Nord Ovest
	2023-	Authorised	FR:2023-11-29, ES:2023-	Locally advanced or metastatic		FR:Pending, IT:Pending,	

- No DMD/BMD data available
- Less trial data available than clinicaltrials.gov

More information at:
https://www.duchennedatafoundation.org/
https://repository.duchennedatafoundation.org/
https://www.duchennemap.org/

Industry Use Cases for clinical trials data

Presented by

Martin O'Kane - Regional Head RA EU Policy & Liaison Novartis / EFPIA

efpia
European Federation of Pharmaceutical Industries and Associations

Vaccines Europe
An industry for healthy lives

EUCROF
European CRO Federation

ACRO
Innovate
Advocate
Collaborate

EuropaBio
The European Association for Bioindustries

EUCOPE
European Confederation of Pharmaceutical Entrepreneurs AISBL

ACT EU Clinical Trials Analytics Workshop

Martin O'Kane, Novartis

25-26 January 2024

Session 2: Clinical trials data: present and future

- **Industry Use Cases for clinical trials data held in CTIS/EudraCT:**
  - What it has been helpful for?
  - What has been missing?
  - Which questions could I answer with better data access?
  - Potential future uses of the available data

- **Industry Use Cases for data sources beyond CTIS/EudraCT**

Current uses of data held in EudraCT/CTIS

- **Used to interrogate (small numbers of) individual entries to inform study design or study feasibility:**
  - Has a novel endpoint been accepted before?
  - Has the intended patient population (age range, comorbidities etc) been accepted before?
  - Has a novel technology been accepted before?

- **Used to benchmark countries via available metrics:**
  - Expertise/capacity per country per phase
  - Expertise/capacity per country per disease area
  - Expertise/capacity per country per product type (e.g. ATMPs)
  - Attractiveness of EU for conducting CTs
  - Speed of assessment

Current uses of data held beyond EudraCT/CTIS

- **European data sources used to inform the understanding of the disease or the medicine:**
  Some examples:
  - Drug A label expansion using Danish ITP registry,
  - Analysis of UK/German clinical databases to demonstrate no use of Drug B among women of childbearing age to inform pregnancy registry discontinuation
  - Historical comparator data from EU sites to support Drug C approval

- **Observational studies:**
  - many use cases of analysis of non-EU data sources
  - EU PAS register will become an increasingly important database of studies – especially with the increasing use of RWE in regulatory decision-making and Inclusion of study protocols posted by DARWIN EU coordinating centre: the forthcoming relaunch of it in a much more user-friendly format will be a huge improvement.

Gaps limiting use of available data

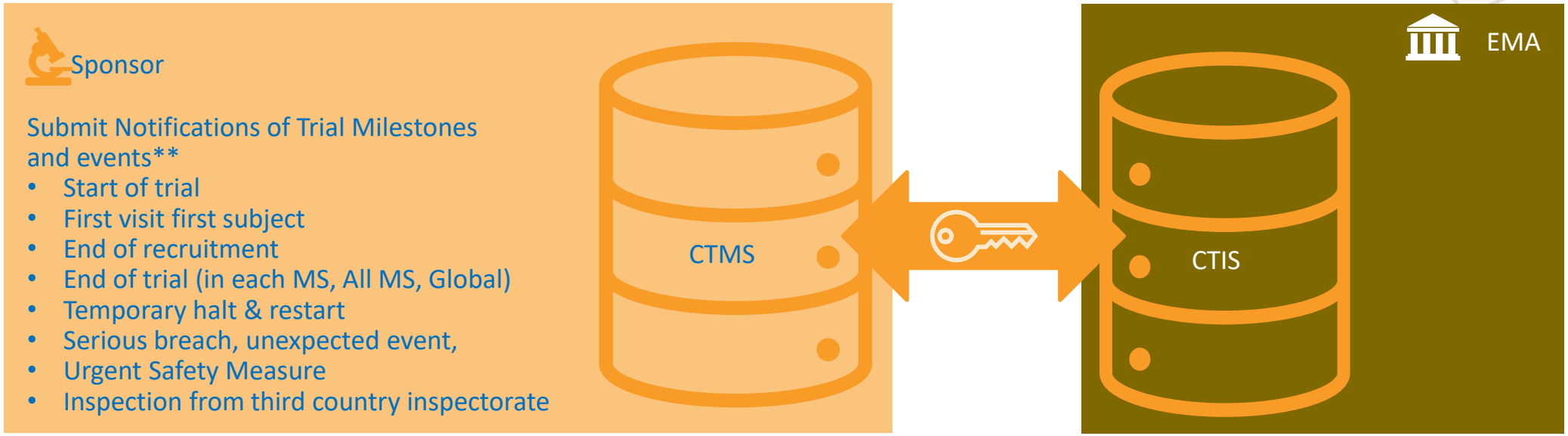
General awareness that the databases exist is low (e.g. patient organisations)

Not necessarily in data **quantity** but in **functionality and usability** of platforms

Summary results data not structured so currently of limited use.

Interoperability of sponsor data→CTIS database to ensure data quality and standardisation

Future Vision: Direct link between Sponsor CTMS* and the Clinical Trial Information System (CTIS)



- To ensure the timely availability of data in CTIS and avoiding manual entries, a secured transfer of clinical trial milestone data from Sponsor CTMS directly into EMA - CTIS system would be beneficial.
- This will support the CTIS system as a powerful source for data mining and KPI trial metrics.
- Care will be needed when considering end-to-end processes with different database interactions eg CTIS requirement for CSR on MAA can link into CSR EMA requirements to avoid duplication of manual effort in uploading twice and protecting patient data (GDPR) and commercially confidential information(CCI).

*Clinical Trial Master System
**Source: CTIS structured data form - Notifications

Future Vision: Standardisation of protocol data (ICH M11)

Establishing digital standards will pave way to move away from "document centric" to "data centric" protocol development, thereby facilitating real-time alignment and automation of downstream processes.

- One "digital source of truth" and no need to re-enter the data/information manually in downstream documentation/databases, avoiding mistakes, simplifying process, inspections, increasing transparency.

- Digital data and structured content management enable content reuse in other documents/systems: e.g. content is written only once and reused end to end in regulatory documents from protocol to label; protocol content can be reused automatically in training materials for the sites or populating automatically trial master file.

Conclusions

- **Much of the information in EudraCT/CTIS is supplied directly by trial sponsors**

- **Current use of the available data is limited to:**
  - benchmarking or metrics generation
  - conducting targeted searches of approved trials

- **Future curation, standardisation, intra-operability and user friendliness enhancements will support:**
  - better public and HCP engagement with clinical research --> access to innovation
  - more efficient site selection and patient recruitment
  - more efficient data transfer between (global) systems and interrogation of the data (eg AI)
  - linkages to other data sources, boosting observational research in the EU
  - 'predictive safety' to enhance protocol design for safety monitoring and reporting
  - better understanding of both the IMP and the disease
  - more efficient regulatory oversight and monitoring of innovation
  - the continuum from clinical trial to marketing authorisation and new medicines for patients

Use Case from ethics perspective

Presented by

Michael Zwaan – Pediatric oncologist and Chairman of the Dutch Association for Medical Research Ethics Committees (NVMETC)

Centrale Commissie Mensgebonden Onderzoek

ACT EU Clinical Trials Analytics workshop

Session: Clinical Trials Data – Present and Future
Use case from ethics perspective*

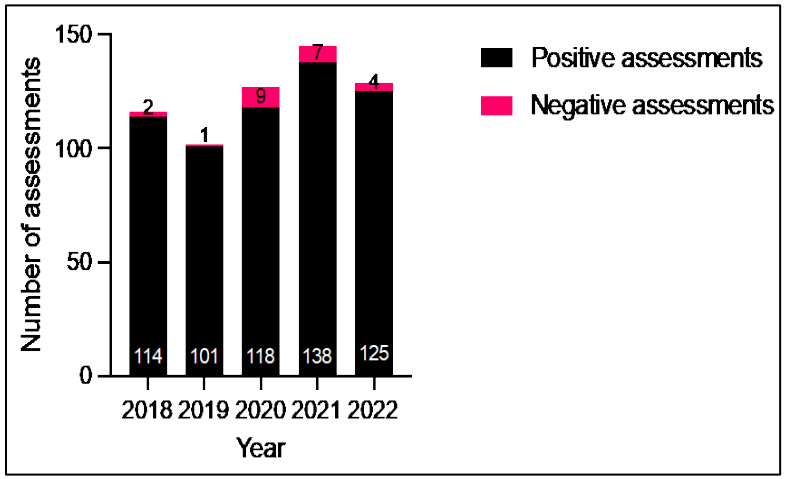
Prof. Dr. Michel Zwaan, pediatric oncologist and Chair Dutch Association of Medical Research Ethics Committees (NVMETC) The Netherlands

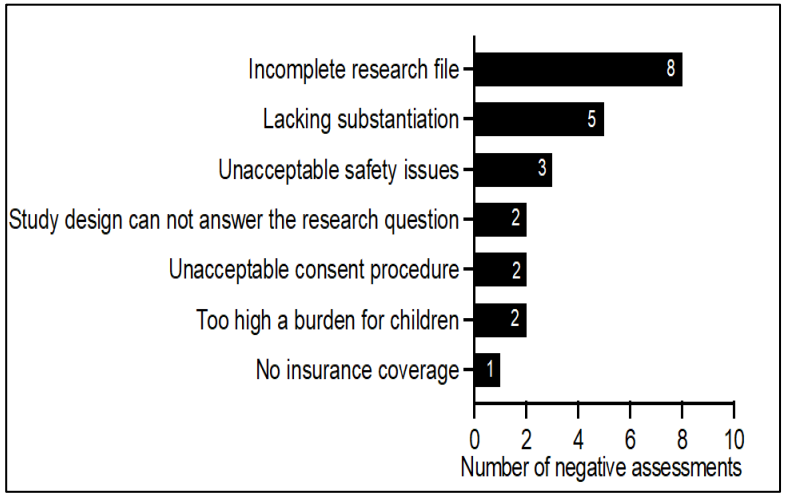
* USE CASES FROM CCMO AND NVMETC, THE NETHERLANDS

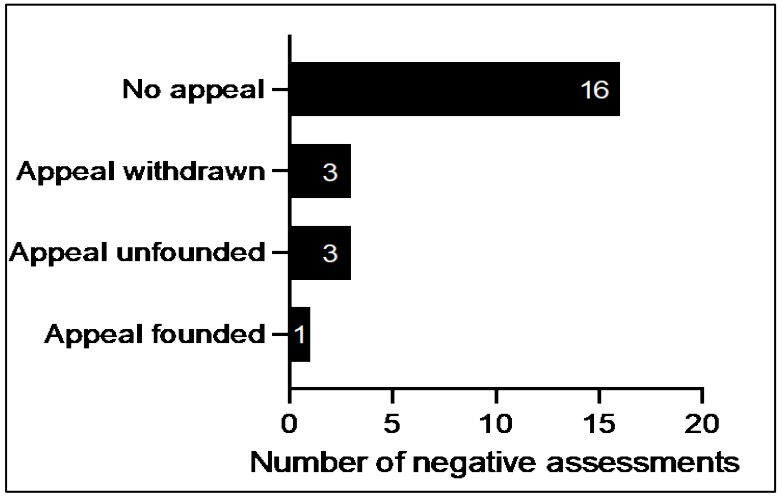
ACT EU PA05 WORKSHOP, EMA

AMSTERDAM 25-26 JANUARY 2024

Use Case (1): MREC 'NEDMEC' negative decisions (23/596 dossiers ~4%)







Central ethics committee: 1.7% negative decisions in the NL

Analyses of reasons to reject clinical trials may provide info/guidance to investigators, sponsors and regulators

Heinsbroek et al, In press, Journal of Trial and Error

Use Case (2): Number of clinical trials with antisense nucleotides/oligonucleotides and products on the market/in development

Data sources:

- ToetsingOnline (Database with structured and open text fields on studies in NL submitted for review by MRECs : https://english.ccmo.nl/about-ccmo/toetsingonline (not active anymore for clinical trials: CTIS and national collaboration platform for clinical trials)
- EMA database: https://www.ema.europa.eu/en/medicines
- FDA databases: https://www.fda.gov/drugs/drug-approvals-and-databases/resources-information-approved-drugs

Outcome:

	ASO ('..rsen')		siRNA ('...siran')		other*	
Number of Studies	83		38		9	
Rejections/Withdrawals	13	(16%)	3	(8%)	1	(11%)
Number of Compounds	49		16		6	
Development Stopped/Uncertain	21	(41%)	1	(6%)	1	(17%)
Development Ongoing	22	(47%)	9	(56%)	5	(83%)
Registration Pending/Completed (EMA/ *FDA*) *(italics: no studies in NL)*	3 nusinersen (SMA-1) volansorsen (FHC) *fomivirsen (CMV retinitis)* 7 mipomersen (FHT) viltolarsen (DMD) casimersen/golodirsen eteplirsen (DMD) *inotersen (TTA-P/C)* *tofersen (SOD1-ALS)*	(6%) *(14%)*	6 givosiran (porphyria) inclisiran (FHC) lumasiran (PH-1) patisiran (TTA-P/C) vutrisiran (TTA-P/C) teprasiran (graft protection)	(38%)	-	-

Analyses of reasons for rejection of clinical trials, product development program, and obtained marketing authorisation → potential consequences for next CTs with these compounds

Use Case (3): Evaluation ethical considerations paediatric clinical trials: direct benefit, group benefit, no benefit, group relatedness and risk and burden for the trial participants

Data sources:

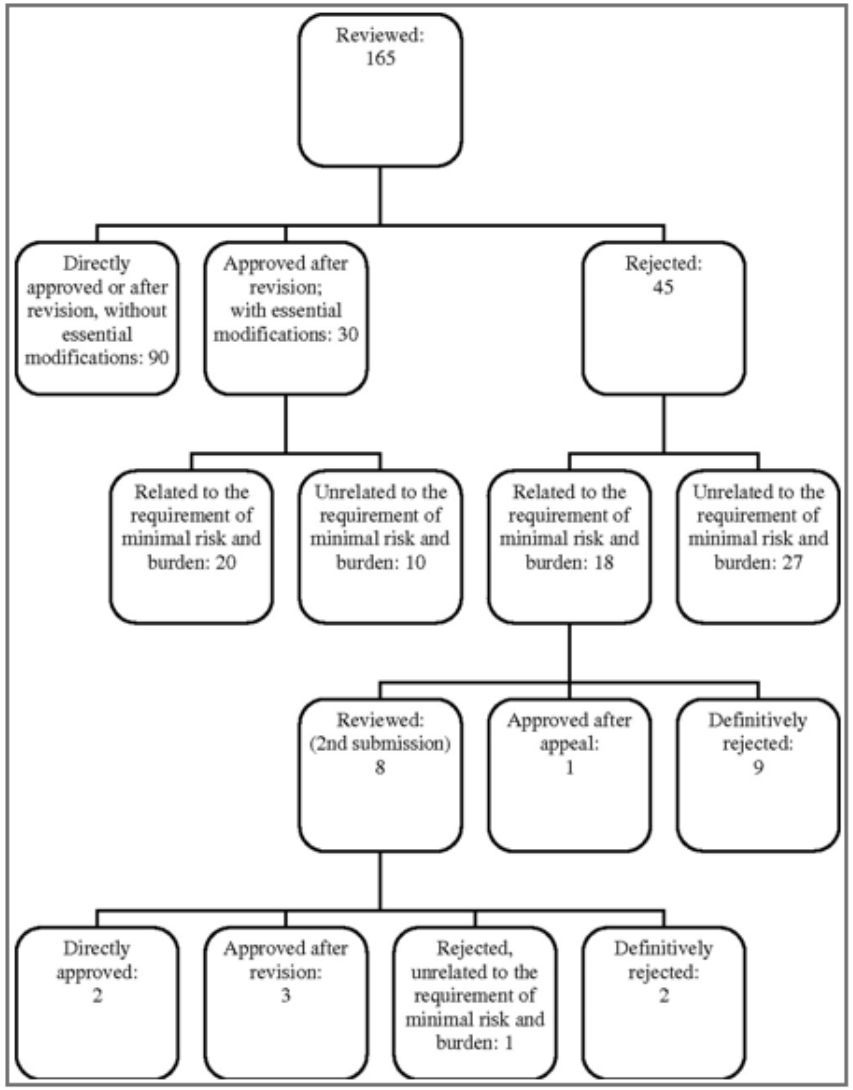
- ToetsingOnline (Database with structured and open text fields on studies in NL submitted for review by MRECs : https://english.ccmo.nl/about-ccmo/toetsingonline (not active anymore for clinical trials: CTIS and national collaboration platform for clinical trials)
- CCMO/MREC document management system (local, not public)

Outcome: report with in-depth analysis: Rapport Westra Evaluatie CCMO-beoordelingen niet-therapeutisch onderzoek met minderjarigen | Rapport | Centrale Commissie Mensgebonden Onderzoek

In CTIS no structured data fields for easy selection on clinical trials in paediatric population (or other populations) without direct benefit.

Evaluation of ethical considerations used for national legislation, recommendation paper, and harmonised approach on assessing paediatric clinical trials.

The committee's decisions on the 165 protocols.

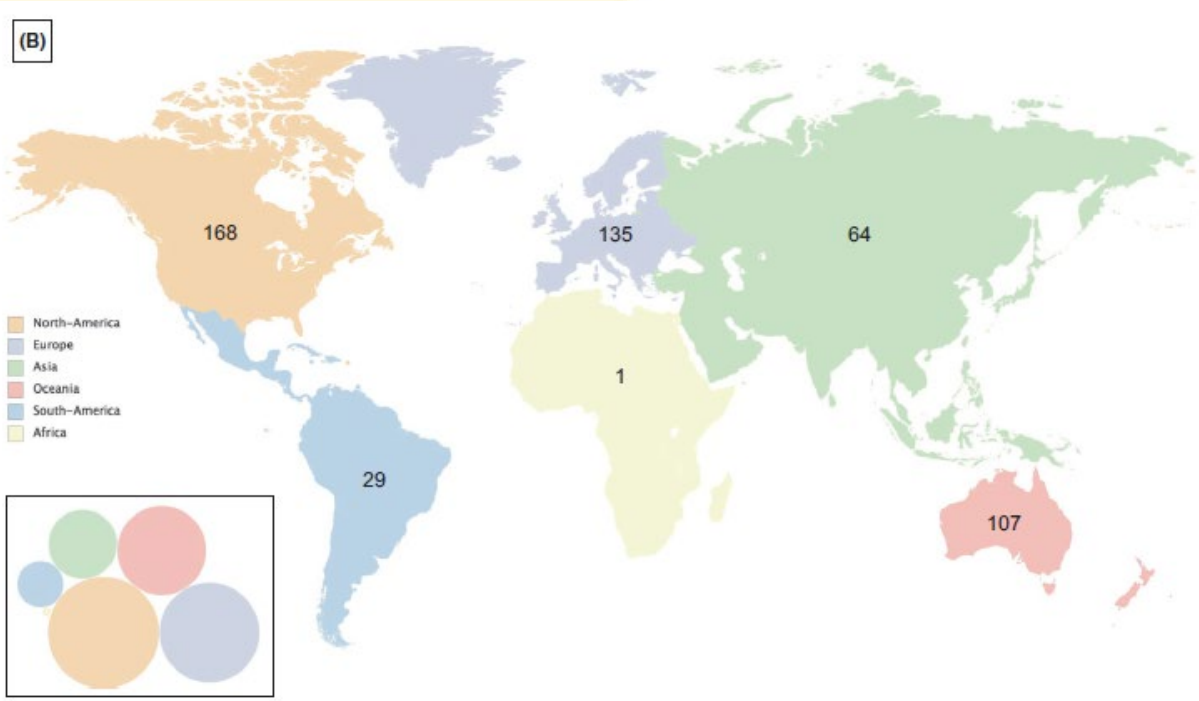


Anna E Westra et al. J Med Ethics 2010;36:420-424

Use Case (4):

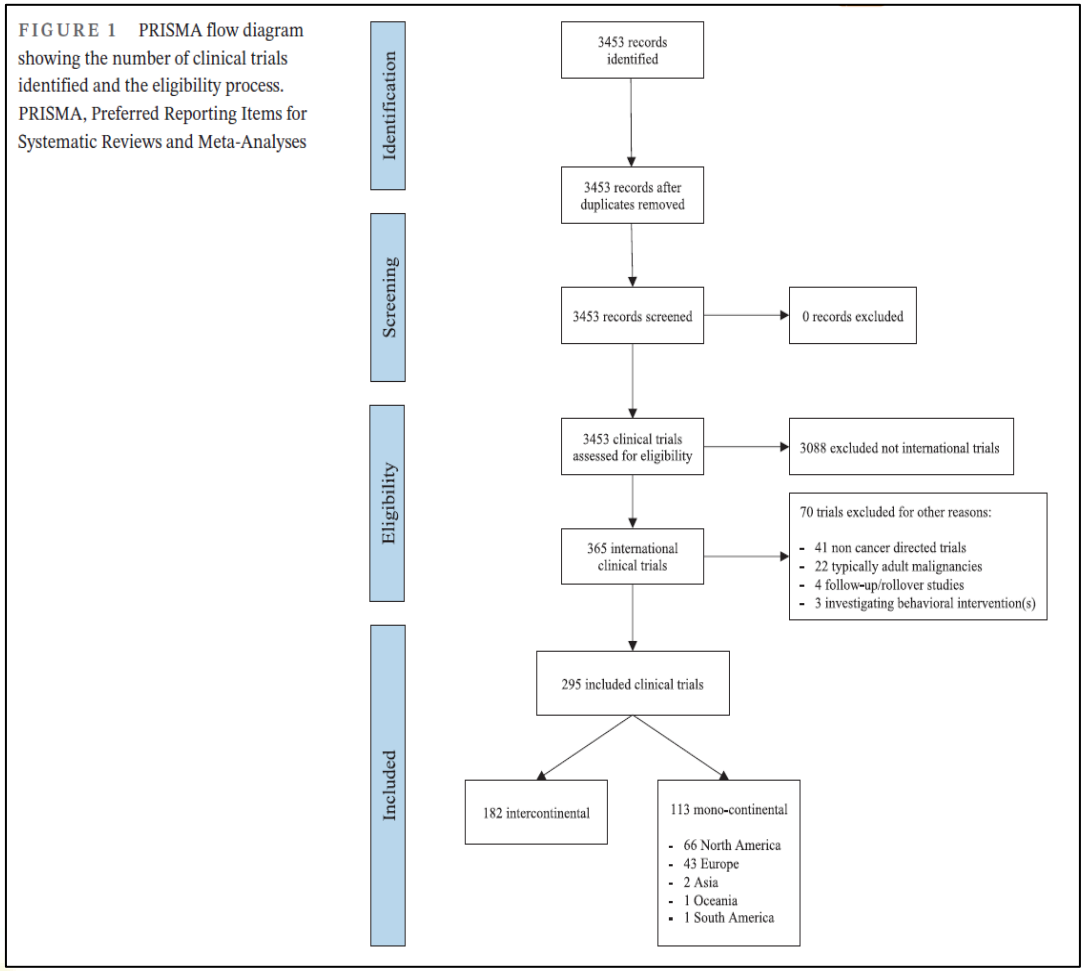
Transatlantic Ped Oncology studies

Only Clin Trials.gov was used – lack of European standard database



Intercontinental collaboration in clinical trials for children and adolescents with cancer—A systematic review by ACCELERATE

Teresa de Rojas[1] | Andrew J. Pearson[1] | Nicole Scobie[2] | Leona Knox[3] | Darshan Wariabharaj[4] | Pamela Kearns[5] | Gilles Vassal[1,6] | Gregory Reaman[7]

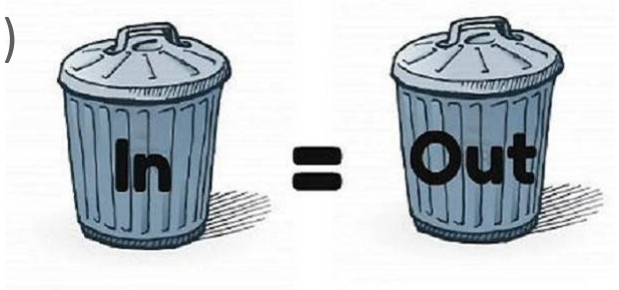


Global footprint: standardisation and easy access to datasources worldwide

Data analytics: potential topics of interest for data collection

- **Clinical trials rejected:** how many and reasons
- **Clinical trials authorised and number of products on the market:** how many and reasons
- **Clinical trials with vulnerable populations:** minors, incapacitated persons, pregnant and lactating women, emergency situations and specific requirements (CTR chapter V): analysis of the specific requirements for guidance development
- **Are considerations of CAs/ethics committees** taken into account by the RMS?
- **Addition of MSs in an authorised clinical trial**: percentage of clinical trials with MS added later, number of opt-outs, number of MSs involved in the first authorisation: an acceptable strategy?
- **Number of clinical trials on hold** with premature end or re-start including the reasons
- **Number of clinical trials withdrawn and re-submitted** including the reasons (reason: no structered data field)
- **Number of clinical trials** with a “drop the age” approach
- **Number of clinical trials** (prematurely) ended and the **publication of results** (public databases: clinicaltrials.gov, clinicaltrialregister.eu, Dutch trial register, Pubmed)
- **Post-trial access** (structured data field!)

Crucial:
- Standardisation and generating of reliable data
- Central monitoring



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www.ccmo.nl

THANK YOU!

Questions?

Contact: nvmetc@gmail.com

Clinical Data Neutrality

Presented by

Shu Chin Ma – VP of MIDD and Quantitative Medicine, The Critical Path Institute (C-Path)

Clinical Data Neutrality: its Role in Transforming Data into Solutions

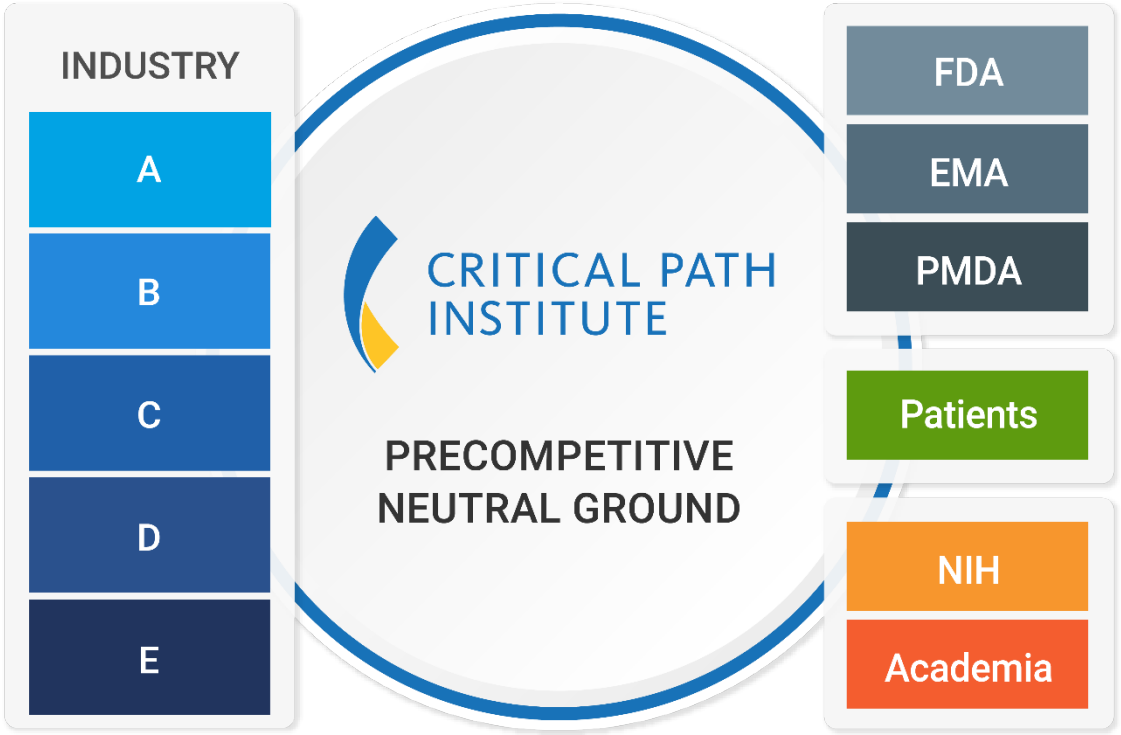
Transforming data into actionable knowledge for drug development

Shu Chin Ma, PhD, VP for MIDD and Quantitative Medicine

CRITICAL PATH INSTITUTE

The Critical Path Institute: A Neutral Party

- Public-Private Partnerships (PPP)
- Convene scientific consortia of industry, academia, and government for sharing of data/expertise
  - ✓ The best science
  - ✓ The broadest experience
  - ✓ Active consensus building
- Enable iterative EMA/FDA/PMDA participation in developing new methods to assess the safety and efficacy of medical products
- Official regulatory endorsement of novel methodologies and drug development tools



Collaboration Contributed to a Transformation

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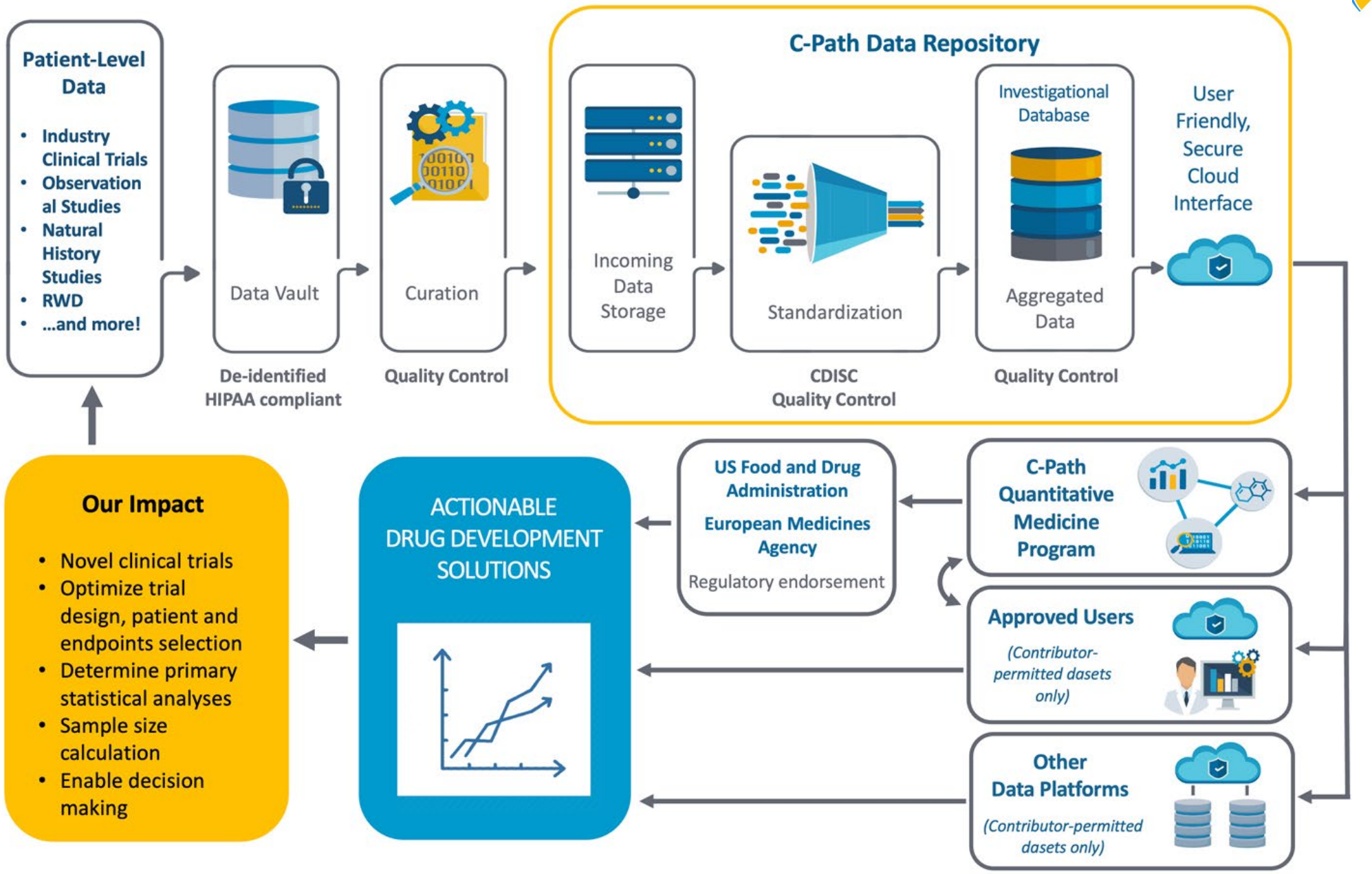
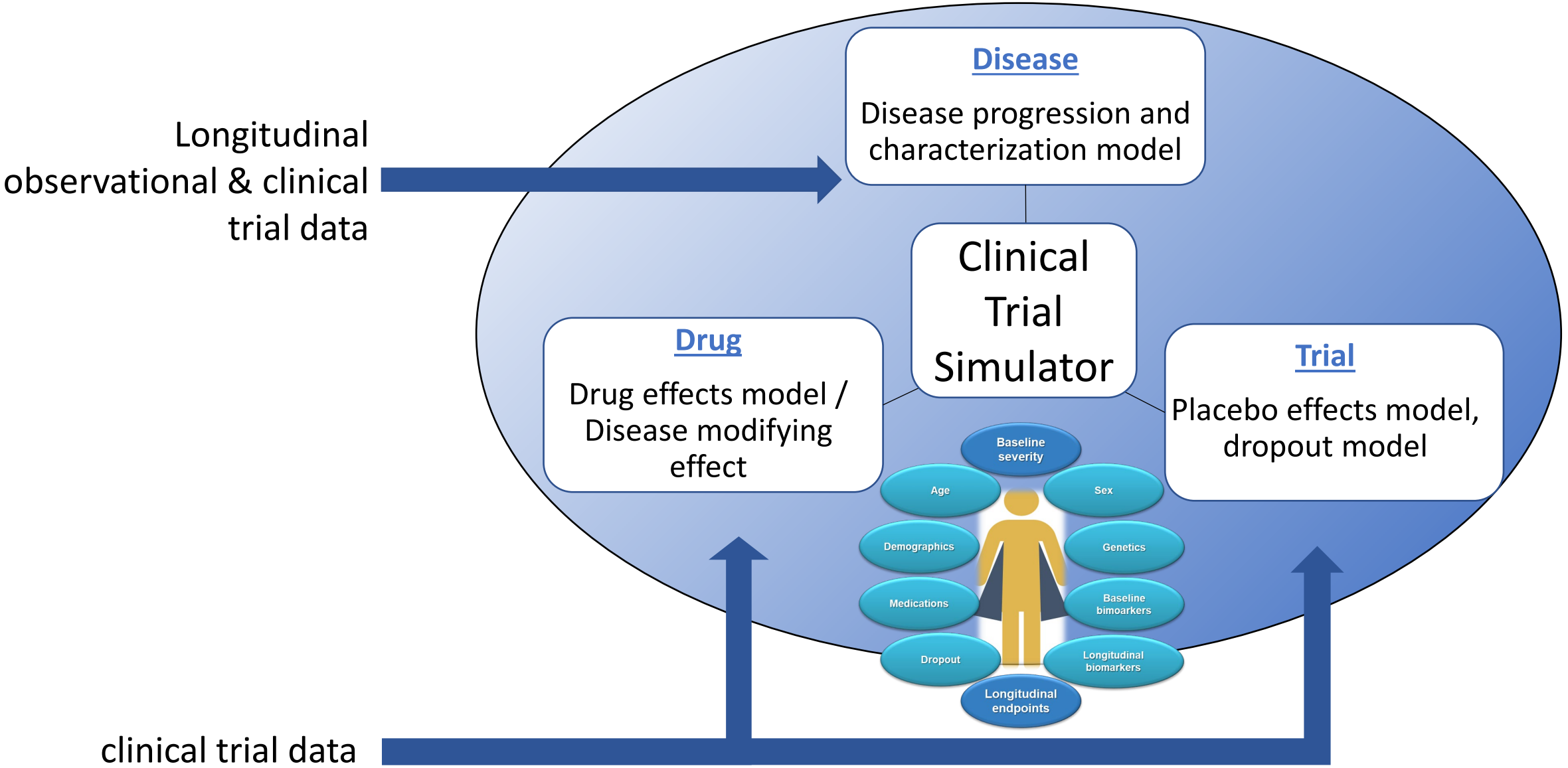


Example: drug-disease-trial modeling



Alzheimer's Disease

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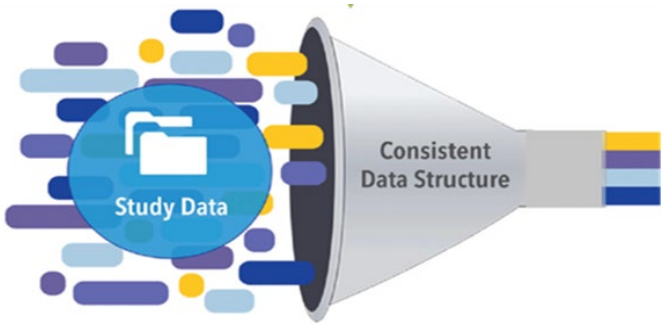
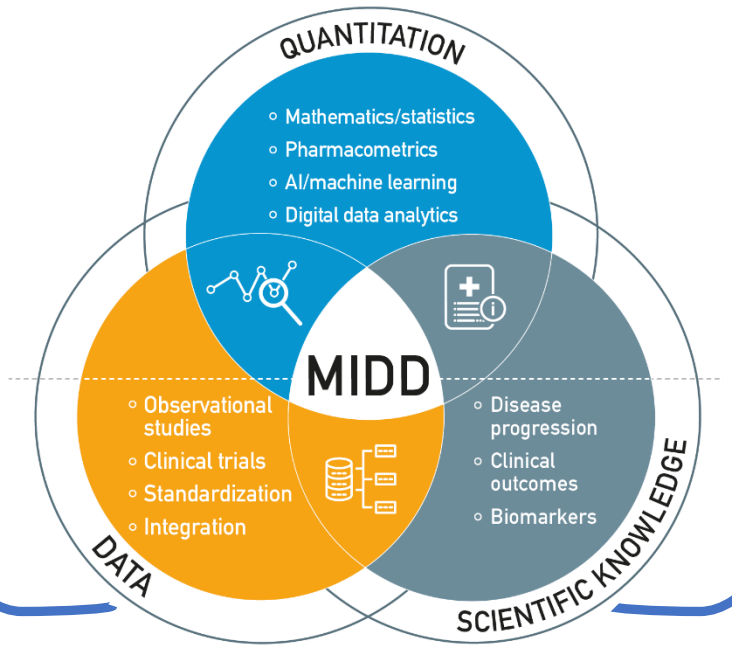
QUANTITATIVE MEDICINE

DATA COLLABORATION® CENTER





CPAD
CRITICAL PATH FOR ALZHEIMER'S DISEASE

First Regulatory Endorsement of a Quantitative Drug Development tool

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Drug Development Tools: Fit-for-Purpose Initiative

2013 FDA endorsement decision:

- Clinical trial simulations relying on this model can provide support for the choice of trial design features and can facilitate protocol review by Center for Drug Evaluation and Research (CDER) staff. End-of-Phase 2A meeting requests can be supported through the use of trial simulations based on this model or a modified version when clearly described.

There was a need to go earlier into the disease continuum

Letter of support for Model-based CT enrichment tool for CTs in aMCI

2018 EMA Letter of Support decision:

- The EMA supports the primary objectives of the applicant and has decided to issue a Letter of Support to the CPAD Consortium, while also encouraging the CPAD team to disseminate and provide access to the current version of the model for implementation by sponsors actively designing clinical trials in amnesic mild cognitive impairment (aMCI).

Incorporating Lessons From the Pandemic

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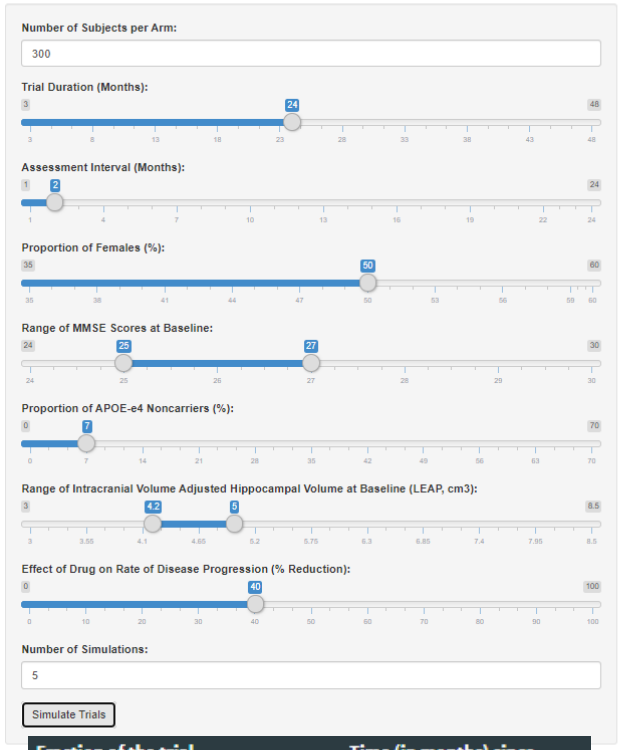
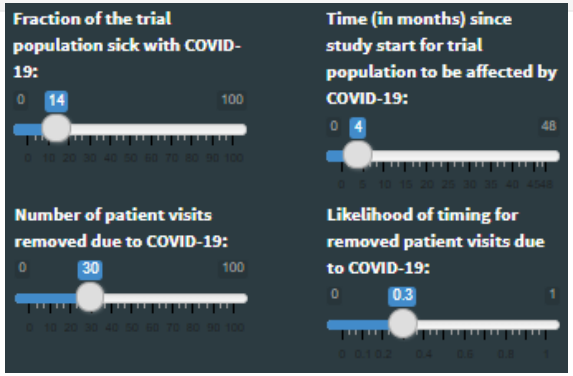
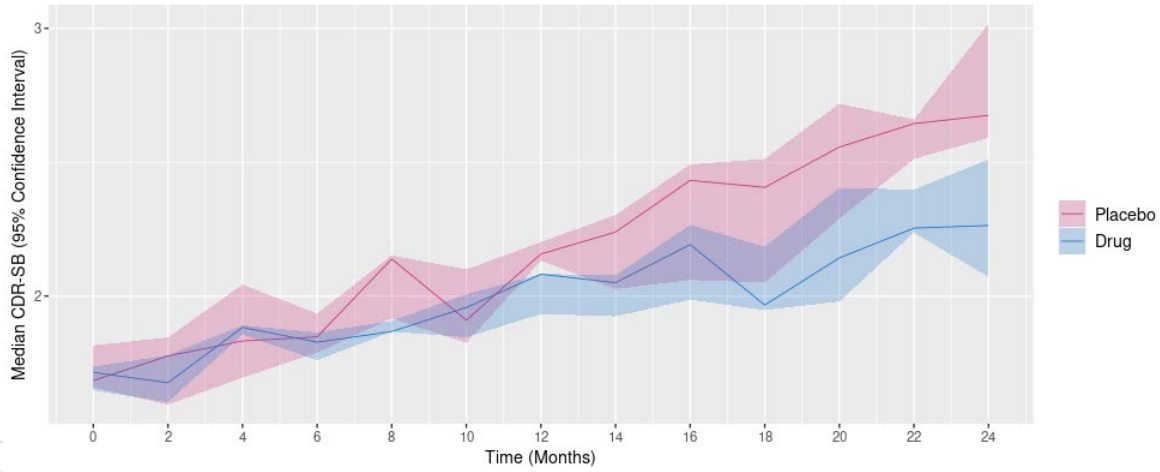
Hippocampal Neuroimaging-Informed Amnestic MCI Clinical Trial Simulator

Simulate clinical trials on patients with amnestic mild cognitive impairment

CPAD
CRITICAL PATH FOR ALZHEIMER'S DISEASE
CRITICAL PATH INSTITUTE







Total Number of Subjects	600
Study Duration (Months)	24
Assessment Interval (Months)	2
Effect of Drug on Rate of Disease Progression (% Reduction)	40
Proportion of Female (%)	50
Range of MMSE Scores at Baseline	[25, 27]
Proportion of APOE-e4 Noncarrier (%)	7
Range of Intracranial Volume Adjusted Hippocampal Volume at Baseline (cm3)	[4.2, 5]
Median Age at Baseline (95% Confidence Interval) (Years)	74 (74, 74)
Median MMSE Score at Baseline (95% Confidence Interval) (Points)	26 (26, 26)
Median Intracranial Volume Adjusted Hippocampal Volume at Baseline (95% Confidence Interval) (cm3)	4.7 (4.7, 4.7)
Number of Simulations	5
Monte-Carlo Standard Error for Calculation of Confidence Interval for Statistical Power (%)	0
Statistical Power (%, 95% Confidence Interval)	100 (47.8, 100)

From data, to solutions, to impact

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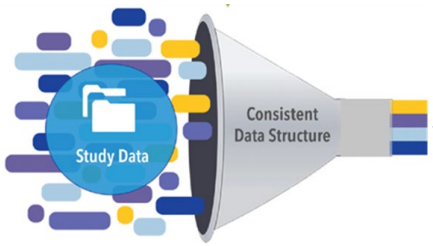
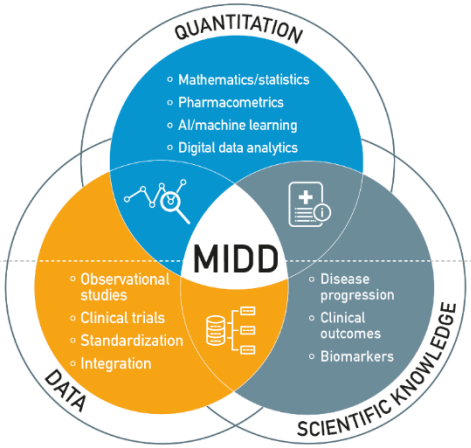
QUANTITATIVE MEDICINE

DATA COLLABORATION® CENTER





Indication	Solutions	Impact
Alzheimer's disease	2CTS tools, 2 biomarkers	First 2 disease-modifying drugs
Tuberculosis	Multiple quantitative tools	First new drug and drug regimen
PKD	PKD	First disease-modifying drug
Type 1 Diabetes	Model-based biomarkers	First prevention drug
Duchenne Muscular Dystrophy	5 disease progression models	Transformed trial design paradigm
Kidney Transplantation	Composite biomarker endpoint	Transformed trial design paradigm
Parkinson's disease	3 CTS tools, 1 biomarker, multiple DHT solutions	Transformed trial design paradigm
Huntington's disease	Staging system, 3 disease progression models	Transformed trial design paradigm

Thank you!

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Advancing Drug Development.

Improving Lives.

Together.

Back up slides

C-Path's Active Programs

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Active Consortia/Programs

BmDR	Biomarker Data Repository	**DCC**	Data Collaboration Center	**PSTC**	Predictive Safety Testing Consortium
CDRC	Cure Drug Repurposing Collaboratory	**D-RSC**	Duchenne Regulatory Science Consortium	**QuantMed**	Quantitative Medicine
CPA-1	Critical Path for Alpha-1 antitrypsin deficiency (pre-consortium)**	**eCOA Consortium**	Electronic Clinical Outcome Assessment Consortium	**RDCA-DAP**	Rare Disease Cures Accelerator- Data and Analytics Platform
CPAD	Critical Path for Alzheimer's Disease	**ERA4TB**	European Regimen Accelerator for Tuberculosis*	**RD-COAC**	Rare Disease Clinical Outcome Assessment Consortium
CPLD	Critical Path for Lysosomal Disorders (pre-consortium)**	**HD-RSC**	Huntington's Disease Regulatory Science Consortium	**T1D**	Type 1 Diabetes Consortium
CPP	Critical Path for Parkinson's Disease	**INC**	International Neonatal Consortium	**TOMI-T1D**	Trial Outcome Markers Initiative in T1D Consortium
CPTA	Critical Path to Therapeutics for the Ataxias	**MSOAC**	Multiple Sclerosis Outcome Assessment Consortium	**TRxA**	Translational Therapeutics Accelerator
CP-SCD	Critical Path for Sickle Cell Disease	**PKDOC**	Polycystic Kidney Disease Outcomes Consortium	**TTC**	Transplant Therapeutics Consortium
CPTR	Critical Path to TB Drug Regimens	**PredicTox KE**	PredicTox Knowledge Environment	**UNITE4TB**	Worldwide Accelerator for Tuberculosis*
CP-RND	Critical Path for Rare Neurodegenerative Diseases	**PRO Consortium**	Patient-Reported Outcome Consortium		

****Pre-Consortia** *** C-Path Europe**

Session 2- Question and Answers session

Julian Isla
Chief Scientific Officer,
European Dravet Syndrome Federation

Till Bruckner
Founder of TranspariMED

Jakob Wested
Industrial postdoc, DKMA

Helga Gardarsdottir
Associate professor,
Division Pharmacoepidemiology & Clinical Pharmacology, Utrecht University

George Paliouras
Chairman of the Board (voluntary), Duchenne Data Foundation, and Research Director, National Centre for Scientific Research "Demokritos"

Martin O'Kane
Regional Head RA EU Policy & Liaison
Novartis / EFPIA

Michel Zwaan
Pediatric oncologist and Chairman of the Dutch Association for Medical Research Ethics Committees (NVMETC)

Shu Chin Ma
VP of MIDD
and Quantitative Medicine, The Critical Path Institute (C-Path)

Any Questions?
Go to **www.sli.do**

Use event code
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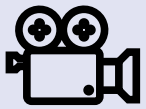
Coffee break

Next up

17:15 Session 3: Structuring data to facilitate analysis

Chat is disabled



Recorded Event

Write your questions in Slido

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Use event code
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Or use Slido QR code

Session 3: Structuring data to facilitate analysis

Co-chairs

Frank Petavy– Head of TDA-MET, EMA

Marianne Lunzer – Chair of CTCG, Austrian Medicine Agency

Clinical electronic Structured Harmonised Protocol (CeSHarP)-ICH M11 EWG

Presented by

Noemie Manent – Principal Scientific Administrator, EMA and regulatory chair of ICH M11 Expert Working Group

Mumtaz Sultani – Scientific Officer, EMA

Content

What is ICH?

- **International Council on Harmonisation (ICH) was launched in 1990**
- **Purpose:**
  - To promote public health through international harmonization that contributes to:
    - Prevention of unnecessary duplication of clinical trials and post market clinical evaluations
    - Development and manufacturing of new medicines
    - Registration and supervision of new medicines
    - Reduction of unnecessary animal testing without compromising safety and effectiveness

Accomplished through **Technical Guidelines** that are implemented by the regulatory authorities

https://ich.org/

Overview of the ICH M11 Deliverables

A new **harmonized guideline** on the clinical protocol that specifies comprehensive organization with standardized content for interventional clinical trials. Additional deliverables include:

- A **Template** that includes identification of headers, common text and a set of data fields and terminologies which will be the basis for efficiencies in data exchange.

- A **Technical Specification** that uses an open, non-proprietary standard to enable electronic exchange of clinical protocol information.

ICH M11 Scope

Scope:

The Guidelines, Template and Technical Specification are applicable to **interventional clinical trials** of medicinal products across all phases and therapeutic areas of clinical research.

Out of scope:

- Neither the Guideline nor the Template or Technical Specification are intended to specify processes related to development and maintenance of a protocol or a clinical trial.
- They do not supersede or negate other guidelines that establish requirements for protocol content.
- They do not provide instruction on the development of a well-designed trial or characterize a well-crafted final protocol.

Why Clinical electronic Structured Harmonised Protocol (CeSHarP)?

The Problem

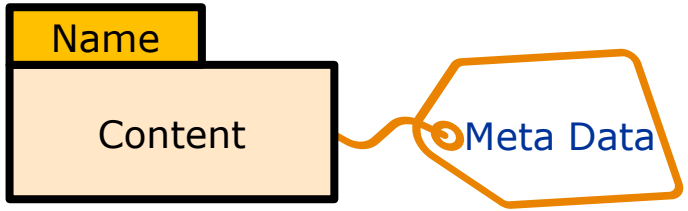
- No **internationally harmonized standard** template for the format and content to support consistency across sponsors and data exchange of protocol information
- Lack of harmonization **contributes to inefficiencies** and difficulties in reviewing and assessing clinical protocols by regulators, sponsors, ethical oversight bodies, investigators, and other stakeholders. We receive protocols in many different formats
- **Format and core content** of study protocols vary from sponsor to sponsor with duplication of content, multiple terms for the same meaning, making interpretation difficult for researchers, sponsors, investigators, regulators and ethics bodies

ICH M11: What is Structured Content?

*"**Structured content** is information or content that is organized in a predictable way and is usually classified with metadata."* https://en.wikipedia.org/wiki/Structured_content

*"**Metadata** (or metainformation) is "data that provides information about other data", but not the content of the data itself, such as the text of a message or the image itself."*

https://en.wikipedia.org/wiki/Metadata



Examples of metadata:

Creation date, update date, author, classification, keywords, associated projects, version, and permissions/security…

Benefits of Harmonised and Structured Clinical Protocol

Predictable

- Format and Structure – *Table of Contents*
- Core Content and Instructions - *common set of information unnecessary & avoiding repetition*
- Terms and Definitions – *uses controlled terminology to reduce v*ariability in data collection and analysis

Provides flexibility where needed – *recommended and optional text / sections*

Consistency with all other relevant ICH Guidelines, where possible

Efficient Collaboration - Enhance the ability of sponsors, regulators, investigators, and other stakeholders to collaborate effectively with streamlined communication and coordination

Facilitate Review and Approval - Ensures compliance with regulatory requirements and expedites the approval process

Acceptable in all ICH regions

Conclusions

- ICH M11 deliverables:
  - Promote **harmonisation** across ICH regions
  - **Foundational step** toward a "digitized protocol"
  - Maintain **flexibility** for technical innovation and region-specific use
- A harmonised clinical protocol Template and Technical Specification for electronic exchange of protocol information will enhance the ability of sponsors, regulators, investigators, and other stakeholders to initiate, review, and conduct clinical research, resulting in more efficient drug development and delivery of medicines to patients

Overall impact: contributes to more efficient drug development and delivery of medicines to patients

Demo on CT navigator

Presented by

Ina-Christine Rondak – Biostatistician, Methodology Workstream, Data Analytics and Methods Task Force

Session 3- Panel discussion

Benjamin Speich

PD, PhD, Division of Clinical Epidemiology, Department of Clinical Research, University Hospital Basel

Vada Perkins

Vice President, Global Head of Regulatory Intelligence & Policy, Boehringer Ingelheim Pharmaceuticals, Inc.

Hans Hillege

Seconded National Expert at EMA, Department of Cariology/Epidemiology, University Medical Centre Groningen

Any Questions?
Go to **www.sli.do**

Use event code
#ACTEUJan24

Or use Slido QR code

European Clinical Trial Register– challenges from an academic perspective

Presented by

Benjamin Speich, PD, PhD – University Hospital Basel

Universität Basel

Departement Klinische Forschung

Universitätsspital Basel

European Clinical Trial Register– challenges from an academic perspective

ACT EU Clinical Trials Analytics Workshop
25-26 Jan 2024

Benjamin Speich, PD, PhD
CLEAR-Methods Center
Division of Clinical Epidemiology | Department of Clinical Research
University Hospital Basel

Is the information on a trial registry reliable?

JAMA Network | Open

Original Investigation | Statistics and Research Methods

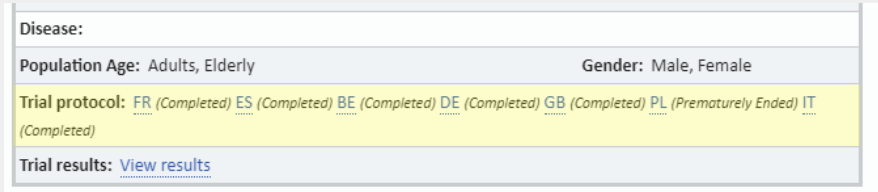
Reliability of Trial Information Across Registries for Trials With Multiple Registrations
A Systematic Review

197 RCTs registered in more than 1 registry (e.g. EudraCT and Clinicaltrials.gov)

Agreement of trial characteristics:
- 90% Sponsor
- 78% Primary outcome
- 63% Target sample size
- 46% Trial status

→ Interviews with Clinical Trial Registry Representatives
- Some efforts to harmonise trial registries ongoing (e.g. meetings organised by the WHO)
- Main hurdle for better harmonisation: Different legislation requirements
- Lack of regular updates to all trial registries assumed to be the main reason for the inconsistencies between trial registries

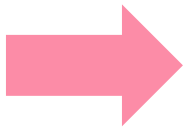
Specific for EudraCT
- Updating information does not seem to be common (user-friendliness?)
- No history of changes available
- Different entries for participating countries (reliability?)



Speich et al., 2022, JAMA Network Open

Further aspects from our meta-research

	Clinicaltrials.gov	EudraCT
Availability of full trial protocols	42% (137/332) 	 ?
Statement about sharing individual patient data	 optional	 ?
Specific features for new adaptive designs/platform trials (e.g. start and end date, status, and samples size for individual arms)		



- Meta-research relevant to improve research process
- Burdensome process (manual extraction in duplicate); export function needed
- Important to assess how trial registries can provide useful and reliable information

Schönenberger et al., 2022, JCE
Griessbach et al., 2022, (resubmitted to JAMA Network Open)

ICH M11:
Clinical electronic Structured Harmonised Protocol (CeSHarP)

Presented by

Vada A. Perkins - VP, Global Head of Regulatory Intelligence & Policy, ICH M2 EFPIA Topic Leader, Boehringer-Ingelheim

European Federation of Pharmaceutical Industries and Associations

ACT EU: Clinical Trial Data Analytics Workshop

ICH M11: Clinical electronic Structured Harmonised Protocol (CeSHarP)

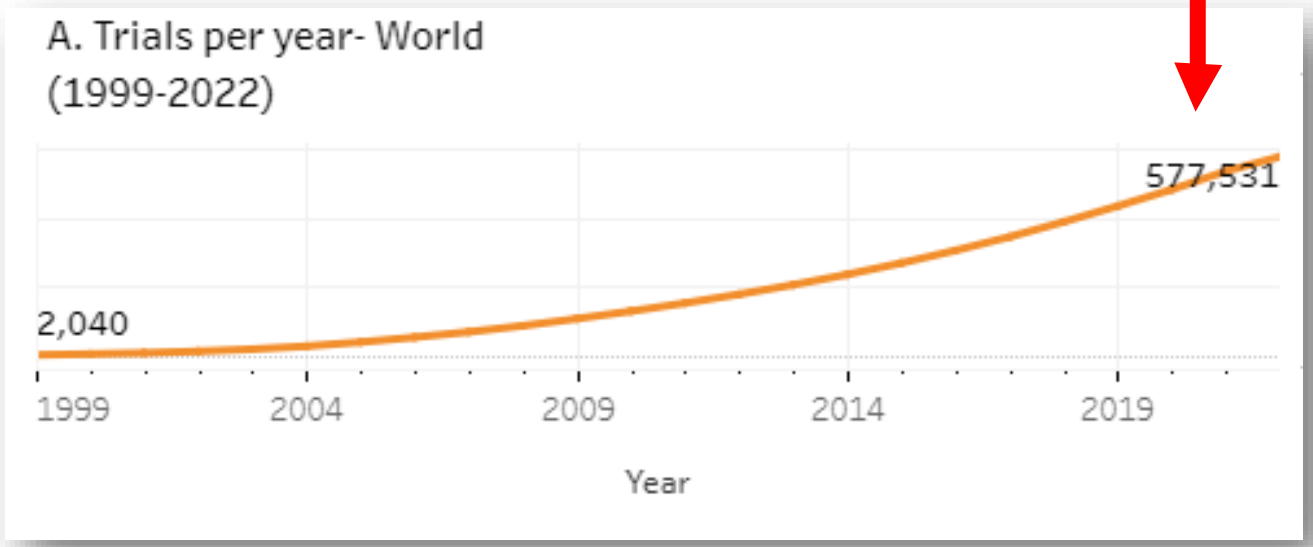


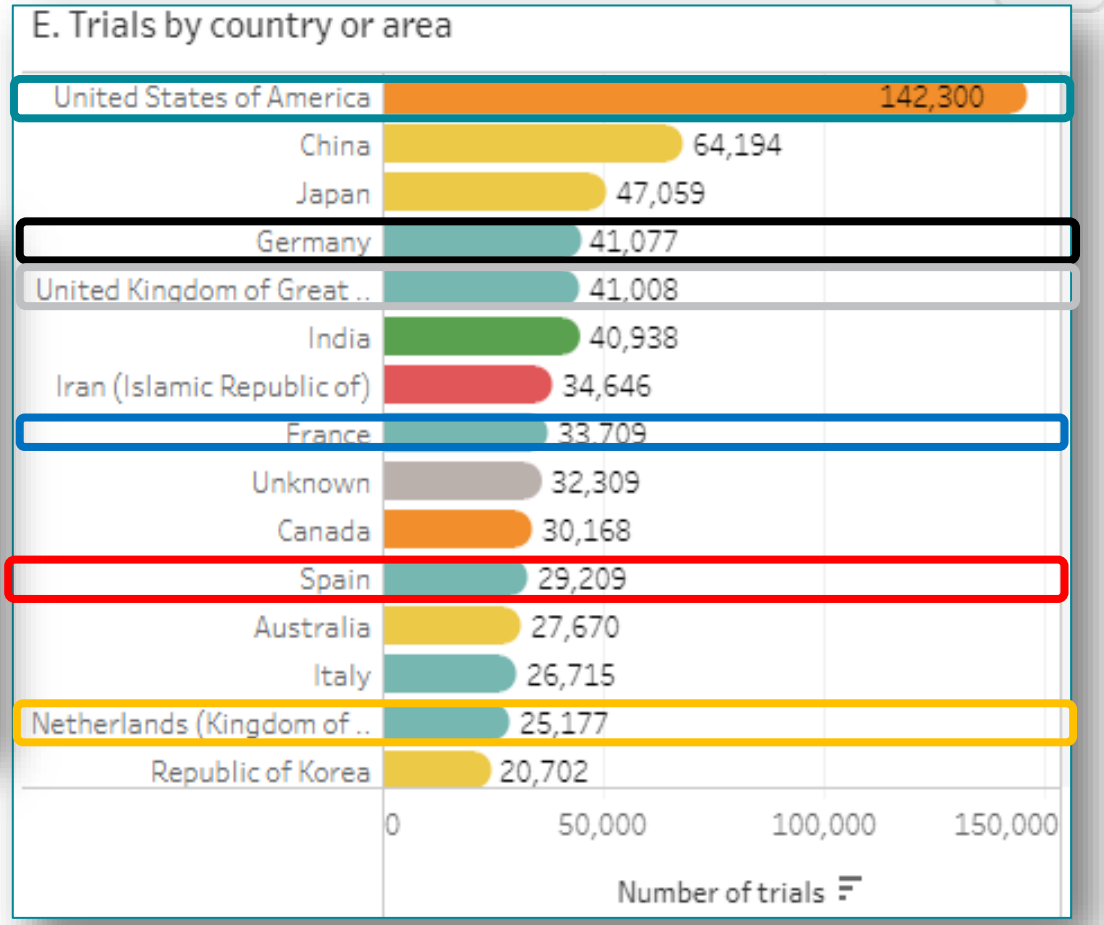



Vada A. Perkins
VP, Global Head of Regulatory Intelligence & Policy
ICH M2 EFPIA Topic Leader
Boehringer-Ingelheim
Jan 2024

Number of Interventional Clinical Trials in 2022

577,531



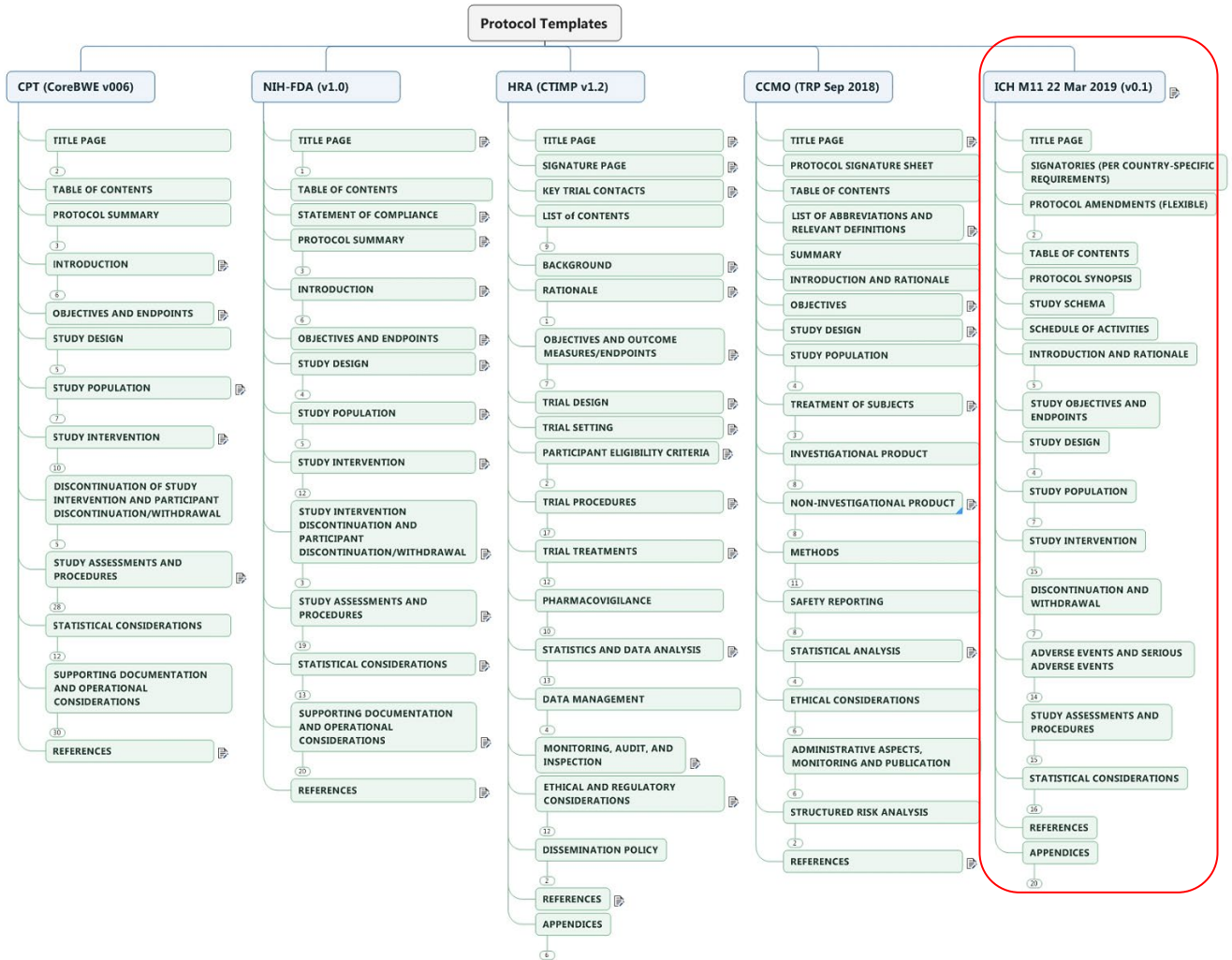


Number of trial registrations by location, disease, phase of development, age and sex of trial participants (1999-2022) (who.int)

Impact without an Internationally Standardised Clinical Protocol

- Delayed timelines due to inconsistency and lack of clarity
- **Resource-intensive manual activities**
- Increased costs
- **Inefficient reuse of knowledge** and duplication of effort
- Inability to leverage tools for **review**, **analysis**, and **reporting**
- **Limited exchange/utilization** of data collected in each protocol

M11 Clinical Protocol Template Landscape



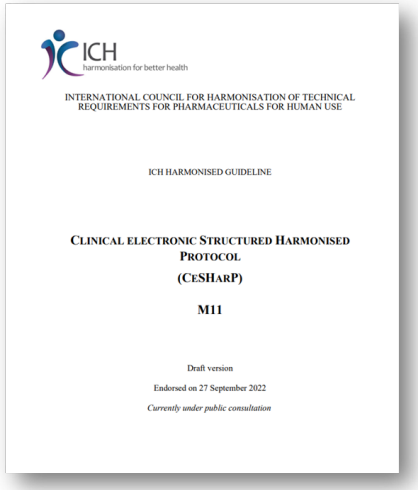
1. TCB, 2. NIH-FDA, 3. NHS Health Research Authority, UK, 4., Central Committee on Research, NL

M11 Collaborations w/other ICH EWGs

- Structure & Content of Clinical Study Reports
- Ethnic Factors in Acceptability of Foreign Data
- Good Clinical Practice
- General Considerations in Clinical Trials
- Statistical Principles for Clinical Trials
- Clinical Trials in Pediatric Populations
- Multi-Regional Clinical Trials
- Adaptive Clinical Trials
- Electronic Standards

ICH M11 Template can be exchanged using many formats

Guideline & Template → Tech Spec → Technical Implementation Guide → FHIR Profiles


ICH
harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

CLINICAL ELECTRONIC STRUCTURED HARMONISED PROTOCOL

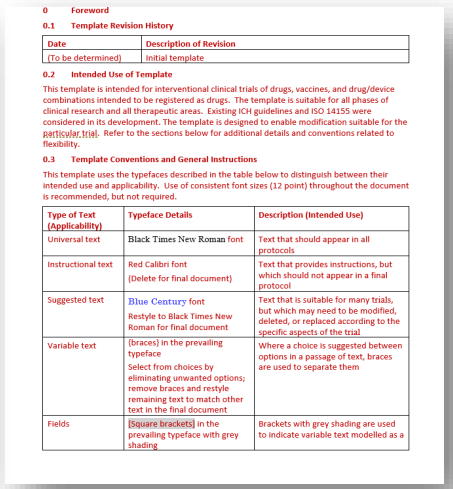
(CESHARP)

M11

Draft version

Endorsed on 27 September 2022

Currently under public consultation


0 Foreword

0.1 Template Revision History

Date	Description of Revision
(To be determined)	Initial template

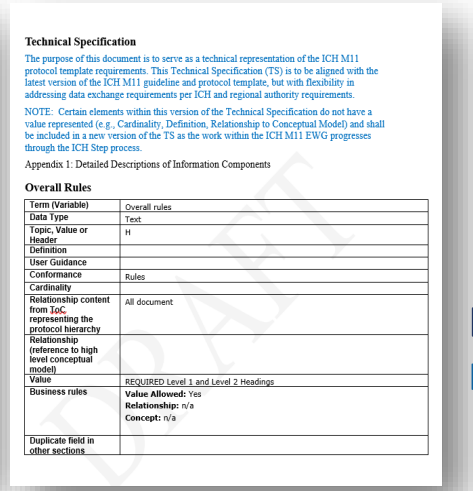
0.2 Intended Use of Template

This template is intended for interventional clinical trials of drugs, vaccines, and drug/device combinations intended to be registered as drugs. The template is suitable for all phases of clinical research and all therapeutic areas. Existing ICH guidelines and ISO 14155 were considered in its development. The template is designed to enable modification suitable for the particular trial. Refer to the sections below for additional details and conventions related to flexibility.

0.3 Template Conventions and General Instructions

This template uses the typefaces described in the table below to distinguish between their intended use and applicability. Use of consistent font sizes (12 point) throughout the document is recommended, but not required.

Type of Text (Applicability)	Typeface Details	Description (Intended Use)
Universal text	Black Times New Roman font	Text that should appear in all protocols
Instructional text	Red Calibri font (Delete for final document)	Text that provides instructions, but which should not appear in a final protocol
Suggested text	Blue Century font Restyle to Black Times New Roman for final document	Text that is suitable for many trials, but which may need to be modified, deleted, or replaced according to the specific aspects of the trial
Variable text	(braces) in the prevailing typeface Select from choices by eliminating unwanted options; remove braces and restyle remaining text to match other text in the final document	Where a choice is suggested between options in a passage of text, braces are used to separate them
Fields	[Square brackets] in the prevailing typeface with grey shading	Brackets with grey shading are used to indicate variable text modelled as a


Technical Specification

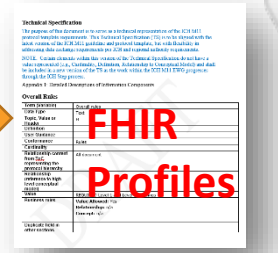
The purpose of this document is to serve as a technical representation of the ICH M11 protocol template requirements. This Technical Specification (TS) is to be aligned with the latest version of the ICH M11 guideline and protocol template, but with flexibility in addressing data exchange requirements per ICH and regional authority requirements.

NOTE: Certain elements within this version of the Technical Specification do not have a value represented (e.g., Cardinality, Definition, Relationship to Conceptual Model) and shall be included in a new version of the TS as the work within the ICH M11 EWG progresses through the ICH Step process.

Appendix 1: Detailed Descriptions of Information Components

Overall Rules

Term (Variable)	Overall rules
Data Type	Text
Topic, Value or Header	H
Definition	
User Guidance	
Conformance	Rules
Cardinality	
Relationship content from IoC representing the protocol hierarchy	All document
Relationship (reference to high level conceptual model)	
Value	REQUIRED Level 1 and Level 2 Headings
Business rules	**Value Allowed:** Yes **Relationship:** n/a **Concept:** n/a
Duplicate field in other sections	



Electronic Document

Human Readable Form

Standard Message Exchange Formats*

cdisc

Machine - Readable Form

Per ICH Regional Requirements

Clinical trial data and B/R assessment of medicines

Presented by

Hans Hillege - Seconded National Expert Department H-TA, EMA / Department of Cardiology/Epidemiology, University Medical Centre Groningen

What is required from a regulatory agency?

"A fair regulatory process requires accountability for reasonableness, i.e., publicity about the reasons and rationales that play a part in decisions"

(Daniels N, Accountability for reasonableness, BMJ, 2000)

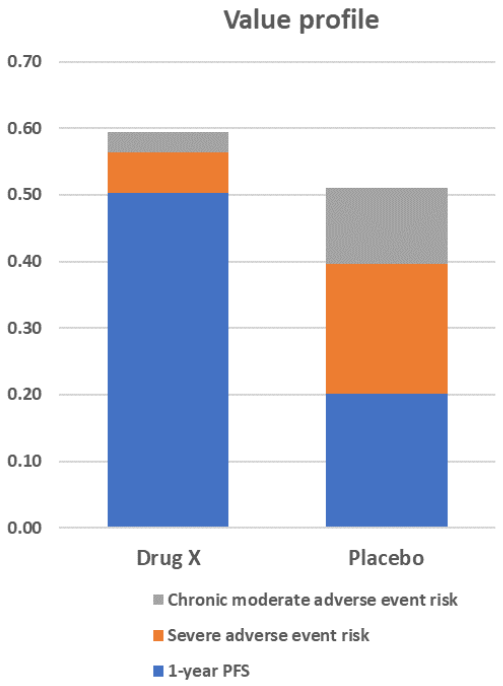
Benefit/Risk

Clinical trial data on efficacy and safety

Attribute	Description	Drug X	Placebo
Favourable effects			
1-year PFS	Percentage of patients being alive and progression-free for 1 year or longer	80% (71%, 87%)	65% (55%, 74%)
Unfavourable effects			
Severe adverse event risk	Risk of experiencing an adverse event that could result in long-term or permanent disability	25% (18%, 34%)	5% (2%, 11%)
Chronic moderate toxicity risk	Risk of experiencing recurrent episodes during which the treatment causes you to feel unwell	55% (45%, 64%)	30% (22%, 40%)

Value judgement

Effect	Max Acc Risk	Worst	Best	Importance
1-year PFS	10%	55%	87%	100%
Severe adverse event risk	30%	2%	30%	33%
Chronic moderate toxicity risk	60%	22%	60%	22%



Thank you for your attention

hans.hillege@ema.europa.eu

Closing remarks

Peter Arlett – Head of TDA, EMA

Lars Bo Nielsen – Director General, DKMA, and member of the HMA Management Group

ACT EU Clinical Trials Analytics Workshop

Day 2

25-26 January 2024

Session 1: Welcome and Setting the expectations for Day 2

Presented by

Lars Bo Nielsen – Director General, DKMA, and member of the HMA Management Group

IJsbrand den Rooijen – Health Data Scientist, ACT EU Analytics co-lead, EMA

Preparing for the breakout sessions

26 January 2024

IJsbrand den Rooijen (EMA)

Preparing for the breakouts

Day 1 was to prepare everyone for the breakouts

Now is the moment to share your ideas, thoughts, experiences, wishes, plans, etc.

If you are joining virtually there is a Webex link for each of the rooms

Question for all breakouts

Can you describe a **specific use case** from your area of work where data on clinical trials play, or could play, a crucial role?

Please include:

- A description of what the use case is and why it is important
- Identification of additional data requirements, including data that goes beyond current EMA sources and data not yet collected but deemed necessary

Session 3: Report back from Break-out sessions

Chair

Rosa Giuliani - co-chair of the Healthcare Professional Working Party

Break-out session on ethics, HTA and HCP

Use case Health Canada

Use case Paediatrics

Other use cases: geriatric populations, vaccins, health care system economics, innovations in preventive area, medical devices

Use case 1: Health Canada

- Clinical trial portal for data from multiple sources under development by HC – external clinical data registries
- Portal primary objective: overview of research conducted in Canada
- Researchers need only to register in one WHO portal and HC can access it so it avoid extra burden on academics
- NLP/ML not AI to use data feeds and cross-check data sources to detect potential frauds
- Metadata from the HC regulatory process matched against clinicaltrial.gov, WHO ITCRP, CTIS is starting
- Transparency on clinical trials and results

Use case 2: Paediatric and Rare Disease

- Diversity representation in CTs
- Patients remote monitoring to complement CTs data
- Platform such as C-Path Rare Disease Cure Accelerator could help
- What is the minimum data set required to answer the research questions
- Make CT information available to patients directly
- Challenges of cross-border
- For HTAs need for local epidemiological data not easily accessible in Europe, so they need to cross-refer data to make an informed decision
- Disease state have different definition according to the regions and may impact cross-country data correlation – standardisation
- Data: sharing, standardisation, interoperability, multiple data sources (validity)

- Important for HTAs to assess CTs use for HTAs decisions
- Payers data could be explored as a good source of data, however data are not interoperable
- IHI project to be launched towards end of 2024 to adress data standardisation looking at diversity parameters in CTs

Breakout session E: Data standardisation priorities

Prepared by Noemie Manent

What are our use cases

- **Interoperability –** One source of truth / the ability to have the data directly from one source to another – directly from your protocol to CTIS with need for controlled terminology
- Standardisation lead to better **quality data** and mitigate differences between sponsors
- **Standardised Trial summary data set** – lots of data coming from protocol- automatically populated data from protocol to – link the protocol template to the summary

- **Patient reporting outcome standardisation**: Validation of measurement/PRO tools to standardise the collection and reporting of data --> Patient reporting outcomes –

e.g. measuring Q of life for certain diseases – the use of technology and devices – using agreed standardised algorithm

Patient reporting outcome is used by HTA – if we know the info is validated and standardised

- Standard model for care/disease treatment : curative and/or prevention – factor for healthiness : Collection of CT data including individual patient data to prepare a model to predict based on patients' characteristics
- Combine results from different trials – if the results are provided in a standardised way, it is easier to combine – what is needed for result (populations, outcome measures are used, = disease focused, product focused

- Standardisation model for historical data/RWD to support comparison of new studies with historical ones (how far...)
- Health systems to be digitalised to facilitate collection of individual health structured health data: European Health Data Space initiatives to be followed with clear agenda to enable further interoperability in the context of clinical development
- Standardised data will contribute to better definition of the safety profile of a product/product class with connection to full patient population (eligibility criteria) - Lifecycle of the medicines

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- Protocol electronic submission and reporting to be more global – need for expand and go beyond ICH M11 to have a common technical process to register and report on CT

Closing remarks

Peter Arlett – Head of TDA, EMA

Lars Bo Nielsen – Director General, DKMA, and member of the HMA Management Group