DARWIN EU®: Multi-stakeholder information webinar

24 February 2022
10:30-12:00 CET

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

HMA
Heads of Medicines Agencies

An agency of the European Union

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Webinar agenda

Peter Arlett
Webinar Chair

01 — Opening remarks
Emer Cooke, *Executive Director of EMA, co-chair of the DARWIN EU® Advisory Board*
Karl Broich, *President of BfArM, Chair of HMA Management Group and co-chair of the DARWIN EU® Advisory Board*

02 — Introduction to DARWIN EU®
Xavier Kurz, *EMA*

03 — Use cases for Real World Evidence
Gianmario Candore, *EMA*

04 — Setting up the DARWIN EU® Coordination Centre
Peter Rijnbeek, *Erasmus MC*

05 — Outlook for 2022
Andrej Segec, *EMA*

06 — Q&A
Panel of experts and stakeholders

Opening remarks

Emer Cooke, *Executive Director EMA, co-chair of the DARWIN EU Advisory Board*

Karl Broich, *President of BfArM, Chair of HMA Management Group and co-chair of the DARWIN EU Advisory Board*

Introduction to DARWIN EU®

Data Analysis and Real World Interrogation Network

Xavier Kurz, *EMA*

DARWIN EU

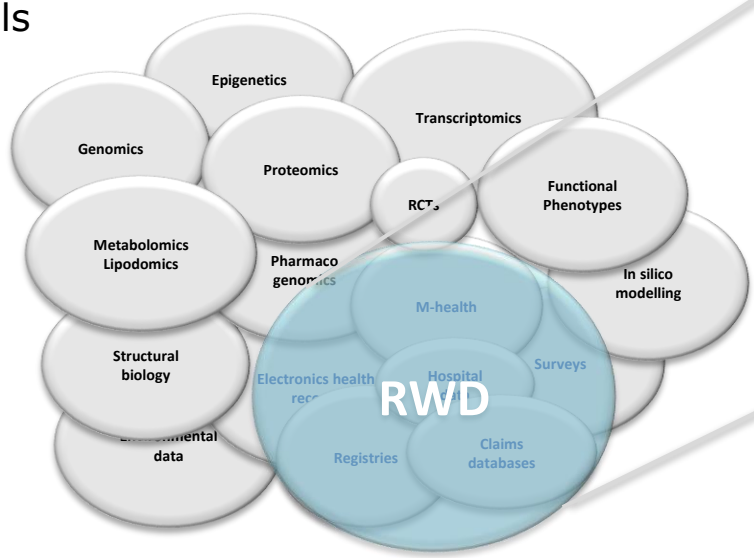
EUROPEAN MEDICINES AGENCY

By 2025 the use of Real-World Evidence will have been enabled and the value will have been established across the spectrum of regulatory use cases

- European Medicines Regulatory Network (EMRN) strategy to 2025 -

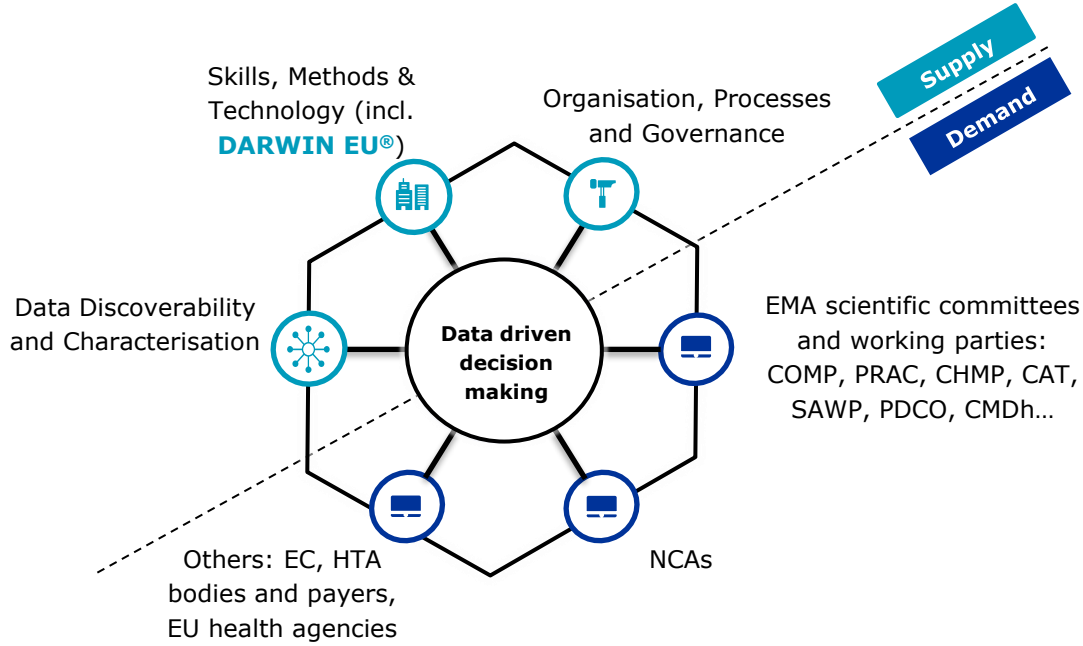
What is real-world data and evidence?

Real-World Data (RWD): routinely collected data relating to patient health status or the delivery of health care from a variety of sources other than traditional clinical trials

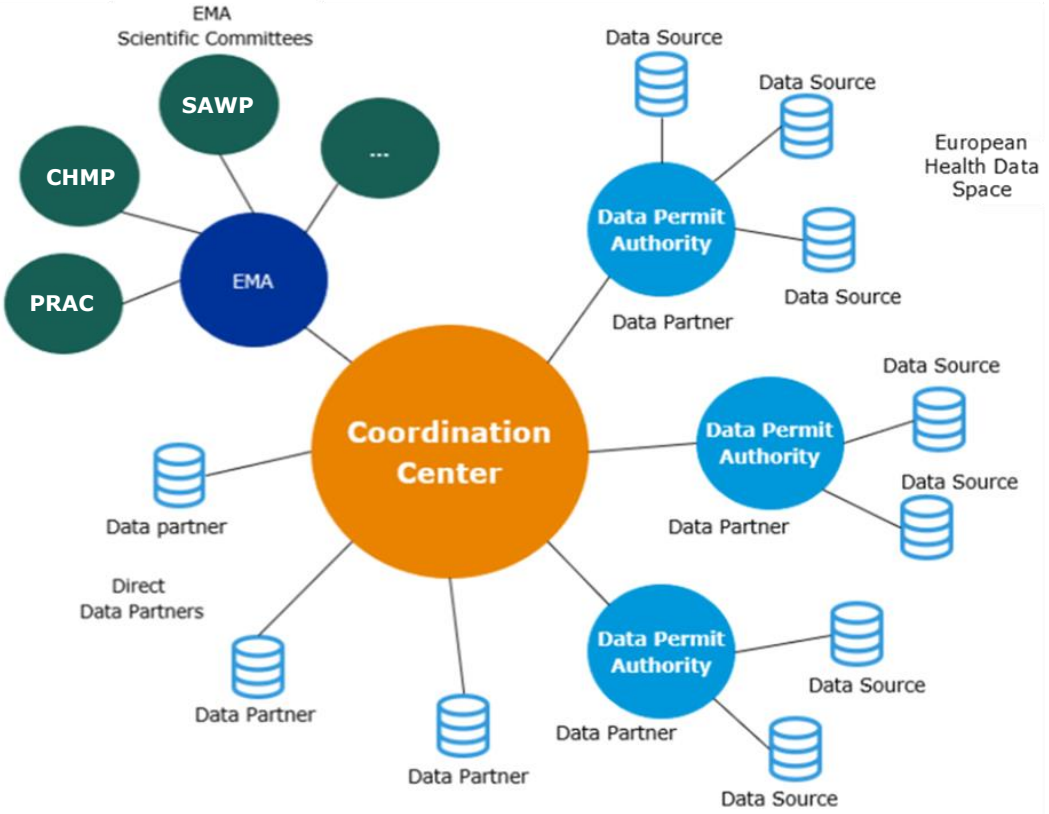


Real-World Evidence (RWE): information derived from analysis of real-world data

How to increase the generation and use of RWE?



DARWIN EU® is a federated **network** of **data**, **expertise** and **services** that supports better decision-making throughout the product lifecycle by generating reliable **evidence from real world healthcare data**



FEDERATED NETWORK PRINCIPLES

- Data stays **local**
- **Use of Common Data Model** (where applicable) to perform studies in a timely manner and increase consistency of results

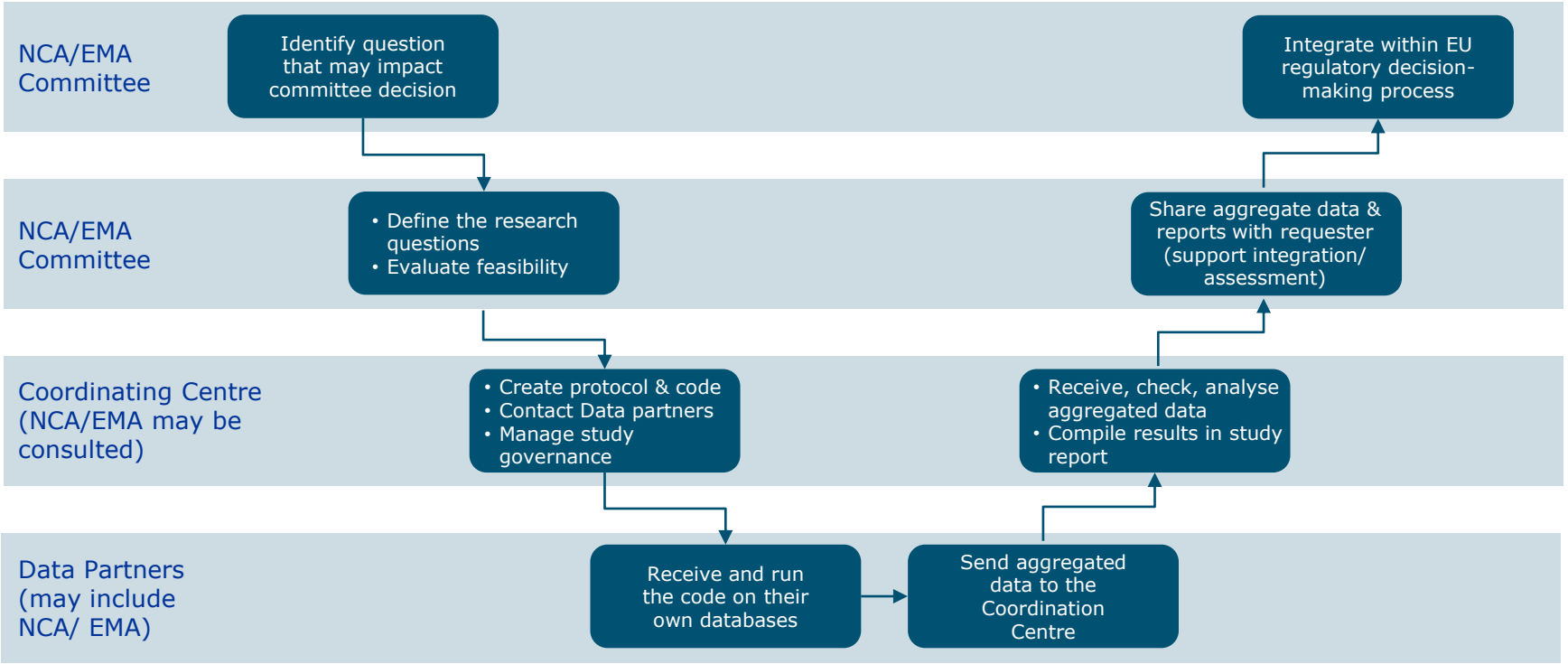
What will DARWIN EU® do?

- Provide scientific expertise in formulating and executing studies and analyses
- Maintain a catalogue of known, relevant data holders, continually ensuring the discoverability & quality of data held by data holders
- Maintain & expand the federated network of data partners, assisting new data holders in conforming with required standards for usage in regulatory context
- Conduct scientific studies and analyses on behalf of the EMRN and EMA scientific committees
- Deliver training, governance, support of business services
- Enable the EMRN, EMA and the scientific committees to make use of the EHDS in the context of medicines regulation, acting as EHDS ‘pathfinder’

What analyses and studies will DARWIN EU® deliver?

Category of observational analyses and studies	Description
Routine repeated analyses	Routine analyses based on a generic study protocol • Periodical estimation of drug utilisation • Safety monitoring of a medicinal product • Estimation of the incidence of a series of adverse events
Off-the-shelf studies	Studies for which a generic protocol is adapted to a research question • Estimate the prevalence, incidence or characteristics of exposures • Health outcomes • Describe population characteristics
Complex Studies	Studies requiring development or customisation of specific study designs, protocols and Statistical Analysis Plans (SAPs), with extensive collection or extraction of data • Etiological study measuring the strength and determinants of an association between an exposure and the occurrence of a health outcome considering sources of bias, potential confounding factors and effect modifiers
Very Complex Studies	Studies which cannot rely only on electronic health care databases, or which would require complex methodological work • Studies where it may be necessary to combine a diagnosis code with other data such as results of laboratory investigations, or studies requiring additional data collection

What is the DARWIN EU® process for conducting studies?



Which data sources will DARWIN EU® use?

Data sources will be onboarded over time taking into account the following criteria:

- Data sources collecting health data routinely and representative of the different types of real-world data in terms of data elements, setting (primary & secondary care), population, origin (e.g. electronic health care records, claims)
- Data sources which collectively provide a broad geographical cover
- Data sources containing patient-level data with a unique patient identifier linking all records relating to a given patient
- Medicines prescribed or dispensed identifiable with quantities (e.g. doses, package size) and dates allowing to calculate cumulative doses and duration of use and linked to individual but unidentifiable patients
- Clinical events formally coded, with accurate dates and linked to individual but unidentifiable patients
- Data already converted or planned to be converted into a common data model

Who will benefit from DARWIN EU®?

EU medicines regulators

- Drug development – disease epidemiology, unmet need, historical controls, planning
- Authorisation – contribution to benefit-risk, controls, extrapolation to general and/or special populations
- Post-authorisation – benefit-risk monitoring, extension of indication, risk minimisation measures

DARWIN EU® will **increase the capacity** of the EMRN to undertake high-quality observational studies based on RWD and **reduce the time** per study

EU patients and healthcare professionals
Faster access to innovative medicines and safe and effective use

European Commission
Key use case for the European Health Data Space

National competent authorities
Support health policy and delivery of healthcare systems

HTA bodies and payers
Support better quality decisions on cost-effectiveness

EU and international health agencies
Use cases specific for other EU Agencies such as ECDC

Academia and research organisations
Increase use of RWE, methodology development, and better data quality

Industry
Enable better evidence supporting decision-making, increase receptiveness for RWE in MA submissions, and reduce time & cost of drug development

Use cases for Real World Evidence

Gianmario Candore, *EMA*

Why can RWD analyses generated by DARWIN EU® be useful?

Ultimate goal: better informed and more efficient regulatory decision-making

To help fill knowledge gaps

- Providing additional information needed for decision-making such as more recent data or additional sensitivity analyses, or access to more and different databases (e.g. those established and maintained by public health authorities)

Transparent and tailored analyses

- Transparent and trusted sources of RWD
- Tailored to the Committee's questions, with involvement of the Committee/requester at every step

Faster evidence generation, avoiding the procedural steps for imposing and supervising MAH sponsored studies

Ability to study multiple substances of the same class avoiding unnecessary duplication and inefficiency that might be feature of studies done by industry

Three main areas for which RWD analyses can support committees' decision-making

1. Support the planning and validity of applicant studies
2. Understand the clinical context
3. Investigate associations and impact

Three main areas of committees' decision-making for which RWE can be requested

Use case objective

1 **Support the planning & validity of applicant studies**

Use case category

Design and feasibility of planned studies

Representativeness and validity of completed studies

Inform recruitment in pre and post authorisation studies

- Number of incident and/or prevalent patients per year (for diseases and/or drugs)
- Geographical variation of incident and/or prevalent patients

Example – waiver or paediatric investigation plan modification

- Are clinical studies in young children with a rare haematological conditions feasible?

Examine impact of planned inclusion/exclusion criteria on

- Patient recruitment and its feasibility
- Composition of study population vs. real-world target population

Three main areas of committees' decision-making for which RWE can be requested

Use case objective

1 **Support the planning & validity of applicant studies**

Design and feasibility of planned studies

Use case category

Representativeness and validity of completed studies

Evaluate external validity

- Measure the representativeness of the CT population (treatment and control arm) vs. the real-world target population
  - Similar age distribution, gender, severity of underlying illness…
- Evaluate whether the standard of care used in the control arm of a CT is comparable with the current real-word standard of care

Three main areas of committees' decision-making for which RWE can be requested

Use case objective

2 **Understand clinical context**

Support the evaluation of incidence and prevalence of diseases

Example – prevalence for orphan designation or maintenance

- Do recent data and from a broader set of databases support the maintenance of an orphan designation?

Support better understanding of the disease and its progression

- Baseline factors at diagnosis and post-diagnostic characteristics

Use case category

Disease epidemiology

Clinical management

Generate evidence on the actual clinical standards of care and compare in different populations

- How are patients diagnosed and treated?
- Medicines used according to the authorised indication or off-label
- Treatment patterns

Drug utilisation

Three main areas of committees' decision-making for which RWE can be requested

Use case objective

2 **Understand clinical context**

Use case category

- Disease epidemiology
- Clinical management
- Drug utilisation

Characterisation of real-world drug use

- Incidence & prevalence of use
- Indication
- Amount and duration of exposure
- Switching of drug use over time

Example – contextualise risk of a possible contamination with a medicinal product

- What is the use of the medicinal product and how has it evolved over time?
- What other medicinal products are available, have they been used?

Three main areas of committees' decision-making for which RWE can be requested

Use case objective

3 **Investigate associations and impact**

Use case category

Effectiveness and safety studies

Investigate the association between treatment exposure and either effectiveness or safety outcomes

- Characterise adverse events occurring in the treated population (incidence of events, time-to-onset, stratification by subpopulations)

Example - association between COVID-19 vaccine and the occurrence of thrombosis with thrombocytopenia syndrome (TTS)

- Proactively initiated a study to calculate background incidence rates; these were used to put into context the first cases of thrombosis events received
- This analysis allowed to investigate the potential signal and was central to the assessment of the committees

Impact of regulatory actions

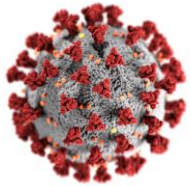
Monitor implementation of risk minimisation measures

- Changes in drug use with time

Monitor effectiveness of risk minimisation measures

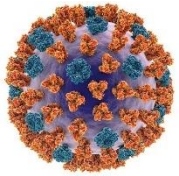
- Changes in incidence of harmful event with time

DARWIN EU® as central pillar for health crisis planning & response



Possible use cases include

- Monitoring the use of medicines to predict demand and shortages
- Understanding the disease natural history to support development of vaccines and therapeutics
- Provide evidence for repurposing existing medicines
- Monitor the safety and effectiveness of vaccines and therapeutics post-authorisation



DARWIN EU® will support future crisis responses with an operational infrastructure for conducting studies

Setting up the DARWIN EU® Coordination Centre

Peter Rijnbeek, *Erasmus MC*

Disclosure

This presentation represents the views of the DARWIN EU® Coordination Centre only and cannot be interpreted as reflecting those of the European Medicines Agency or the European Medicines Regulatory Network

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Sub-contractors

UNIVERSITY OF OXFORD

SYNAPSE
RESEARCH MANAGEMENT PARTNERS

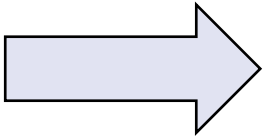
IQVIA

The Hyve

ODYSSEUS
DATA SERVICES INC

DARWIN EU® Implementing a paradigm shift

- A highly needed paradigm shift for the fast delivery of reliable evidence for regulatory decision-making on the utilisation, safety and effectiveness of medicinal products throughout their lifecycle
- A long-term investment needed to significantly scale up the number of studies on more databases and improve public health.

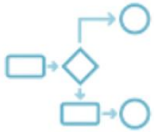


Not possible by simply scaling up the traditional approaches.

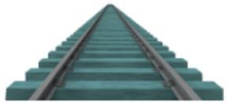
26

What is needed to facilitate observational studies at scale?

Data interoperability



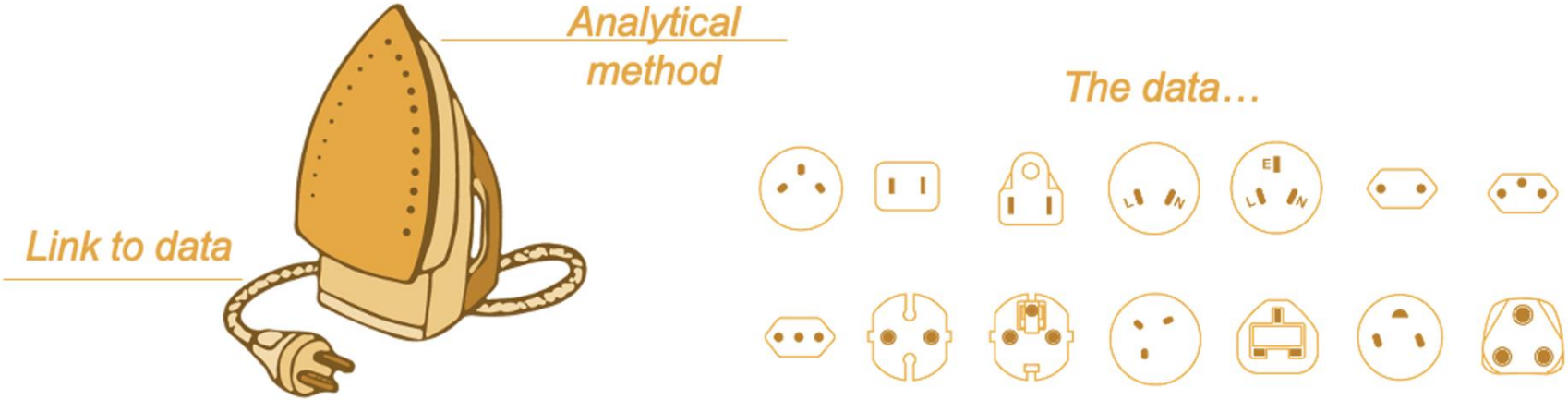
Standardised analytics



Technical Infrastructure

Data network

Improving interoperability of data

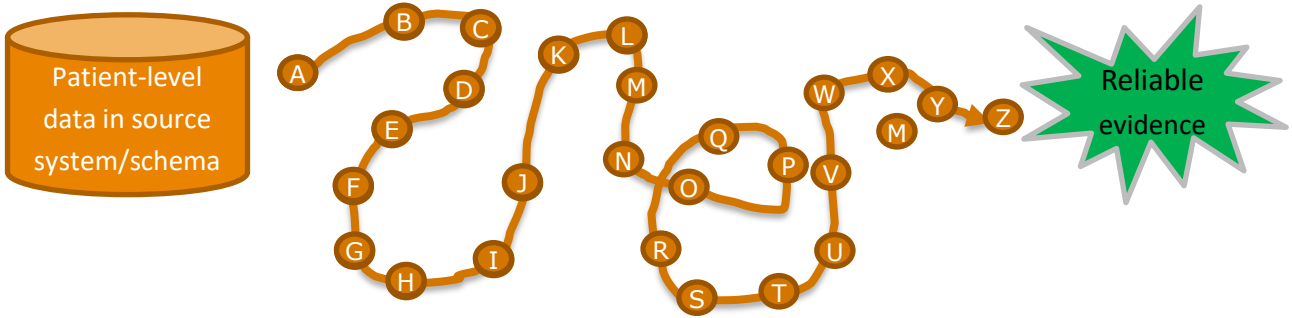


- Increasing productivity to an industrial level requires the automation of the analytical processes, which in turn cannot be done without a rigorous standard representation of the data.

- Full interoperability of the data is needed with respect to structure (syntactic interoperability) and coding systems (semantic interoperability) by using a Common Data Model (CDM)

Generating Reliable Evidence using a Common Data Model

We need to make studies repeatable, reproducible, replicable, generalisable, and robust



A Common Data Model will enable standardised analytics to generate reliable evidence.

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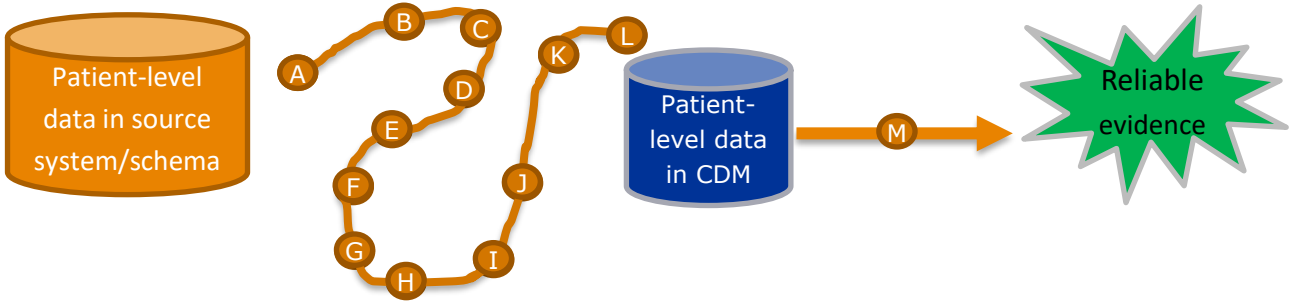
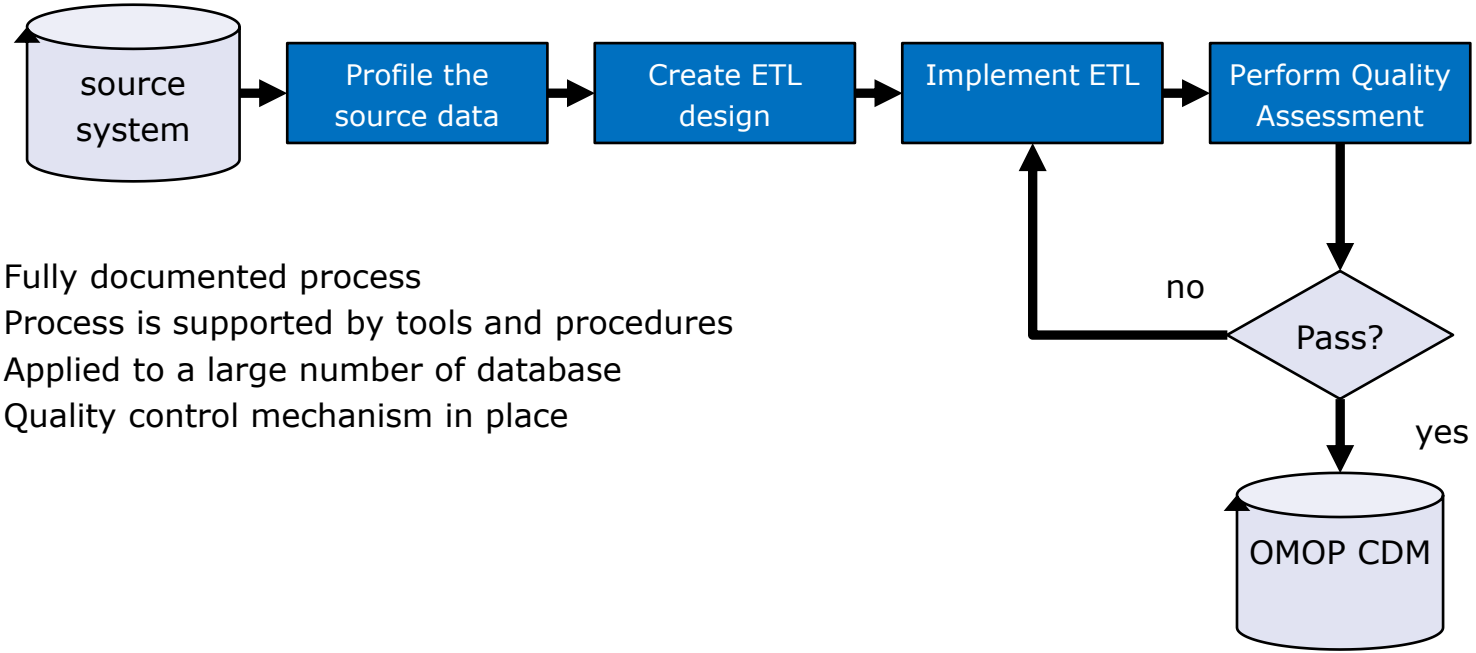


A Common Data Model will enable standardised analytics to generate reliable evidence.

The OMOP Common Data Model

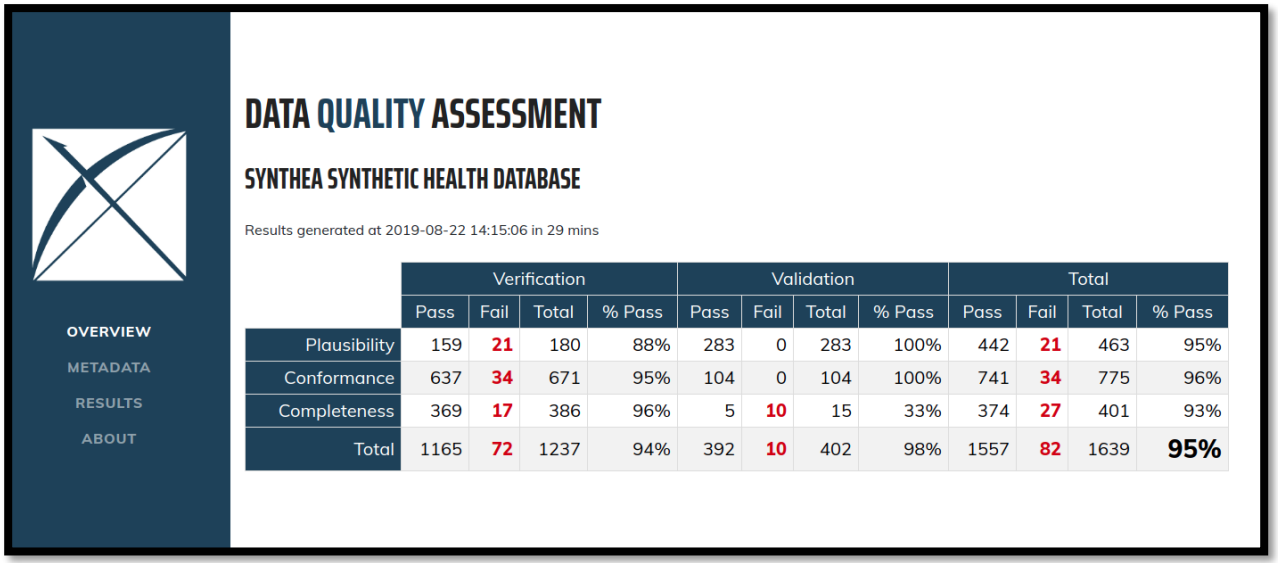
- It is maintained by the Observational Health Data Sciences and Informatics (OHDSI) initiative with an active European Chapter (www.ohdsi-europe.org).
- Many tools are available for data standardisation, data quality, and data analysis.
- It is designed for federated querying and analytics, whereby applications are run locally by the data partners and only aggregated results are shared. This privacy-by-design approach is compliant with data protection requirements.
- It has been used in many observational studies including studies that informed regulatory decision-making.
- The European Health Data and Evidence Network (EHDEN) project is investing €17M private/public funding in standardising health data to the OMOP-CDM through the Innovative Medicines Initiative (www.ehden.eu).

From Source Data to the OMOP CDM: Extraction Transform Load (ETL)



- Fully documented process
- Process is supported by tools and procedures
- Applied to a large number of database
- Quality control mechanism in place

Data Quality Dashboard



OVERVIEW
METADATA
RESULTS
ABOUT

DATA QUALITY ASSESSMENT

SYNTHEA SYNTHETIC HEALTH DATABASE

Results generated at 2019-08-22 14:15:06 in 29 mins

	Verification				Validation				Total			
	Pass	Fail	Total	% Pass	Pass	Fail	Total	% Pass	Pass	Fail	Total	% Pass
Plausibility	159	21	180	88%	283	0	283	100%	442	21	463	95%
Conformance	637	34	671	95%	104	0	104	100%	741	34	775	96%
Completeness	369	17	386	96%	5	10	15	33%	374	27	401	93%
Total	1165	72	1237	94%	392	10	402	98%	1557	82	1639	**95%**

- Framework that can be expanded
- Currently >3300 checks

Blacketer C, Defalco FJ, Ryan PB, Rijnbeek PR. **Increasing trust in real-world evidence through evaluation of observational data quality.** J Am Med Inform Assoc. 2021 Sep 18;28(10):2251-2257.

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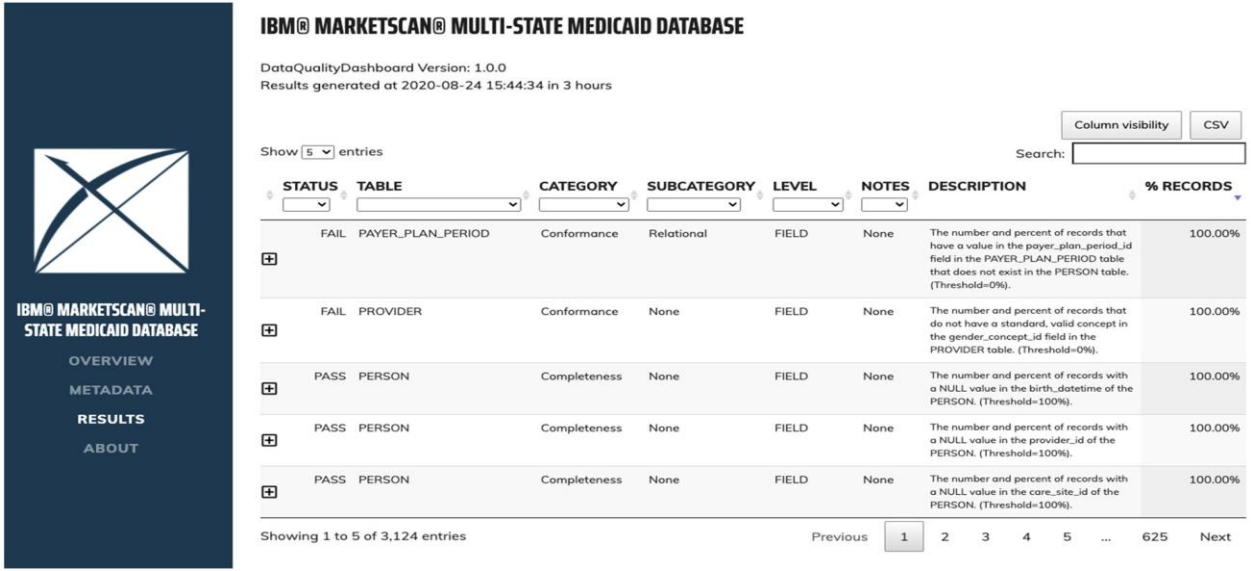
Data Quality Dashboard



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Standardising the analytics

- A catalogue of open source standardised analytics is needed to support ”all” regulatory decision-making on the utilisation, safety and effectiveness of medicinal products

Will require alignment on the priority and choice of the analytical methods, and the standardised output!

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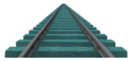
Will require alignment on the priority and choice of the analytical methods, and the standardised output!

- Development will be driven by proof-of-concept studies taking different complexity levels into account.
- The standardised analytics will be based on available tools and methods developed in the OHDSI community.



Creating a strong technical infrastructure

Required components:

- Collaboration Space for CC and Study Teams
- Analytics Platform
- Study Execution Platform
- Training Platform
- Service Desk
- Source Control Repository
- DARWIN EU Website
- …

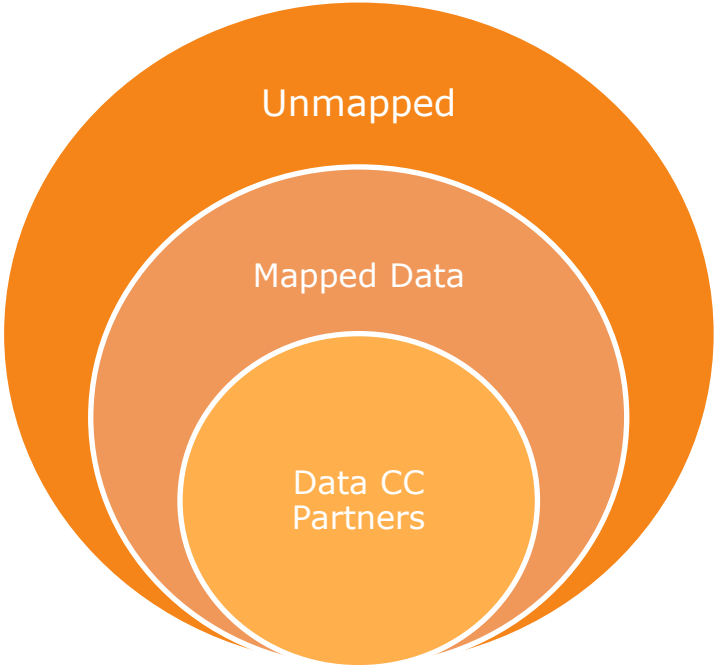
Will build on prior work

Will be developed using short sprints during the establishment phase

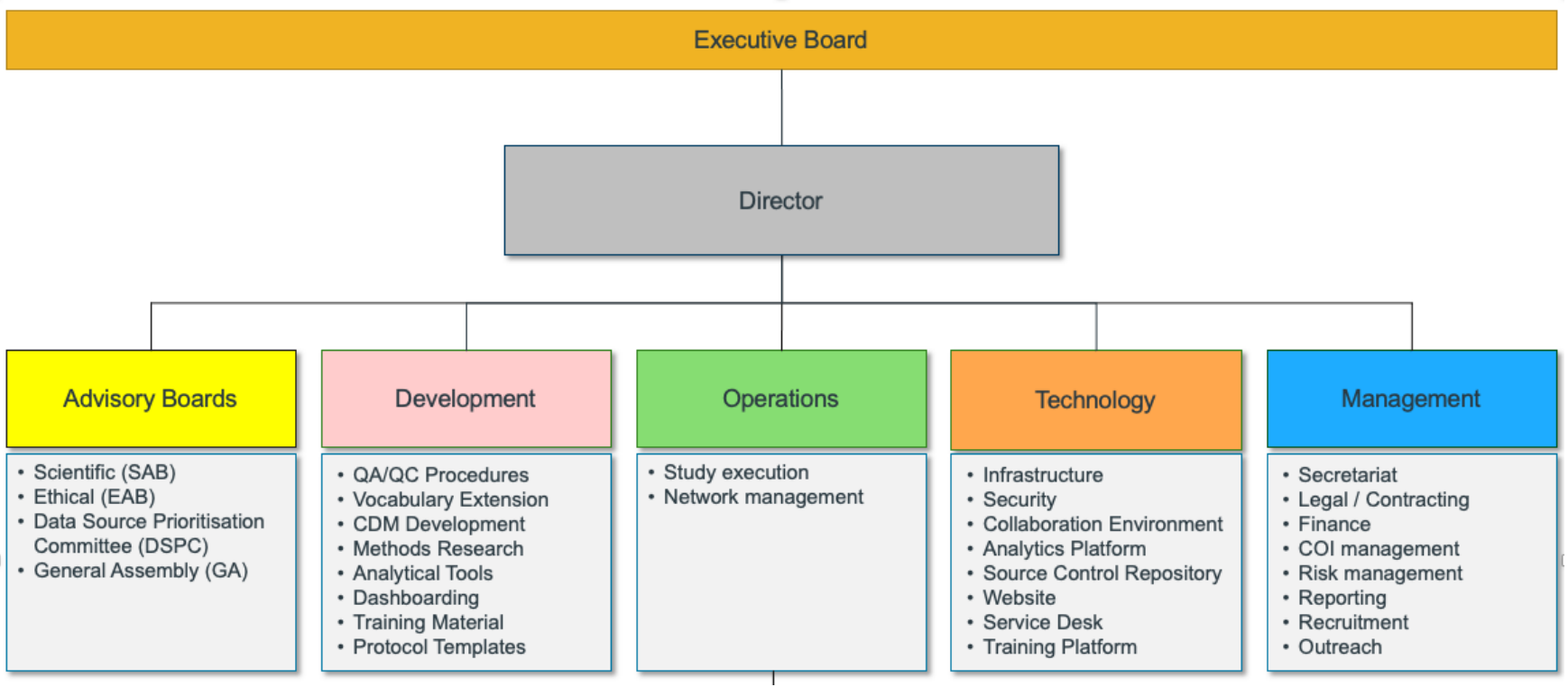
Operating a high-quality Data Network

- Selection of data partners
  1) Prioritisation of already converted data sources
  2) Potentially mapping highly valued data sources

- All data sources will go through a quality control process approved by EMA



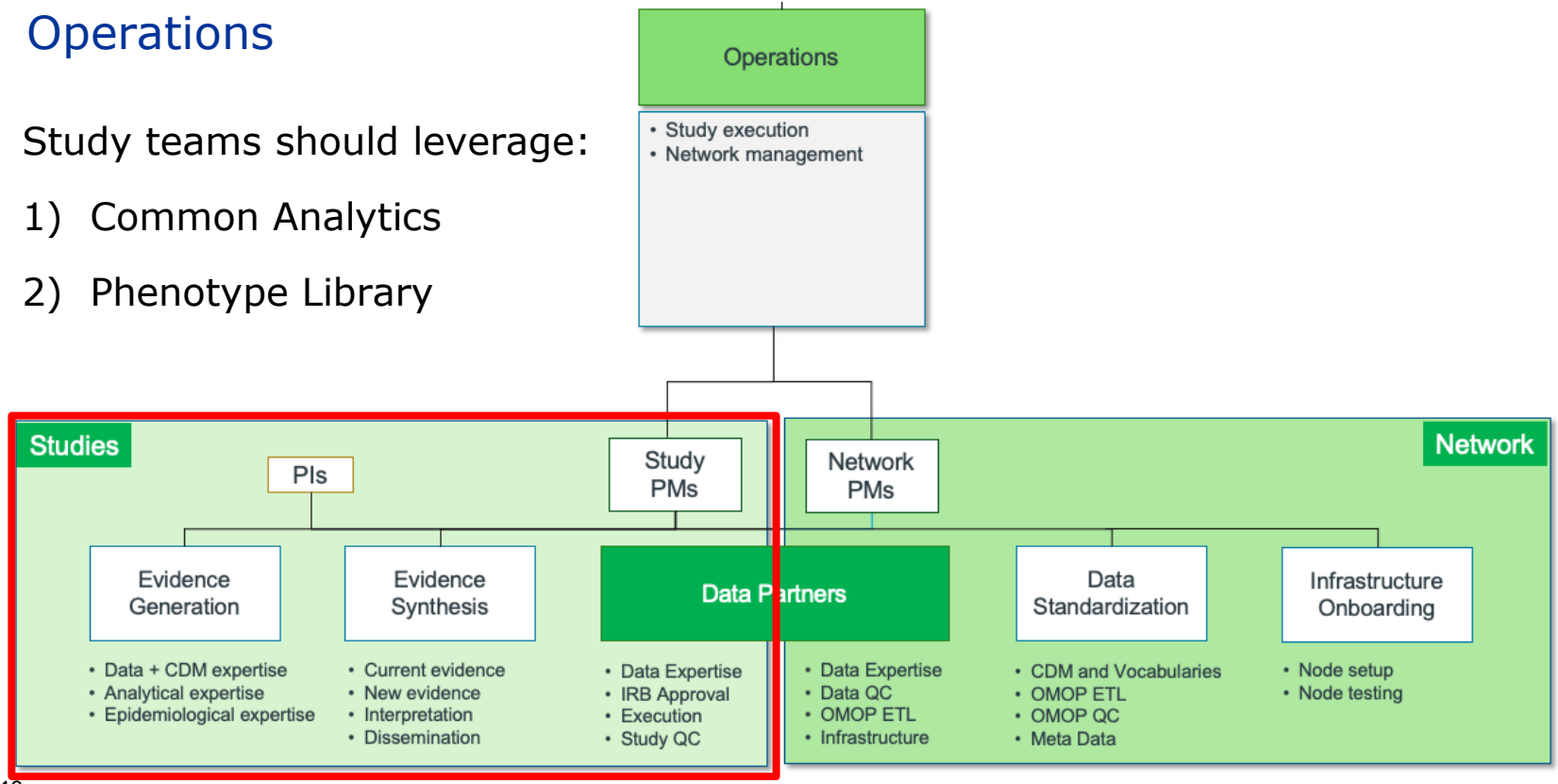
Establishment and Evolution of the Coordination Centre



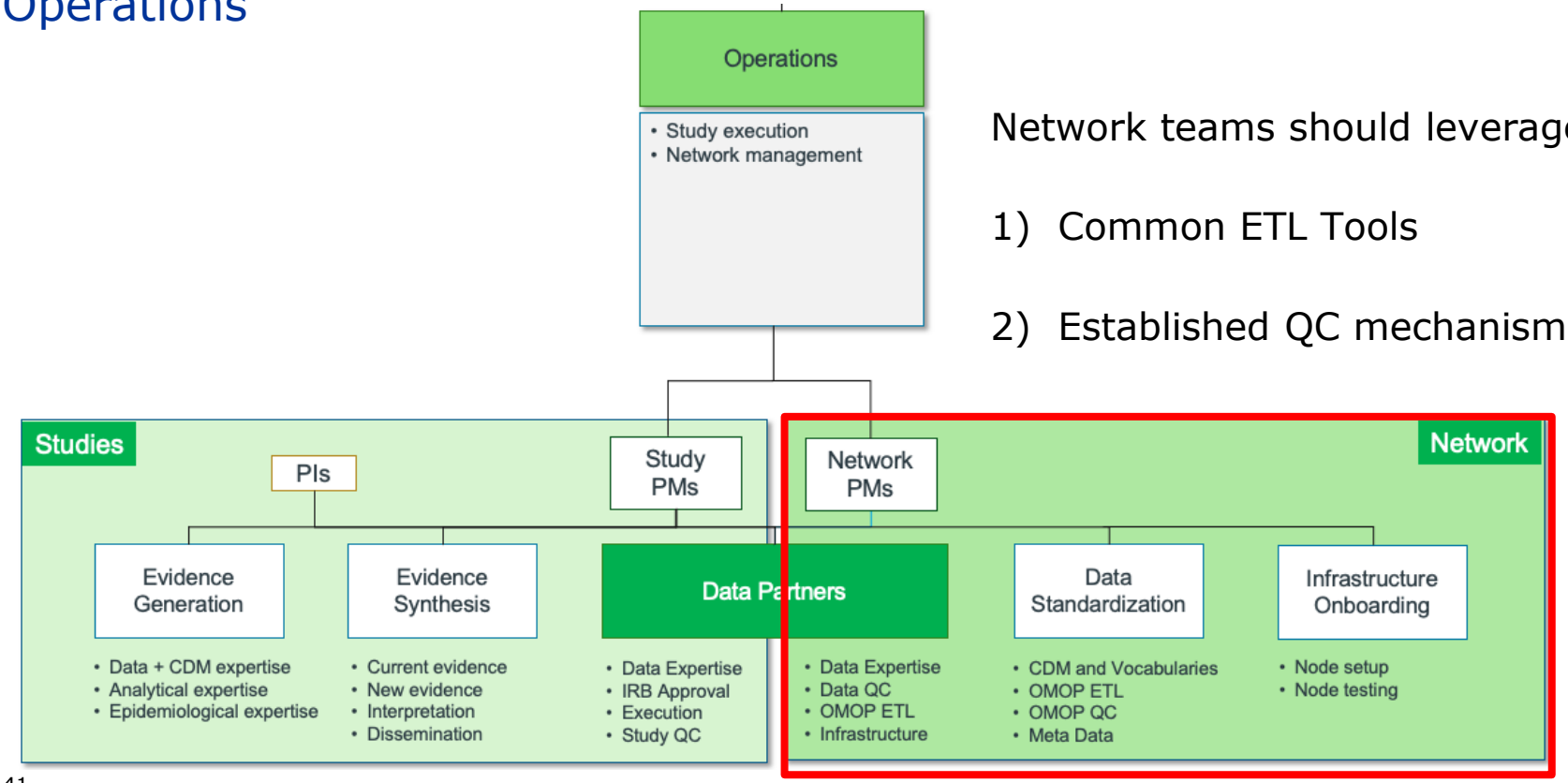
Operations

Study teams should leverage:

1) Common Analytics
2) Phenotype Library



Operations



Network teams should leverage:

1) Common ETL Tools

2) Established QC mechanisms

Questions?

Feel free to reach out to the Coordination Centre.
Questions and suggestions are always welcome.

enquiries@darwin-eu.org

Outlook for 2022

Andrej Segec, *EMA*

Implementation roadmap

Phase I - 2022

- Start running pilot studies to support EMA committees – **first benefits delivered**
  - Coordination Centre set-up
  - Data Protection Impact Assessment
  - Start recruiting and onboarding data partners
  - Pilot with the EHDS model and existing Data Permit Authorities
- Consultation of stakeholders

Phase II - 2023

- Support the majority of Committees in their decision-making with reliable RWE by 2023

Phase III - 2024

Up scale delivery and capacity to routinely support the scientific evaluation work of EMA's scientific committees and NCAs by delivering studies and maintaining data sources.

Operation - 2025/2026

- DARWIN EU® to be fully operational and yearly evolves to meet the needs from the EU Regulatory Network
- **Integration with the EHDS**

Key stakeholders for the establishment of DARWIN EU®

Patients & **Healthcare Professionals**

European commission, including Agencies (ECDC) and initiatives e.g. EHDS & TEHDAS

EU Regulatory Network, e.g. National Competent Authorities, Head of Medicines Agencies, and EMA committees

Health Technology Assessment bodies & **payers**

Data Holders & Partners, e.g. NCAs as data holders, Data permit authorities, Disease Patient registries

Industry

Academia and Research organisations

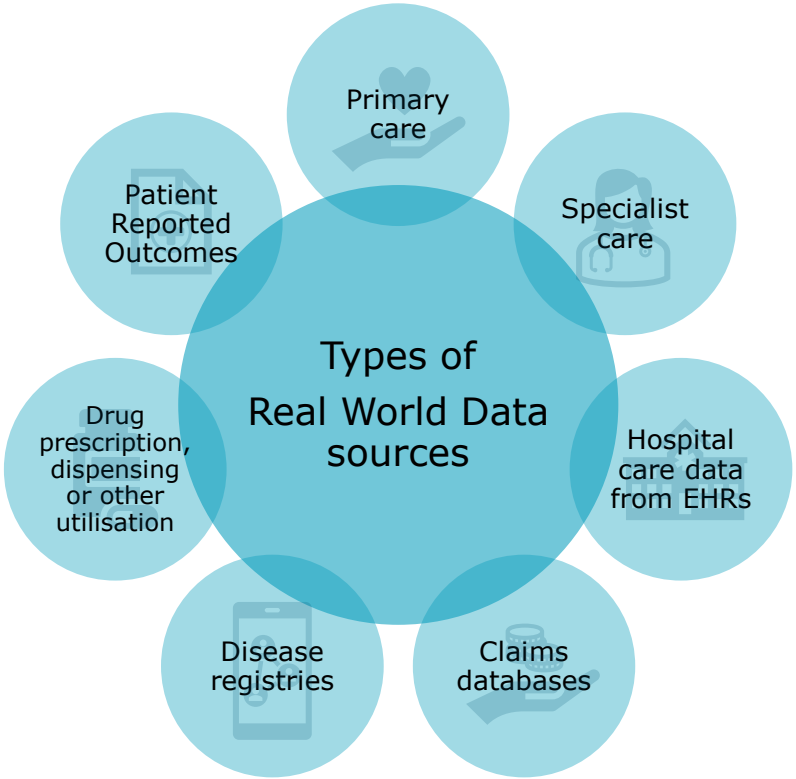
- Representatives from each group are member of the DARWIN EU® Advisory Board. Members have been and will continue to support the implementation of DARWIN EU®, the alignment with EU initiatives and the engagement with stakeholders
- Consultation and dialogue with all stakeholders will be planned e.g. stakeholder fora and workshops
- Implementation will be transparent including on processes and operations

DARWIN EU® - Coordination Centre immediate next steps

- **Formation** of the coordination centre: governance team, technology operations team, governance & boards
- **Project management** (e.g. project plan, risks management, reporting)

- **Strengthening** of the coordination centre:
  - Requirements & solution design
  - Conflict of Interest management process
  - Mandate and composition of the Scientific Panel
  - Change management plan
- **Strategic oversight** of the coordination centre:
  - Management plan and Business plan
- **On-Boarding of data sources templates**:
  - On-boarding specifications, data use agreement
- **Execution of studies templates**:
  - Feasibility assessment form, study outline/protocol/report, Agreement for Study Participation

Looking ahead at 2022: onboarding of data partners and first studies



First pilot studies in 2022 for a number of use cases across the medicine lifecycle

Over 5 years, ~380 studies will be conducted

More Information

Data Analysis and Real World Interrogation Network (DARWIN EU) | European Medicines Agency (europa.eu)

Coordination Centre website – coming soon in 2022!

- For questions to the Coordination Centre, please contact: enquiries@darwin-eu.org

For regular updates on DARWIN EU® Subscribe to the Big Data Highlights newsletter by sending an email to: bigdata@ema.europa.eu

01 Issue 1 February 2022

HMA Heads of Medicines Agencies

EMA EUROPEAN MEDICINES AGENCY

BIG DATA

HIGHLIGHTS

Quarterly update on implementation activities of the HMA-EMA Big Data Steering Group workplan

An agency of the European Union

Editorial

Peter Arlett

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Jesper Kjær

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Welcome to the first edition of the newsletter on Big Data which reports on the implementation of the HMA-EMA Big Data Steering Group workplan 2021-2023 and the data and digital pillar of the Network Strategy 2025.

The BDSG was established in May 2020 with the mandate to take forward and advise on implementation of the priority recommendations set out in the Big Data Task Force final report (phase two). The vision, set out by the Big Data Taskforce that guides delivery of the workplan is that:

by delivering a regulatory system able to integrate Big Data into its assessment and decision making, we can support the development of innovative treatments more quickly and optimise the safe and effective use of medicines.

Big Data Task Force Final Report, Dec 2019

Already in 2021, we have seen an impressive array of activities and outputs that support transformation to data-driven medicines regulation. These include the finalisation of the network's data standardisation strategy and a series of technical workshops covering standardisation, real-world data, artificial intelligence, veterinary data and real-world evidence. More details on the 2021 deliverables are included later in this newsletter.

Moving forward, we are excited to be able to share with you more regular updates on big data and the implementation of the BDSG workplan via this newsletter. We look forward to collaborating and leveraging the work of stakeholders to increase the utility of big data in medicines regulation.

The Big Data Steering Group welcomes your feedback and questions you may have by email at bigdata@ema.europa.eu .

We hope you find the Big Data Highlights informative!

06 - Webinar Agenda

Q&A

Panel of Network experts

Engage via Slido.com

(#DARWINEU)