Relevance of Big Data for Regulatory Procedures

Jesper Kjær
Danish Medicines Agency (DKMA) Data Analytics Centre (DAC)
co-chair HMA / EMA Big Data Steering Group

EU: EMA and HMA - the European strategies

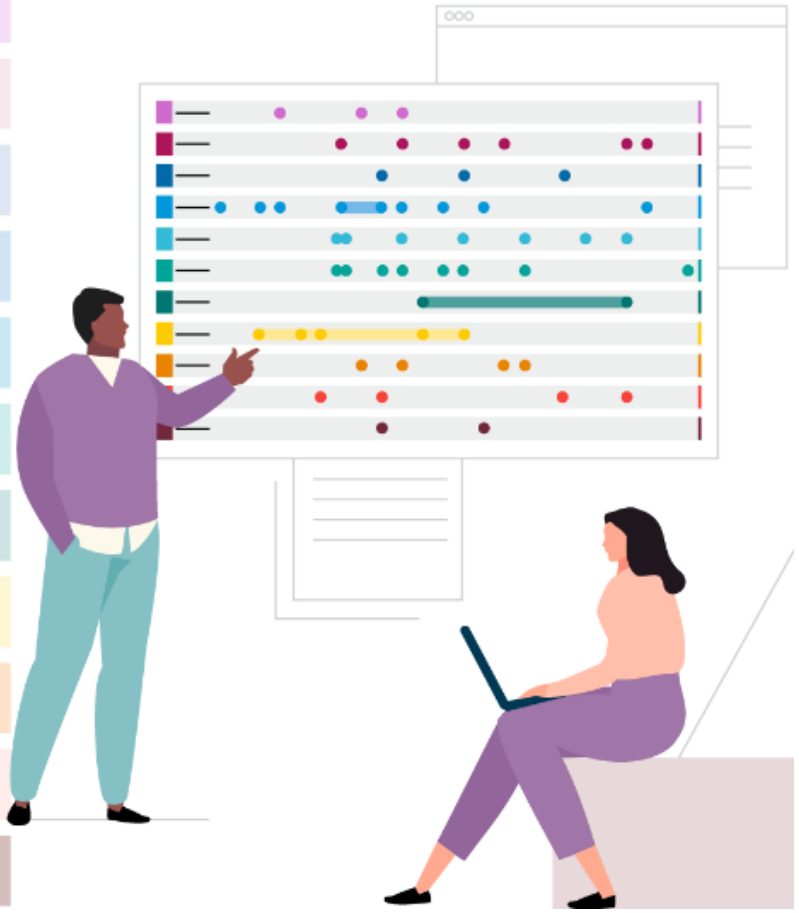
Data analytics at EMA and the network

Source: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf
https://www.ema.europa.eu/en/documents/report/european-union-medicines-agencies-network-strategy-2025-protecting-public-health-time-rapid-change_en.pdf
https://www.ema.europa.eu/en/documents/other/hma-ema-joint-big-data-taskforce-phase-ii-report-evolving-data-driven-regulation_en.pdf

Big Data Steering Group Workplan 2022-2025

Framework - to enable use of big data and facilitate its integration into regulatory decision making

- DARWIN EU
- Data quality & representativeness
- Data discoverability
- EU Network skills
- EU Network processes
- Network capability to analyse
- Delivery of expert advice
- Governance framework
- International initiatives
- Stakeholder engagement
- Veterinary recommendations

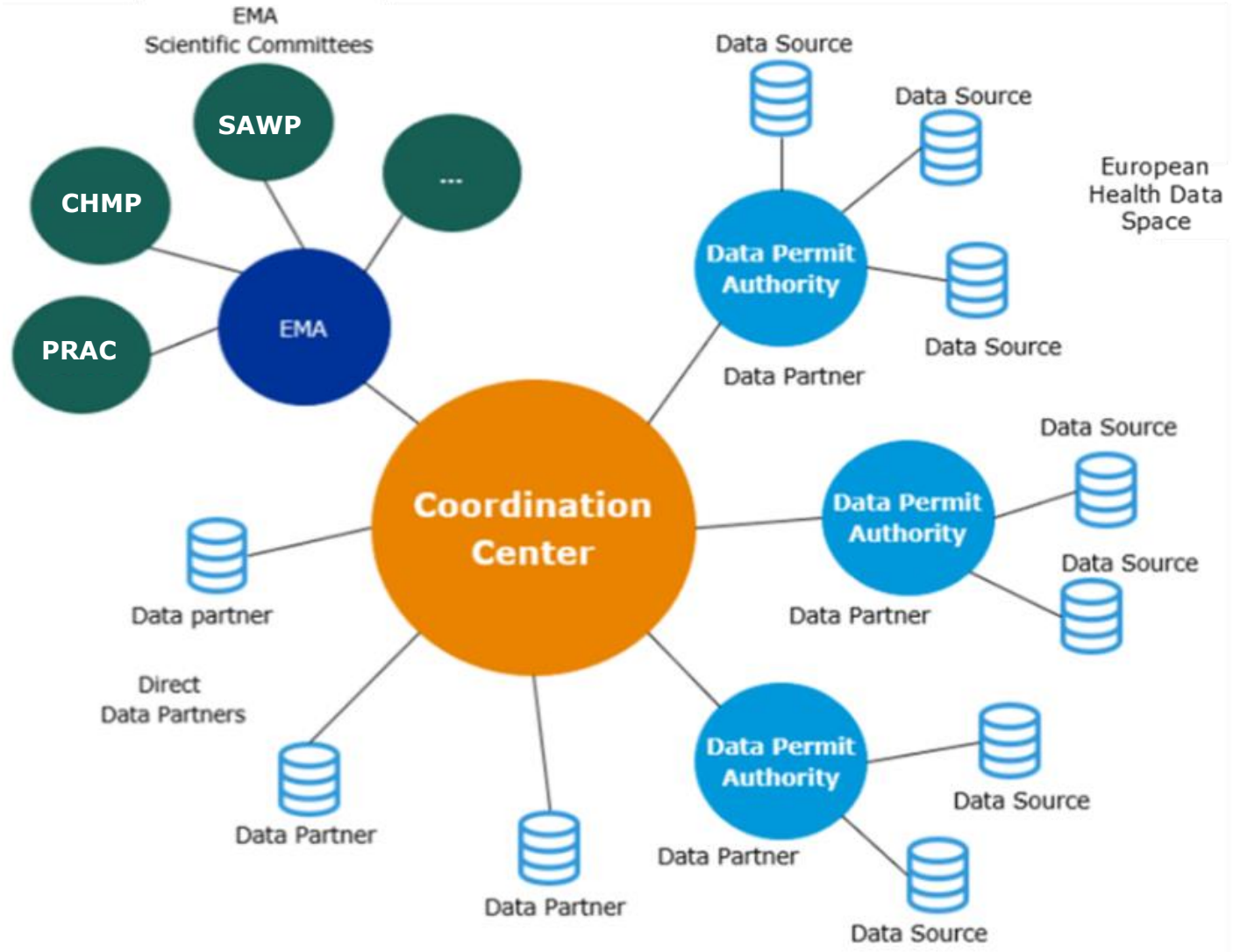


Data Analysis and Real-World Interrogation Network (DARWIN EU®)

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



DARWIN EU® - Estimated number of studies

	Year 1	Year 2	Year 3	Year 4	Year 5
Phases	**Phase I**	**Phase II**	**Phase III**		
Routine repeated Analysis	At least 1 study	At least 6 studies	At least 30 studies	At least 60 studies	At least 60 studies
Off-the-shelf Study	At least 2 studies	At least 6 studies	At least 30 studies	At least 60 studies	At least 60 studies
Complex Study	1	4	12	At least 24 studies	At least 24 studies
Very complex Study	0	0	0	At least 1 study	At least 1 study
Data Sources On-Boarded	up to 10 additional	up to 10 additional	up to 10 additional	up to 10 additional	-

The volume of studies will increase significantly to meet the demand of the EU Network, while the cost and effort required per study will decrease. New data sources will allow to answer new regulatory use cases.

How RWD analyses can support regulators' decision-making?

1 Support the planning and validity

- Design and feasibility of planned studies
- Representativeness and validity of completed studies

2 Understand the clinical context

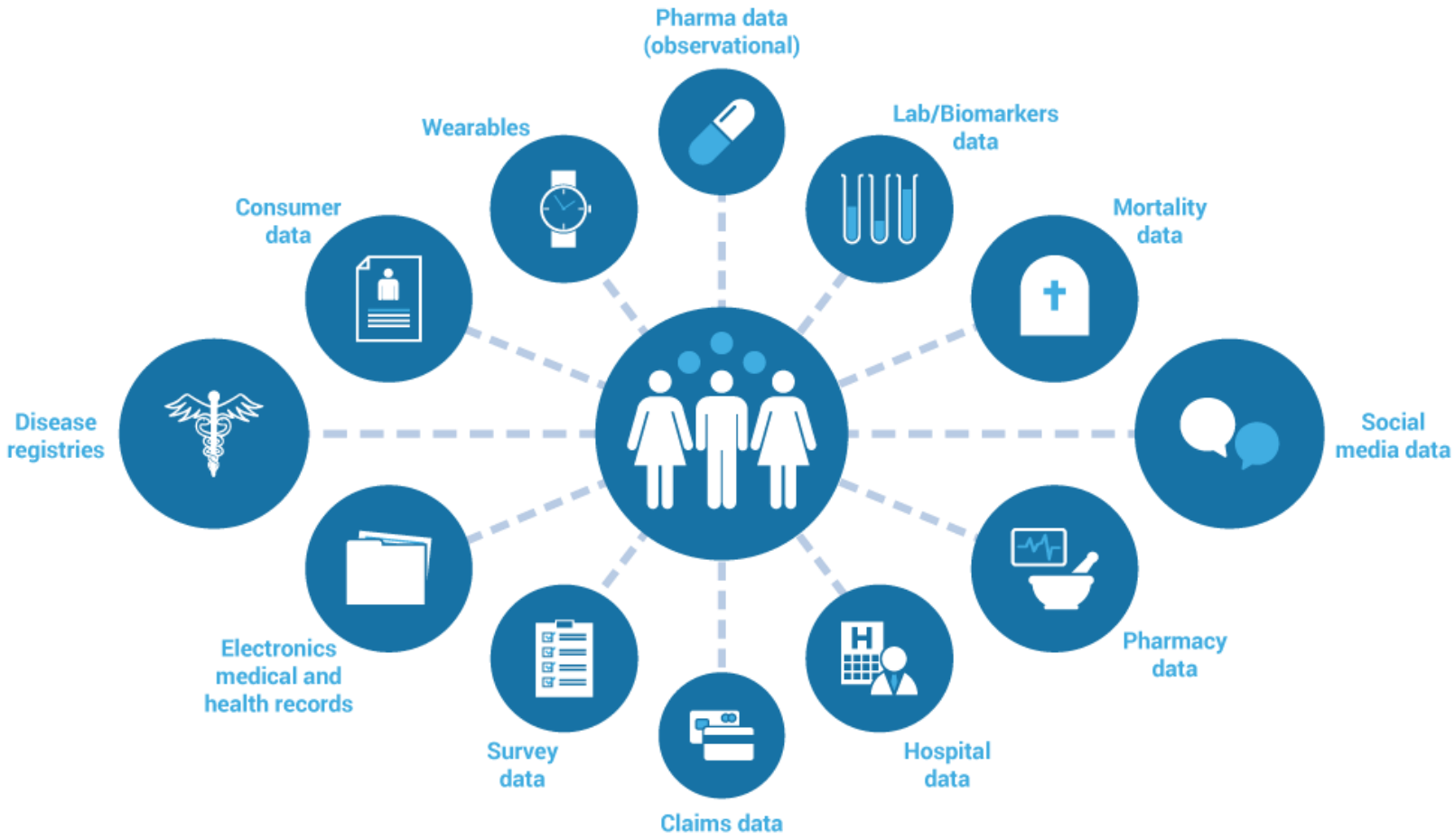
- Disease epidemiology
- Clinical management
- Drug utilisation

3 Investigate associations and impact

- Effectiveness and safety studies
- Impact of regulatory actions

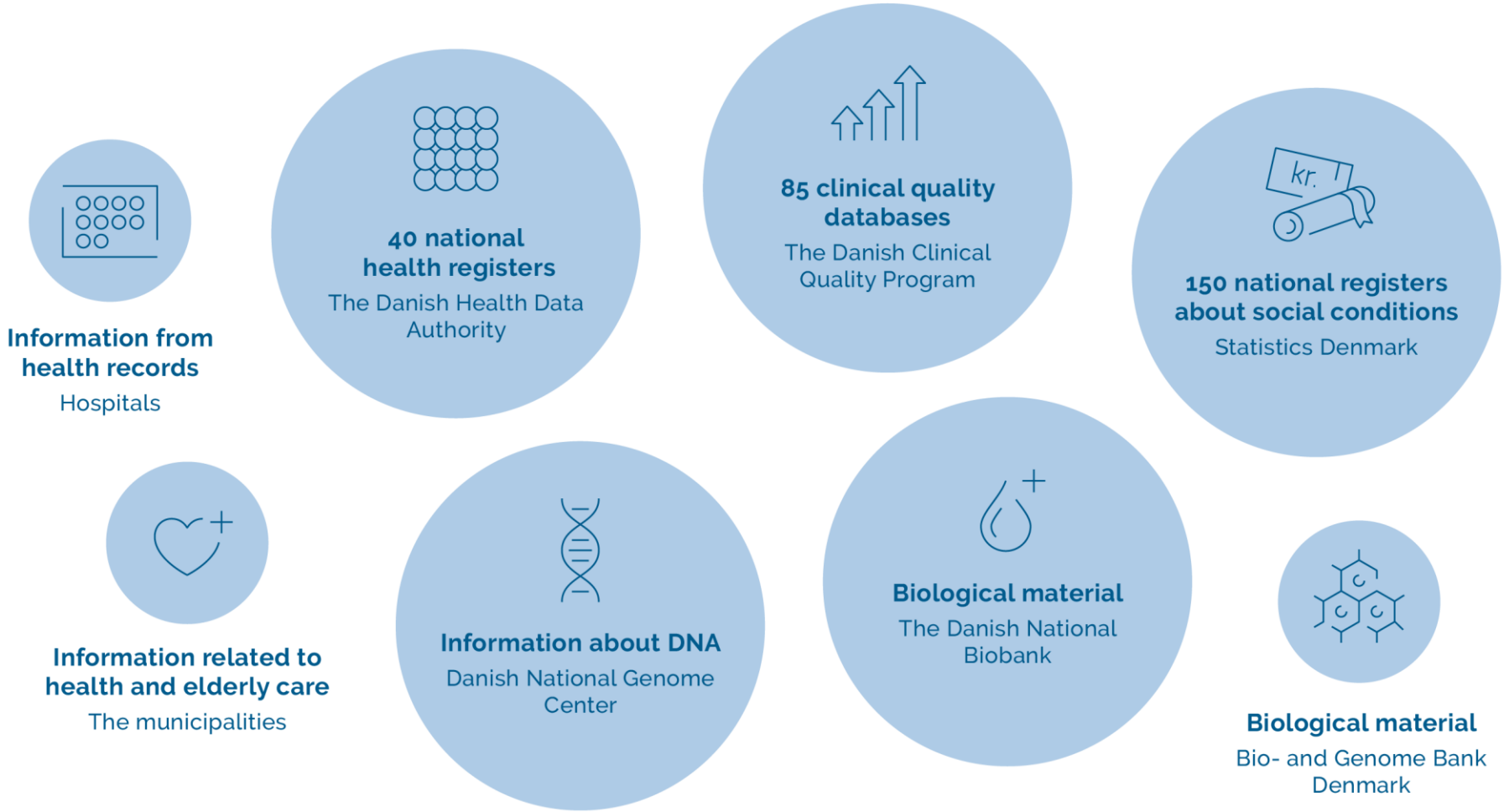
Real world data in Denmark

Real World Data

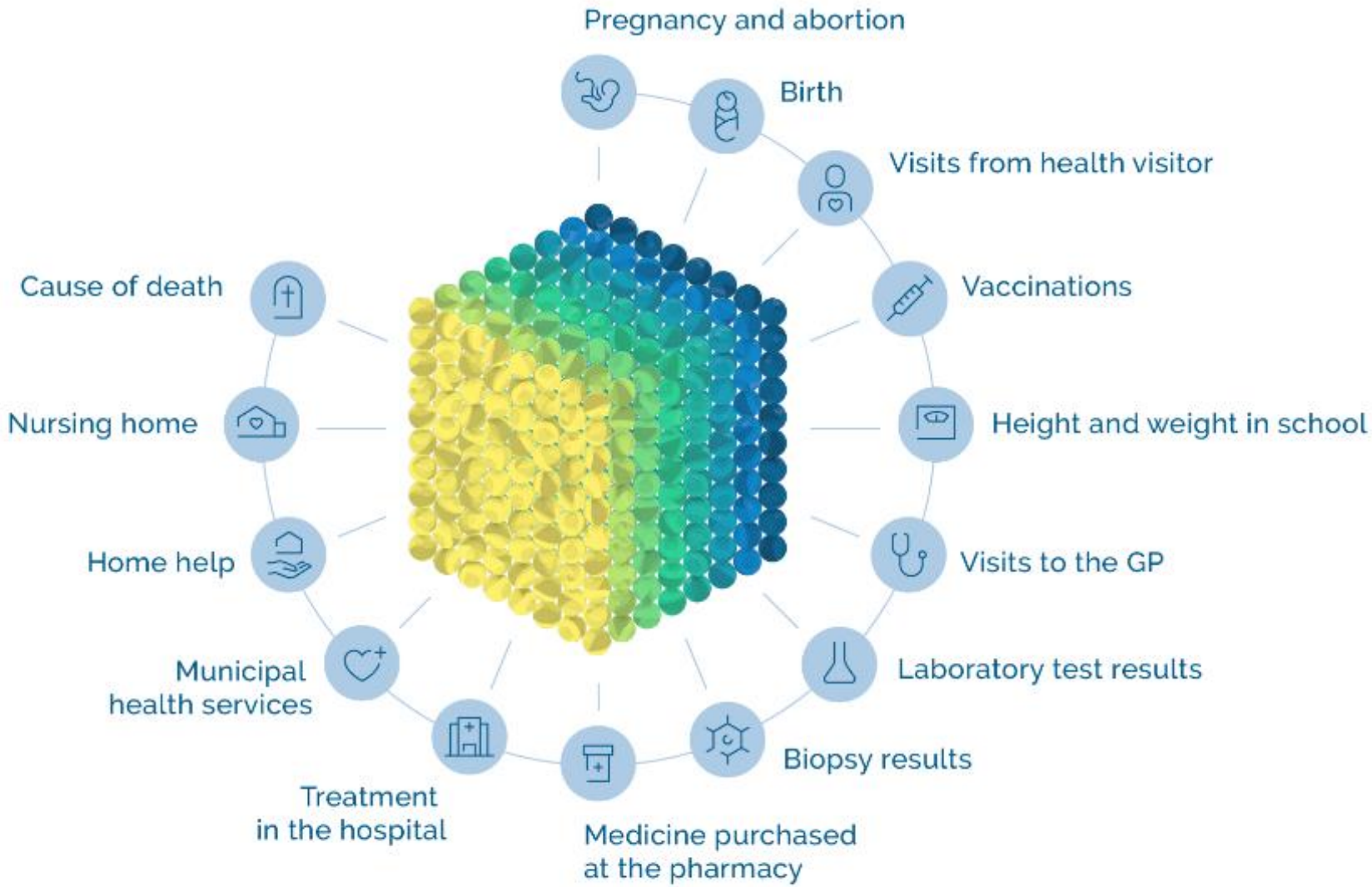


DAC DATA ANALYTICS CENTRE | LÆGEMIDDELSTYRELSEN DANISH MEDICINES AGENCY

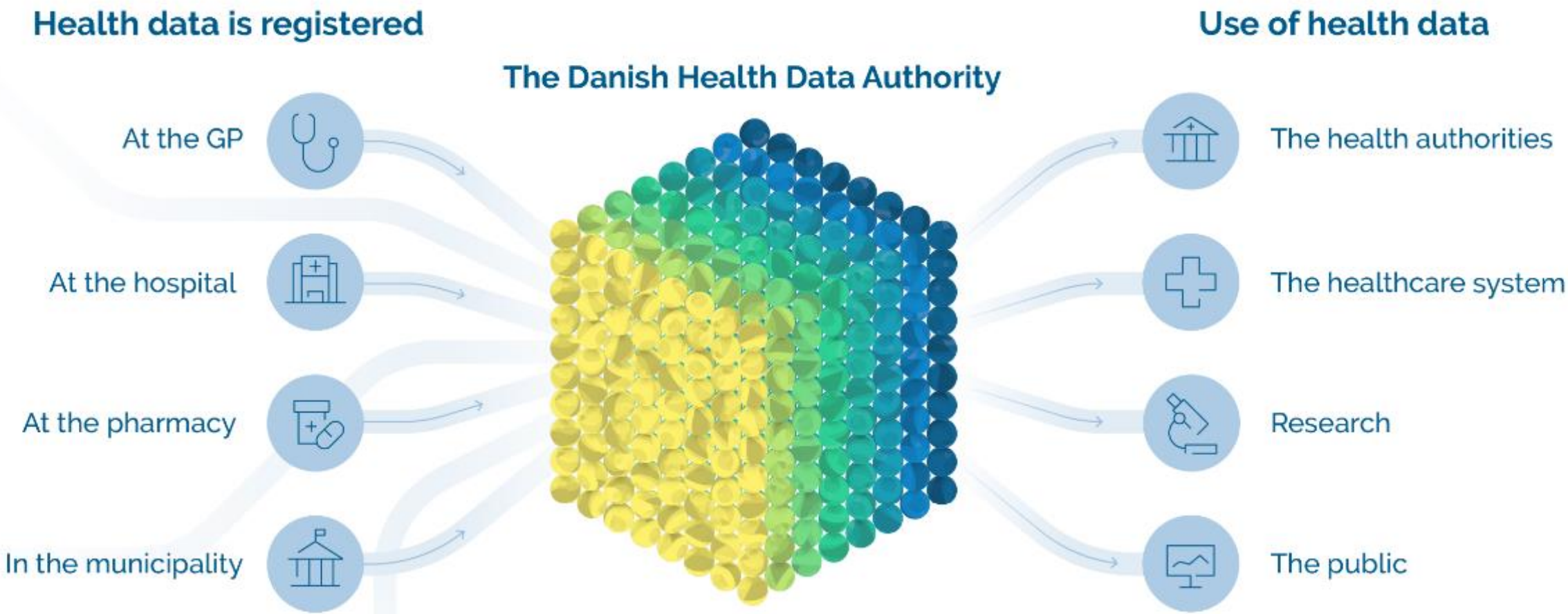
The Danish health data are stored by key agents



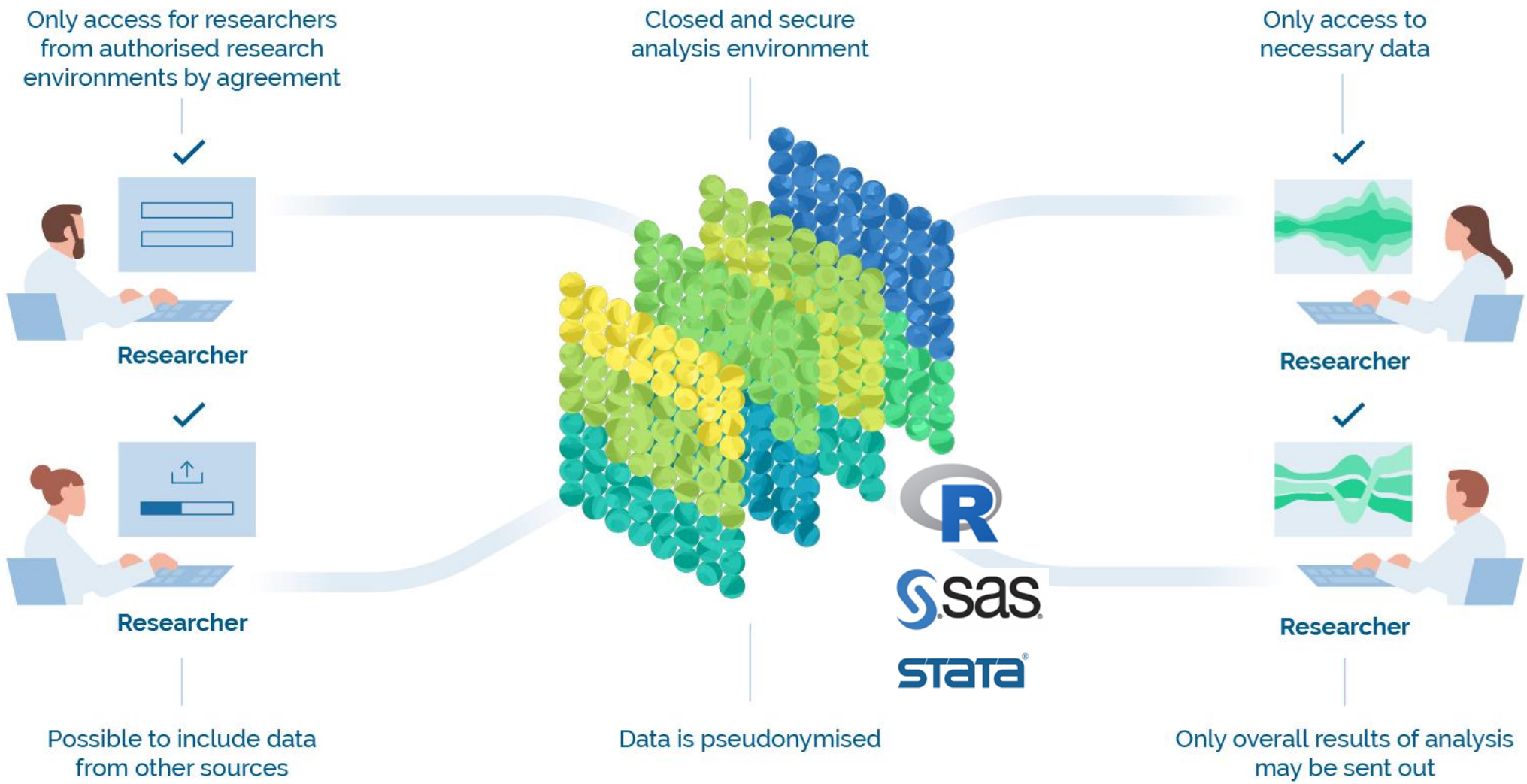
Data in the Danish Health Data Authority



Registration and use of health data

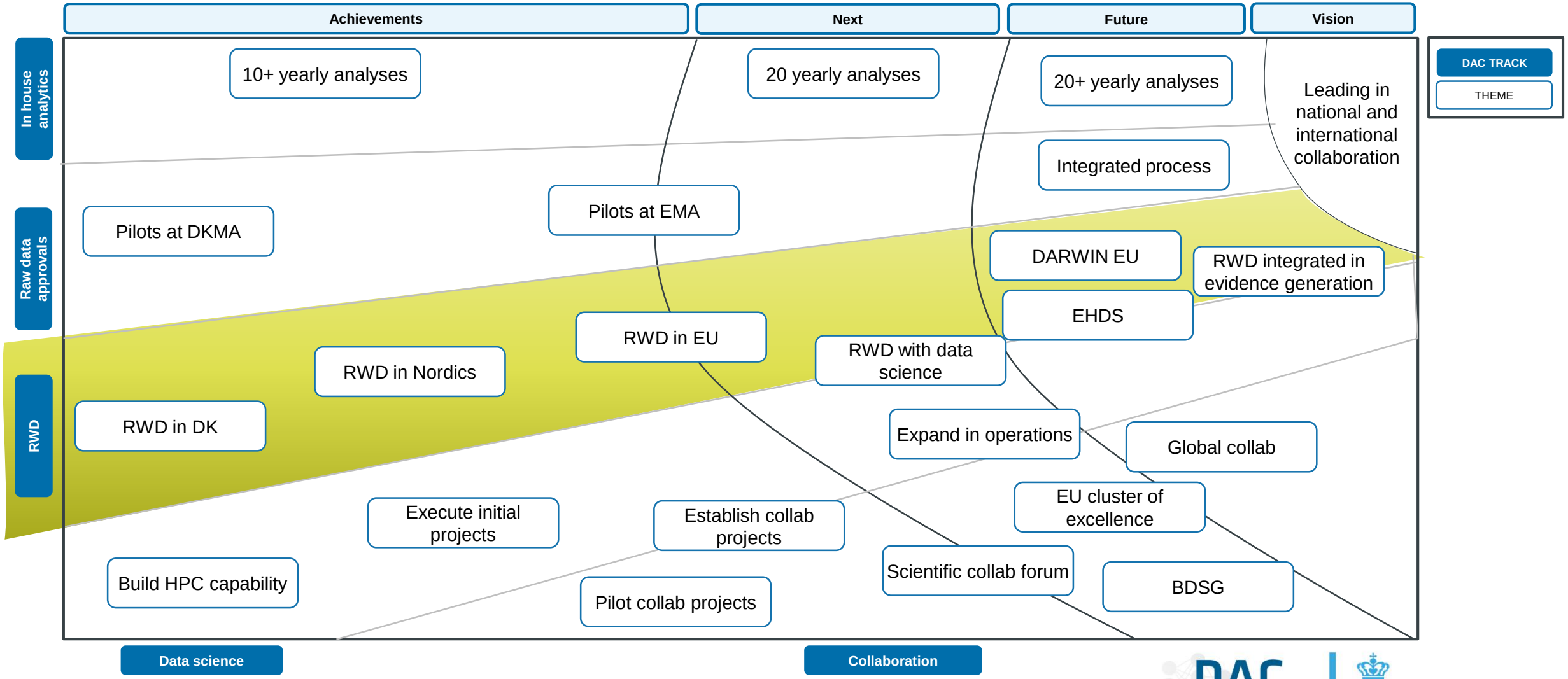


The Secure Research Platform



DAC's strategy map

- create value for people, animals and society through data analytics



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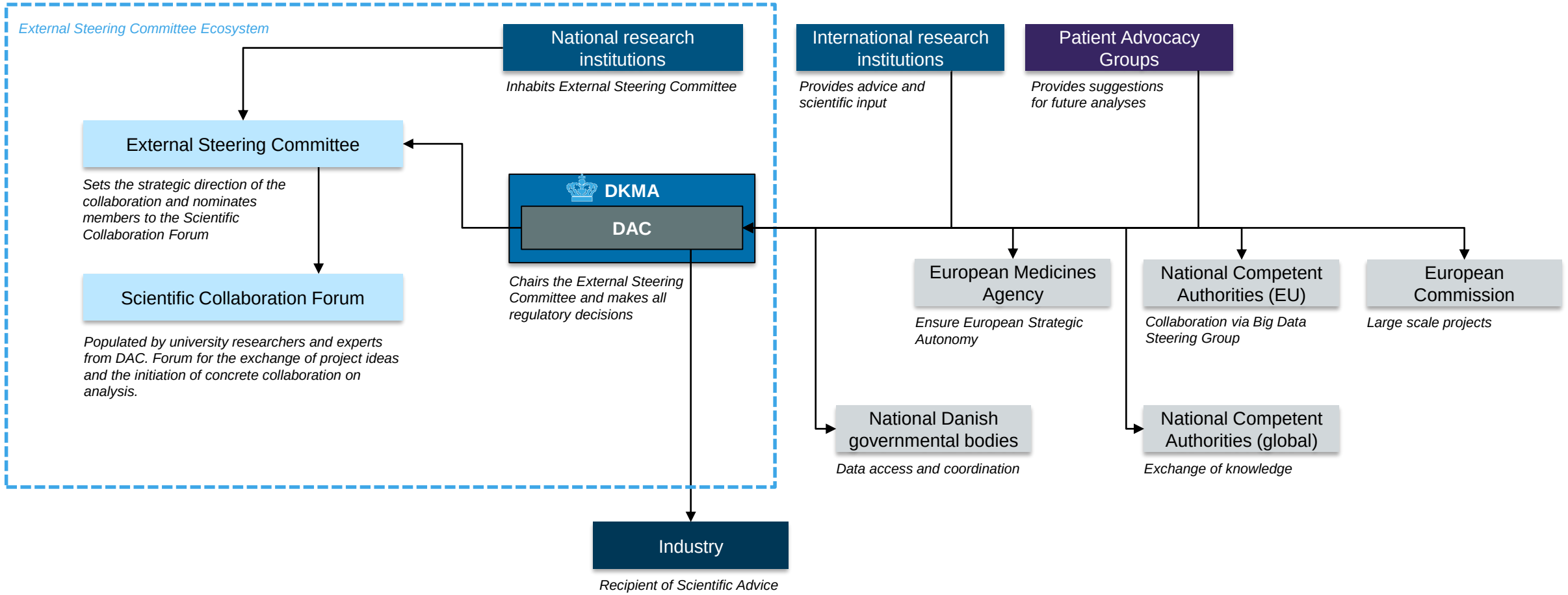
Governance structure and ecosystem of DAC



DAC DATA ANALYTICS CENTRE | LÆGEMIDDELSTYRELSEN DANISH MEDICINES AGENCY

COVID19 to transform regulatory approaches

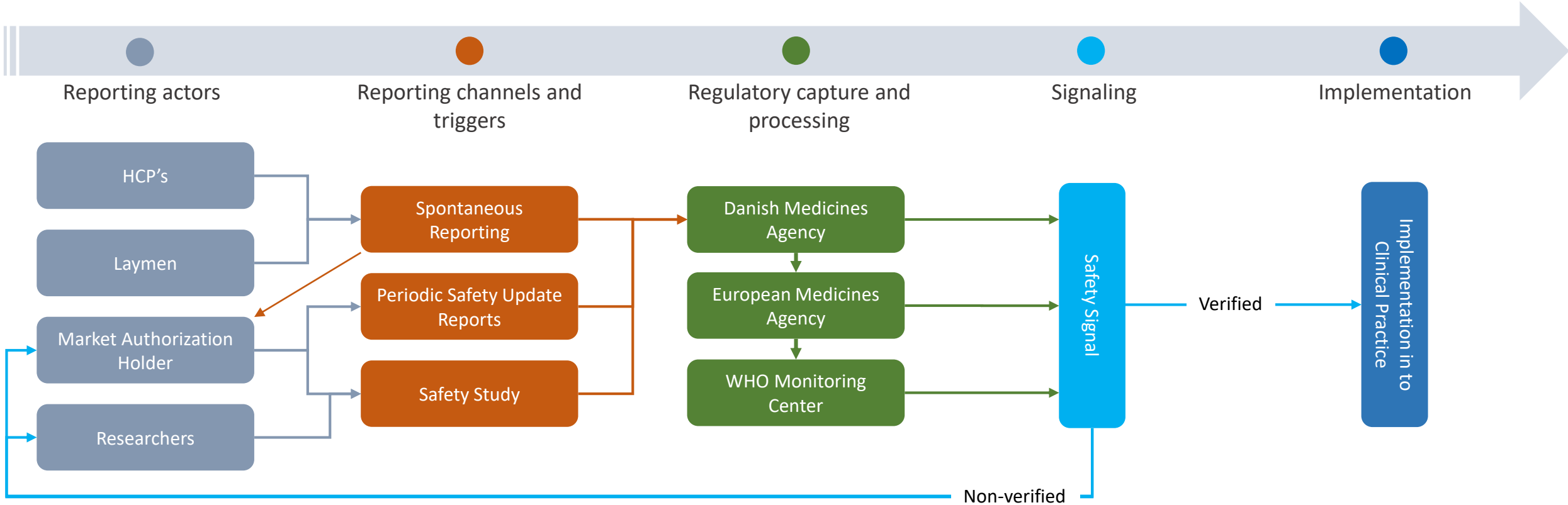
Examples of collaborative projects

Pharmacovigilance today

All medicines have side effects, but they are mild and transient for most medicines.

Side effects are unwanted effects of a medicine. They can range from anything from nausea, headache or a rash to fatal side effects in the worst-case scenario.

People react differently to medicine. Some have side effects, others don't.
Source: dkma.dk



DAC COVID cohort / collaboration est. 27th of Feb 2020

Proposals

Requirements for proposals are specified at www.lmst.dk/daccovid

Steering Committee evaluates proposals

Transparency

DKMA's website and listed in EU-PAS

Proposals not endorsed (due to lack of focus on medicines) → data via the Danish Health Data Agency

Execution

Working group established

Work only took a few weeks to a month to go from proposal to result and into publication

Publication

Papers have been made available in pre-read via medrxiv when possible

- Steering group
  - Decide which analyses the expert group should carry out
    - Danish Medicines Agency, Danish Patients, Health Data Agency, Faculties of Health Science, Regions, Regions Clinical Quality Program, Staten's Serum Institute + two members from the Expert group
- Expert group + project groups
  - Establish a database of COVID-19 patients and perform approved analyses
    - University of Southern Denmark, Aarhus University, Aarhus University Hospital, Statens Serum Institute and Danish Medicines Agency + externals where relevant

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DAC COVID cohort / collaboration results

More than 10 analyses performed and published within 1 year:

- Use of NSAIDs and risk of critical adverse outcomes in patients with COVID-19 (published)
- Renin–angiotensin–aldosterone system inhibitors and severe outcomes in patients with COVID-19
- The role of inhaled anti-inflammatory pharmaceuticals in COVID-19 incidence, morbidity, and mortality
- Prognosis of coronavirus disease in patients with immune-mediated inflammatory diseases treated with immunomodulating agents and biologics
- Risk of venous thromboembolism in patients with COVID-19: A nationwide, population-based matched cohort study
- Impact of use of proton pump inhibitors on susceptibility to infection and risk of severe outcomes in patients with COVID-19
- + two papers published describing the governance and the database

For details see: www.lmst.dk/DACCOVID

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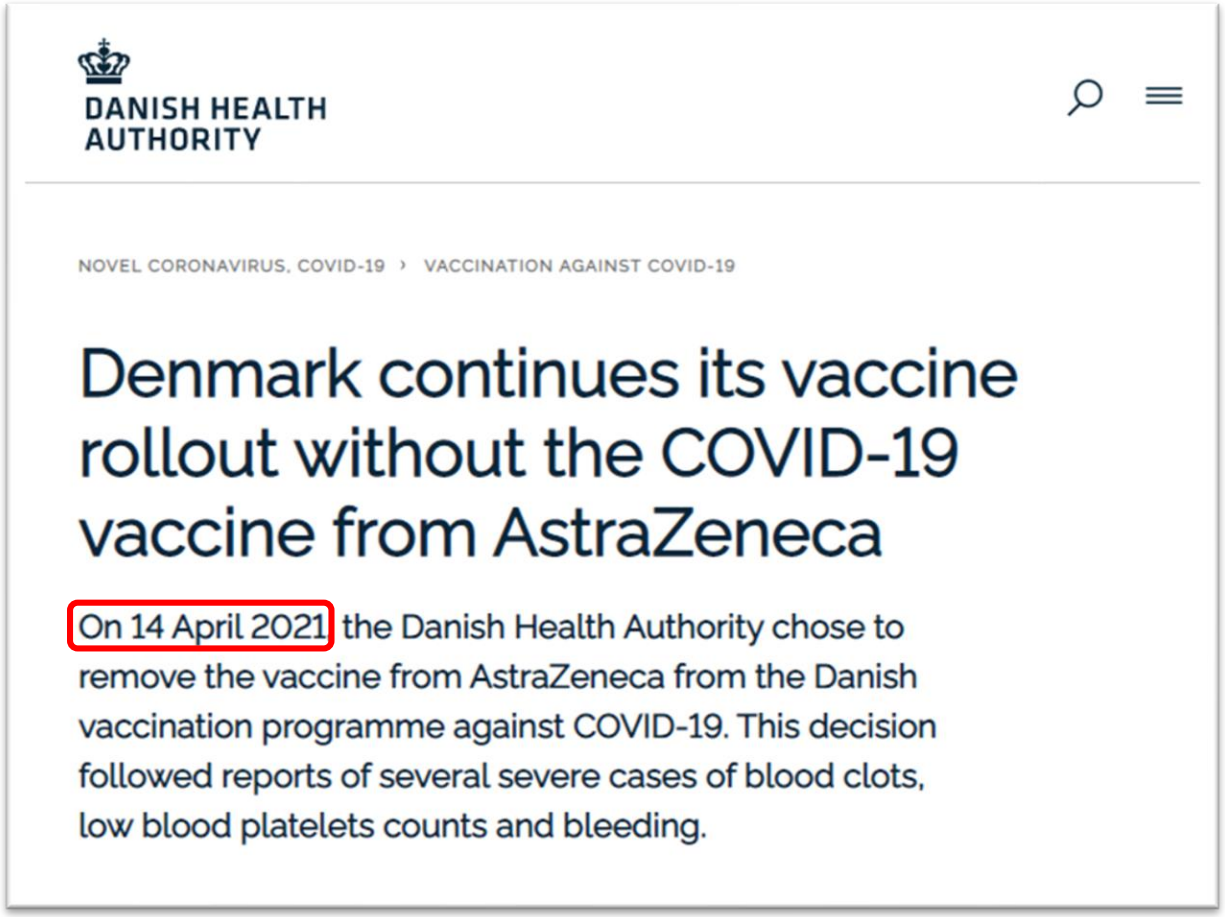
Real time surveillance of COVID19 cross-vaccination

AZ-vaccine is removed from the Danish vaccination program



DANISH HEALTH AUTHORITY

NOVEL CORONAVIRUS, COVID-19 › VACCINATION AGAINST COVID-19

Denmark continues its vaccine rollout without the COVID-19 vaccine from AstraZeneca

On 14 April 2021 the Danish Health Authority chose to remove the vaccine from AstraZeneca from the Danish vaccination programme against COVID-19. This decision followed reports of several severe cases of blood clots, low blood platelets counts and bleeding.

https://www.sst.dk/en/english/corona-eng/vaccination-against-covid-19/astrazeneca-vaccine-paused

*"During **early to mid-March 2021**, vaccination against covid-19 with the Oxford-AstraZeneca vaccine ChAdOx1-S was **paused in several European countries** because of **spontaneous reports** of **severe and sometimes fatal thromboembolic** events among vaccinated people.*

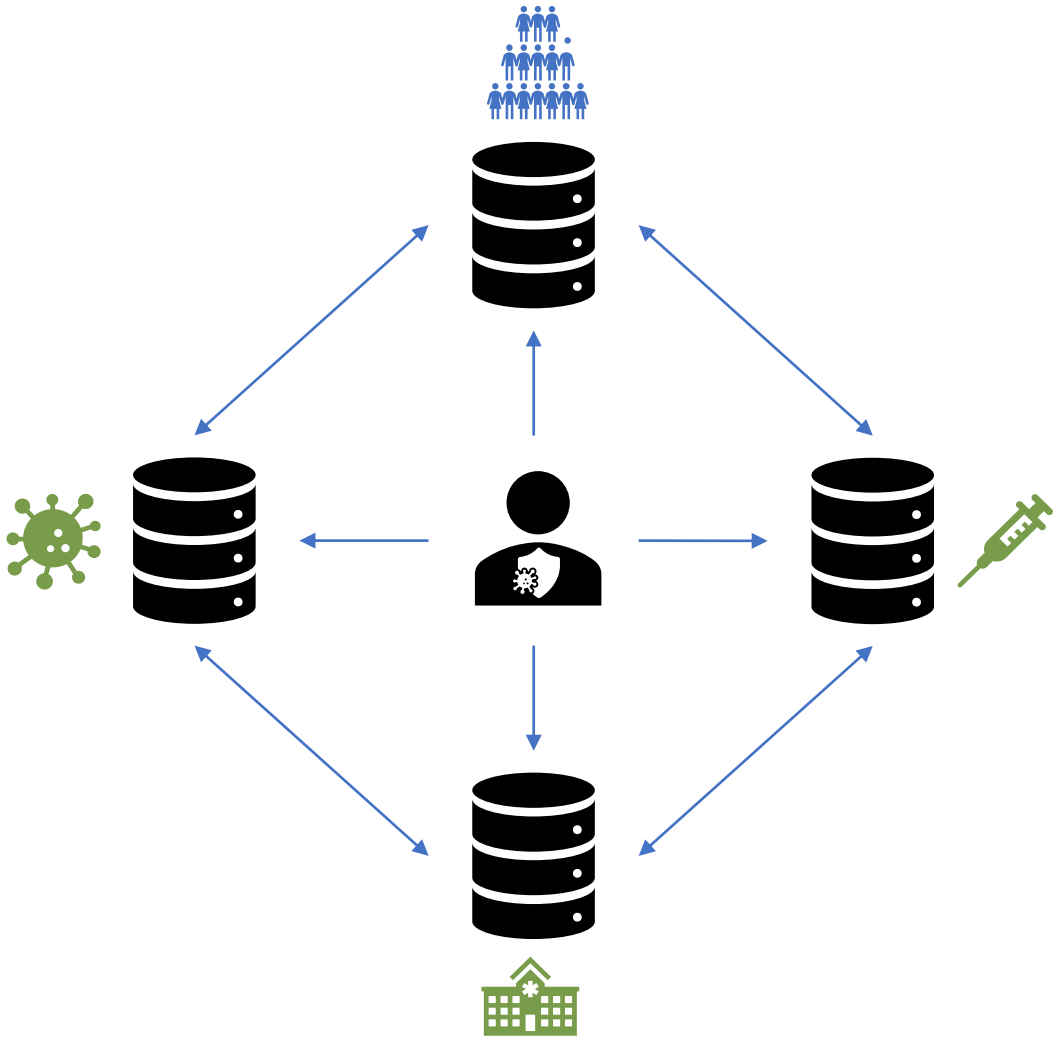
*According to a statement from the European Medicines Agency, **30 cases** of predominantly venous thromboembolic events had been reported by 10 March 2021 among the approximately five million recipients of ChAdOx1-S in Europe at the time."**

The Danish Health Authority decides to complete the vaccination with a mRNA-vaccine, If you have received 1. vaccination with the AstraZeneca-vaccine

Off label use

*Pottegård et al: Arterial events, venous thromboembolism, thrombocytopenia, and bleeding after vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: population based cohort study. BMJ. 2021; 373: n1114. Published online **2021 May 6**. doi: 10.1136/bmj.n1114

Cross-vaccine real time monitoring - Danish data sources



Central person registry

- Person identifier, age gender, civil status, emigration, death

Microbiology Database

- Test results from microbiological departments

Danish Vaccination Registry

- Vaccination status and vaccination dates

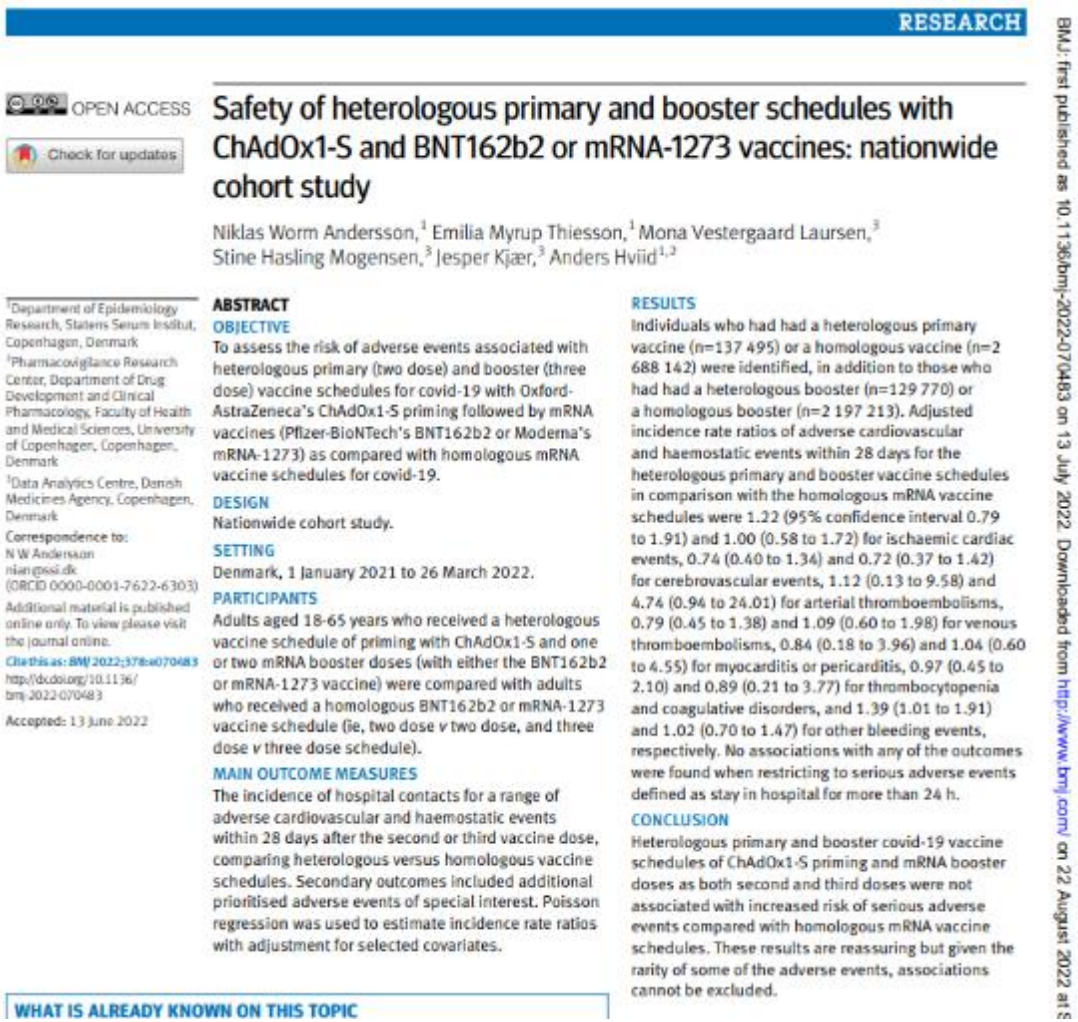
National Patient Registry

- Contacts and admissions to hospital, diagnoses, examinations, treatments

Monitoring off-label cross vaccination in Danish cohort

- **Objective:** Monitor effect and side effects of **off label use** of cross vaccinations between AstraZeneca and mRNA vaccines
- **Design:** Cohort study, interim assesments at 10, 25, 50 and 75% cross vaccinated
- **Setting:** Nationwide Danish healthcare registers
- **Participants:**
  I. All people receiving 1. vaccination with Astrazeneca vaccine, excl. death, emigration and SARS-CoV-2 positive test (N~140.000)
  II. A comparativ cohort of people receiving 1. and 2. vaccination with Pfizer-vaccine

Cross-vaccine real time monitoring – publication



RESEARCH

OPEN ACCESS

Check for updates

Safety of heterologous primary and booster schedules with ChAdOx1-S and BNT162b2 or mRNA-1273 vaccines: nationwide cohort study

Niklas Worm Andersson,[1] Emilia Myrup Thiesson,[1] Mona Vestergaard Laursen,[3] Stine Hasling Mogensen,[3] Jesper Kjær,[3] Anders Hviid[1,2]

[1]Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark
[2]Pharmacovigilance Research Center, Department of Drug Development and Clinical Pharmacology, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[3]Data Analytics Centre, Danish Medicines Agency, Copenhagen, Denmark
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Additional material is published online only. To view please visit the journal online.

Cite this as: BMJ 2022;378:e070483
http://dx.doi.org/10.1136/bmj-2022-070483
Accepted: 13 June 2022

ABSTRACT

OBJECTIVE
To assess the risk of adverse events associated with heterologous primary (two dose) and booster (three dose) vaccine schedules for covid-19 with Oxford-AstraZeneca's ChAdOx1-S priming followed by mRNA vaccines (Pfizer-BioNTech's BNT162b2 or Moderna's mRNA-1273) as compared with homologous mRNA vaccine schedules for covid-19.

DESIGN
Nationwide cohort study.

SETTING
Denmark, 1 January 2021 to 26 March 2022.

PARTICIPANTS
Adults aged 18-65 years who received a heterologous vaccine schedule of priming with ChAdOx1-S and one or two mRNA booster doses (with either the BNT162b2 or mRNA-1273 vaccine) were compared with adults who received a homologous BNT162b2 or mRNA-1273 vaccine schedule (ie, two dose *v* two dose, and three dose *v* three dose schedule).

MAIN OUTCOME MEASURES
The incidence of hospital contacts for a range of adverse cardiovascular and haemostatic events within 28 days after the second or third vaccine dose, comparing heterologous versus homologous vaccine schedules. Secondary outcomes included additional prioritised adverse events of special interest. Poisson regression was used to estimate incidence rate ratios with adjustment for selected covariates.

RESULTS
Individuals who had had a heterologous primary vaccine (n=137 495) or a homologous vaccine (n=2 688 142) were identified, in addition to those who had had a heterologous booster (n=129 770) or a homologous booster (n=2 197 213). Adjusted incidence rate ratios of adverse cardiovascular and haemostatic events within 28 days for the heterologous primary and booster vaccine schedules in comparison with the homologous mRNA vaccine schedules were 1.22 (95% confidence interval 0.79 to 1.91) and 1.00 (0.58 to 1.72) for ischaemic cardiac events, 0.74 (0.40 to 1.34) and 0.72 (0.37 to 1.42) for cerebrovascular events, 1.12 (0.13 to 9.58) and 4.74 (0.94 to 24.01) for arterial thromboembolisms, 0.79 (0.45 to 1.38) and 1.09 (0.60 to 1.98) for venous thromboembolisms, 0.84 (0.18 to 3.96) and 1.04 (0.60 to 4.55) for myocarditis or pericarditis, 0.97 (0.45 to 2.10) and 0.89 (0.21 to 3.77) for thrombocytopenia and coagulative disorders, and 1.39 (1.01 to 1.91) and 1.02 (0.70 to 1.47) for other bleeding events, respectively. No associations with any of the outcomes were found when restricting to serious adverse events defined as stay in hospital for more than 24 h.

CONCLUSION
Heterologous primary and booster covid-19 vaccine schedules of ChAdOx1-S priming and mRNA booster doses as both second and third doses were not associated with increased risk of serious adverse events compared with homologous mRNA vaccine schedules. These results are reassuring but given the rarity of some of the adverse events, associations cannot be excluded.

WHAT IS ALREADY KNOWN ON THIS TOPIC

CONCLUSION

Heterologous primary and booster covid-19 vaccine schedules of ChAdOx1-S priming and mRNA booster doses as both second and third doses were not associated with increased risk of serious adverse events compared with homologous mRNA vaccine schedules. These results are reassuring but given the rarity of some of the adverse events, associations cannot be excluded.

Andersson et al: Safety of heterologous primary and booster schedules with ChAdOx1-S and BNT162b2 or mRNA-1273 vaccines: a nationwide cohort study. BMJ

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Temporary state

COVID19 vaccine surveillance

- side effect reports combined with national registries

2020-2023

Current state

Existing regulatory process

- Traditional surveillance of side effects

2020

Danish Medines Agencys procedure for routine surveillance of side effects

Data reporting:

meldenbivirkning.dk

Via med rec

Eudravigilance

Side effects

Signalanalysis

DKMA in collab. with Health Data Authority and Statens Serum Institure

Onboarding of national registries to analysis-platform

Combining side effect reports vaccination and other nationale registries

Side effects

Patient reg.

Vaccine reg

Citizen reg.

Chronic reg

Surveillance of vaccines via dataanalysis.

PHAIR

Pharmacovigilance by AI Real-time Analysis

Denmark

40.000 serious adverse drug reactions

2.000 deaths

Only 0,1-1% are reported to the authorities

1937 Sulfanilamide

Food and Drug Administration (FDA)

1961 Thalidomide

Spontaneous reporting

1987 Thorotrast

2005 Vioxx

2015 HPV vaccine

2021 COVID-19 vaccines

PHAIR

PARTICIPANTS

Methodology	Infrastructure	Scientific expertise	Patients' perspective	Regulatory usage	Data access
Department of Computer Science (DIKU)	Trifork	Statens Serum Institut	Danish Patients	Danish Medicines Agency's Data Analysis Centre (DAC)	Danish Regions(DR)
		Department of Clinical Pharmacology, Bispebjerg Hospital	IFRO (KU)		Danish Health data Agency
		Department of Public Health, University of Southern Denmark			PLO

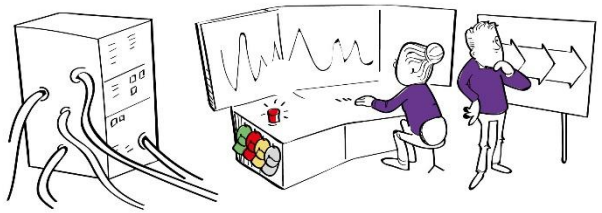
- Public Institution
- Academia
- Patient representative
- Private company

Pharmacovigilance of tomorrow

PHAIR - Pharmacovigilance by AI Real-time Analyses

Fuel with relevant data → Apply AI → Automate Pipeline → Enable near-real time surveillance → **Signaling** and **Hypotheses** generation

- Private medical practitioners EHR
- Hospital EHR
- National Health Registers

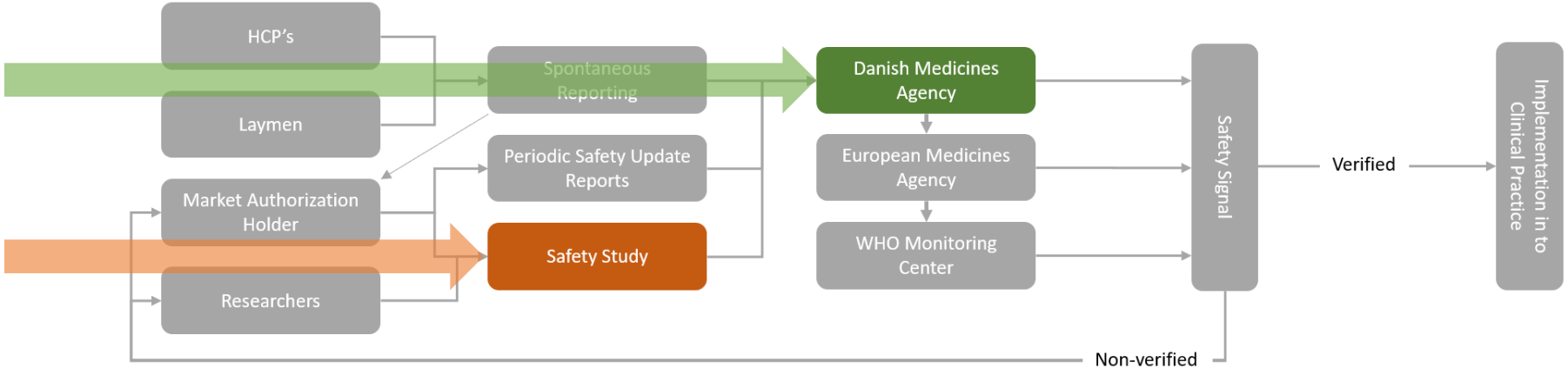


ACCELERATE PROCESS

Reporting actors → Reporting channels and triggers → Regulatory capture and processing → Signaling → Implementation

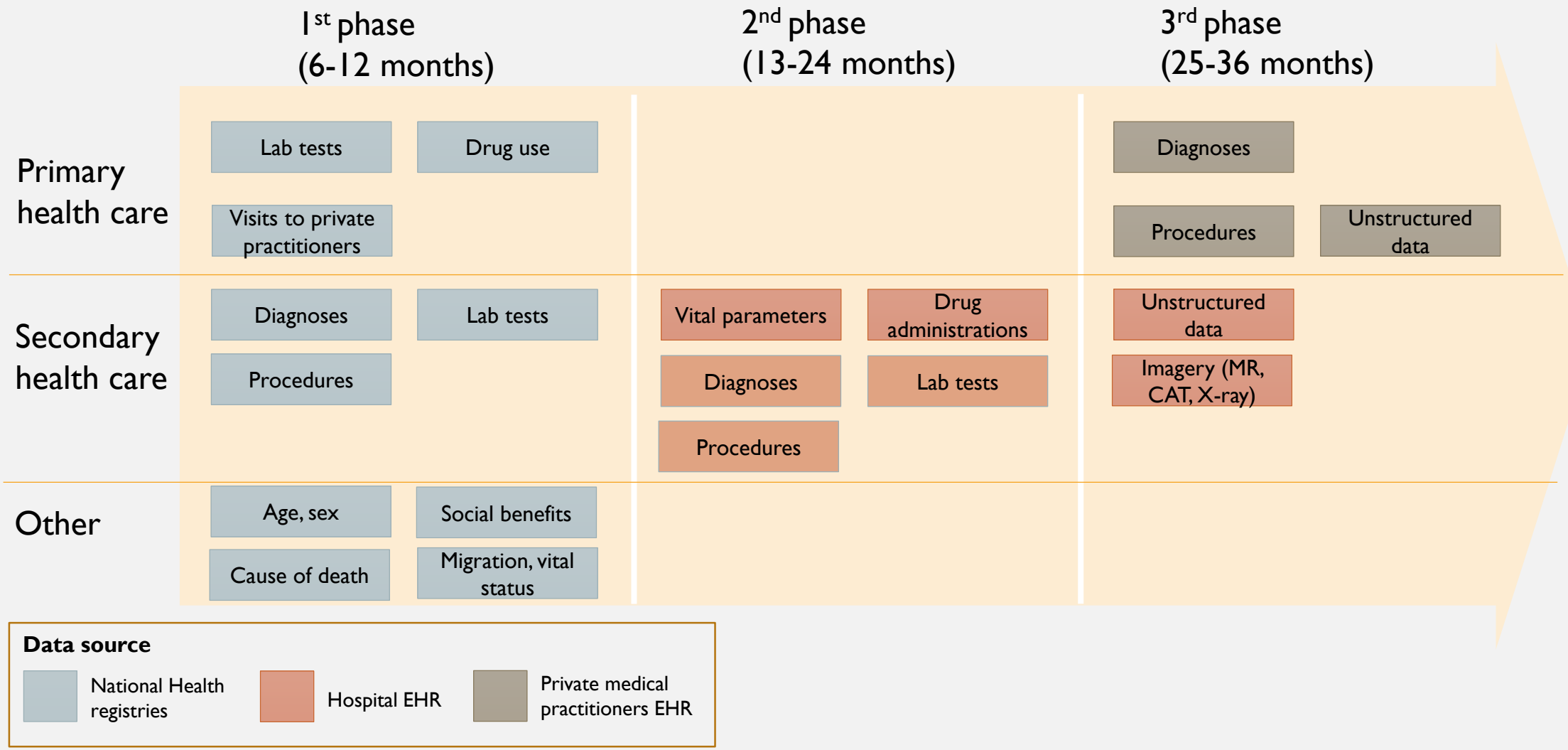
Safety signals

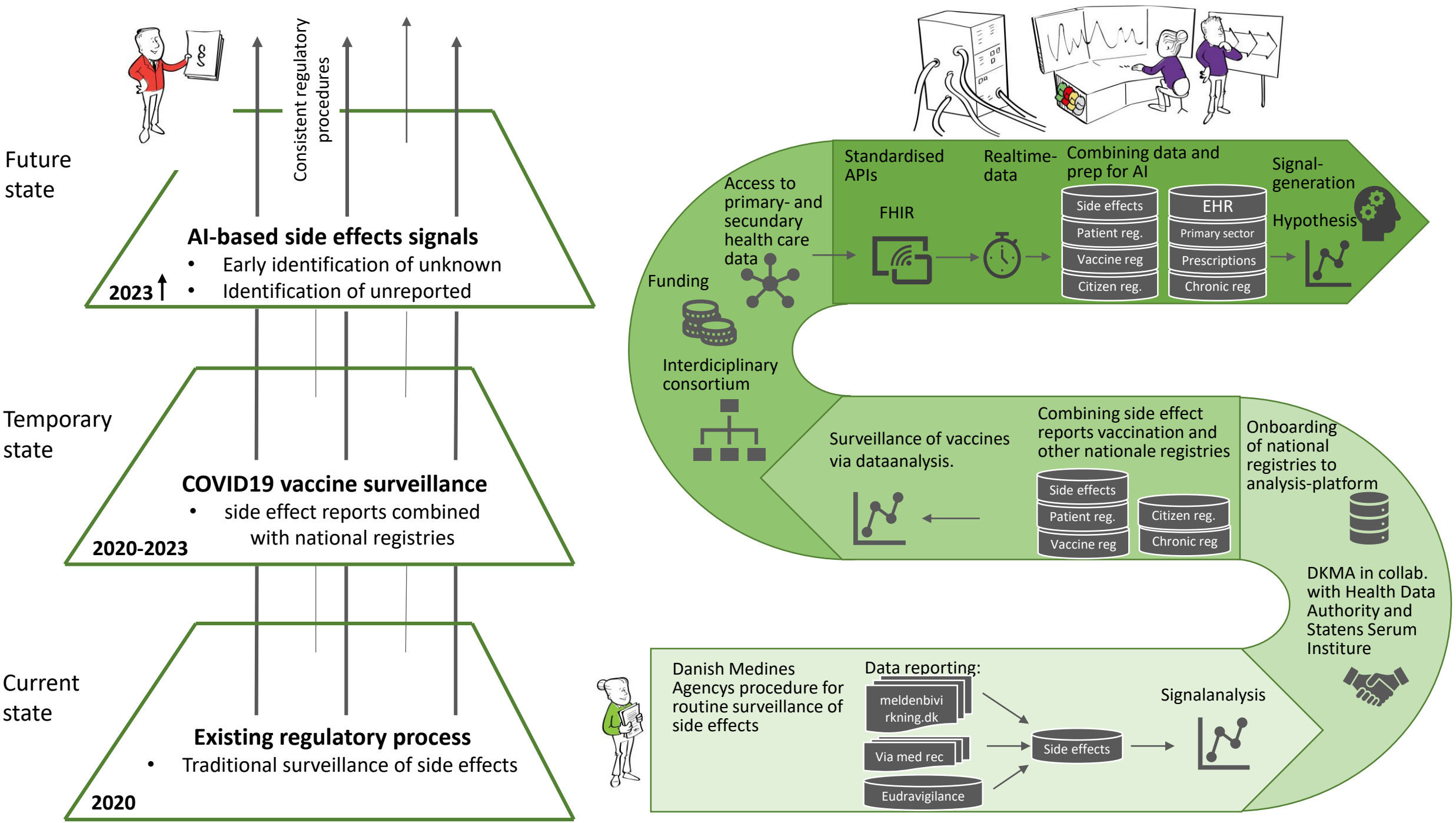
Hypotheses



DATA ROADMAP

AGILE ITERATIVE APPROACH TO INCLUDE MORE AND MORE DATA AND TECHNOLOGY WHILE KEEPING RISK MINIMAL




Future state
Consistent regulatory procedures
AI-based side effects signals
• Early identification of unknown
• Identification of unreported
2023
Temporary state
COVID19 vaccine surveillance
• side effect reports combined with national registries
2020-2023
Current state
Existing regulatory process
• Traditional surveillance of side effects
2020
Standardised APIs
Realtime-data
Combining data and prep for AI
Signal-generation
Access to primary- and secundary health care data
FHIR
Side effects
Patient reg.
Vaccine reg
Citizen reg.
EHR
Primary sector
Prescriptions
Chronic reg
Hypothesis
Funding
Interdiciplinary consortium
Surveillance of vaccines via dataanalysis.
Combining side effect reports vaccination and other nationale registries
Side effects
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Onboarding of national registries to analysis-platform
DKMA in collab. with Health Data Authority and Statens Serum Institure
Danish Medines Agencys procedure for routine surveillance of side effects
Data reporting:
meldenbivirkning.dk
Via med rec
Eudravigilance
Side effects
Signalanalysis

International regulatory collaboration

Real world data for regulatory use

Comparative effectiveness of heterologous and homologous primary- and booster SARS-CoV-2 vaccination schedules in the Nordic countries

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 December 2021
EMA/736228/2021
Data Analytics and Methods

Technical specifications - Invitation to tender

Re-opening of competition no. 07 under the framework contracts following procurement procedure EMA/2020/46/TDA, Lot 5: Pharmacoepidemiological research

Effectiveness of heterologous and booster COVID-19 vaccination in Europe

- Nationwide register-data from Denmark, Finland, Norway and Sweden covering 22 million citizens
- Individual-level information on dates of vaccination and dates of endpoints together with relevant covariate information.
- All Nordic residents are assigned a unique personal identifier at birth or immigration, enabling unambiguous linkage between registers.
- The registers are updated daily to weekly.

https://www.encepp.eu/encepp/viewResource.htm?id=46880

Comparative effectiveness of heterologous and homologous primary- and booster SARS-CoV-2 vaccination schedules in the Nordic countries

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

259. Getting Prepared for COVID-19 Vaccines: How European Regulators Anticipated the Need for Real-World Evidence [1304]

Catherine Cohet[1], Marcia Rueckbeil[1], Kelly Plueschke[1], Kate Browne[2], Thomas Goedecke[2], Robert Flynn[1], Karin Hedenmalm[1], Chantal (
Mathijs Goossens[1], Gianmario Candore[1], Peter Arlett[1], Xavier Kurz[1]
[1]Data Analytics and Methods Task Force, [2]Pharmacovigilance Office; European Medicines Agency, Amsterdam, The Netherlands

Background & Objective

- **Preparedness** initiated by EU regulators at the start of the pandemic, despite uncertainty on timing of availability of COVID-19 vaccines
- During vaccination campaigns: use of EMA **framework contracts** with large research organisations/consortia to tender studies, complementing monitoring by vaccine developers and by Member States
- Real-world evidence generation activities:
  - **Safety:** signal strengthening/evaluation
  - **Effectiveness:** contextualisation of the safety evidence
- Objective: to draw methodological and operational **lessons learned**, based on **selected** EMA-funded **studies**

Key Messages

- Public health emergency **preparedness** is **essential** to develop a framework for agile vaccine monitoring, able to adapt to a changing environment
- By leveraging pharmacoepidemiological expertise and access to several data sources by large organisations, **EMA-funded studies** have contributed to the collective evidence on the benefit-risk of COVID-19 vaccines
- Generation of forefront of E activities
- Effectiveness EMA's extend research und Union support impact of vac
- Future health from DARWI evidence gene operational in conducting st

Example of Effectiveness Study: Heterologous and Homologous Primary and Booster vaccination

- Nationwide register-based cohort study (DK, FI, NO, SE) – period: 27/12/2020 to 28/02/2022 - endpoints: documented infection and severe outcomes

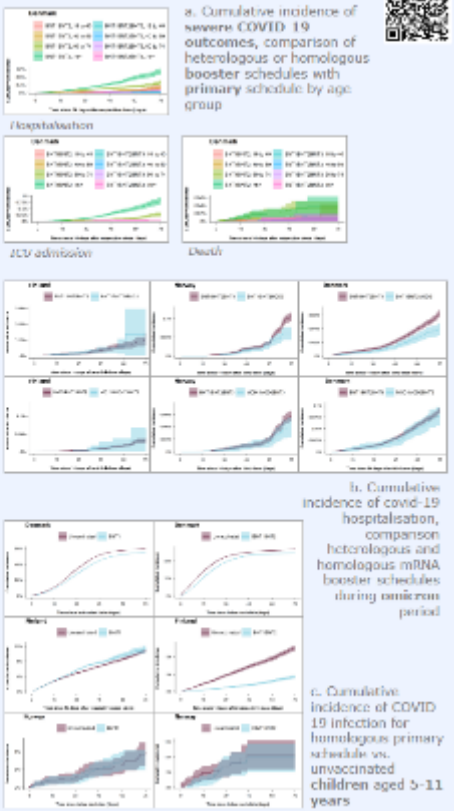
Findings

- **Comparable** effectiveness of **heterologous primary** and **booster** schedules, and **homologous** schedules (Fig. a)
- **Omicron** period: improved protection with heterologous booster, mostly against severe outcomes, vs. primary schedules (Fig. b)
- **Waning immunity** against infection comparable for homologous/heterologous schedules (180-day follow-up)
- Findings confirmed by test-negative case-control analyses
- Early evidence of high effectiveness in **children** (Fig. c), incl. for severe outcomes

Impact

- High-quality nationwide registers (including RT-PCR and vaccination data) linked by unique identifier resulted in valid data representing the 4 Nordic countries
- Data on effectiveness of heterologous booster regimens against **omicron** and data in **children** address current evidence gaps

Selected results



Study plan	10-03-2022
Study Protocol	31-03-2022
Study report	30-06-2022
Manuscript(s)	25-07-2022

https://www.encepp.eu/encepp/viewResource.htm?id=48758
→ New project: Advancing vaccine safety in childhood: current COVID-19 safety concerns and enhancing future surveillance

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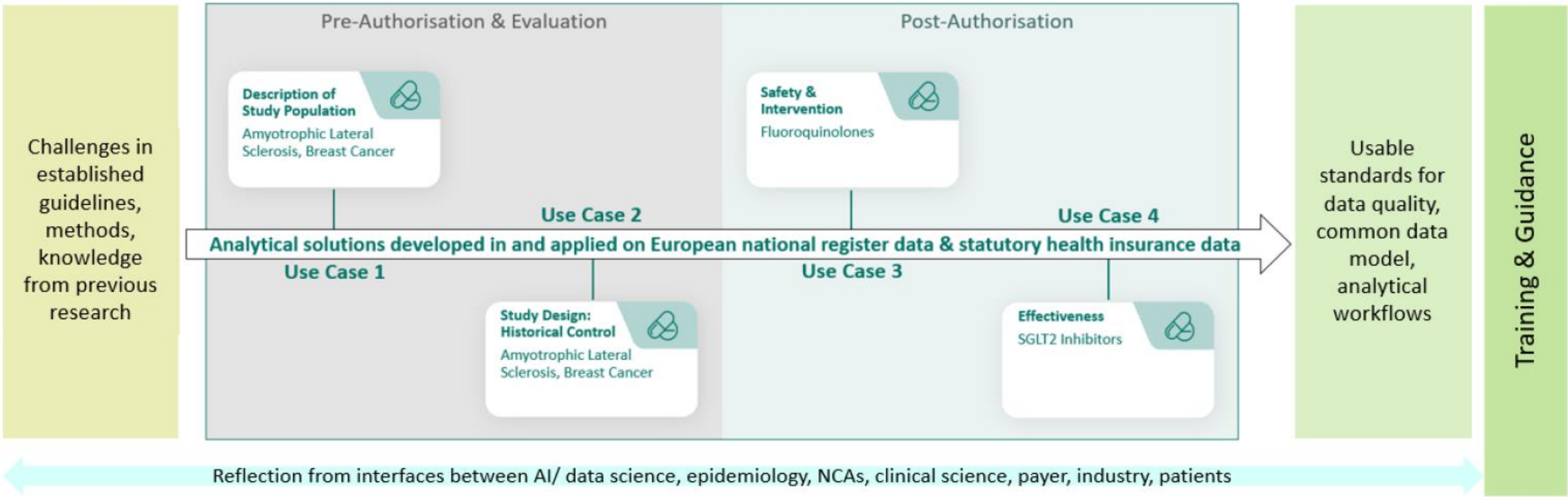
Real4Reg project team

Proposer name	Country
BUNDESINSTITUT FUR ARZNEIMITTEL UND MEDIZINPRODUKTE	DE
ITA-SUOMEN YLIOPISTO	FI
INFARMED - AUTORIDADE NACIONAL DO MEDICAMENTO E PRODUTOS DA SAUDE IP	PT
FRAUNHOFER GESELLSCHAFT ZUR FORDERUNG DER ANGEWANDTEN FORSCHUNG EV	DE
LAEGEMIDDELSTYRELSEN	DK
AARHUS UNIVERSITET	DK
CSC-TIETEEN TIETOTEKNIIKAN KESKUS OY	FI
DEUTSCHES ZENTRUM FUR NEURODEGENERATIVE ERKRANKUNGEN EV	DE
Europese vereniging voor professionals en patiënten met ALS (EUpALS)	BE
EUROPEAN INSTITUTE OF WOMEN'S HEALTH COMPANY LIMITED BY GUARANTEE	IE

Real4Reg – EU Horizon Europe project



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Conclusions

- Drugs must be authorised as effectively as possible
- There will always exist side effects real world situations not uncovered during clinical trials
- The current process does not make efficient use of
  - Real world data
  - Computing power
  - Algorithmic advances in analysing large amounts of data
- We are at a stage where we are ready to combine the domains of
  - Computer science
  - Pharmacoepidemiology
  - Rich real world data

to ensure the safety of the citizens