EHDEN

EUROPEAN HEALTH DATA & EVIDENCE NETWORK

Using Federated Networks to Generate RWE: Why Not Now?

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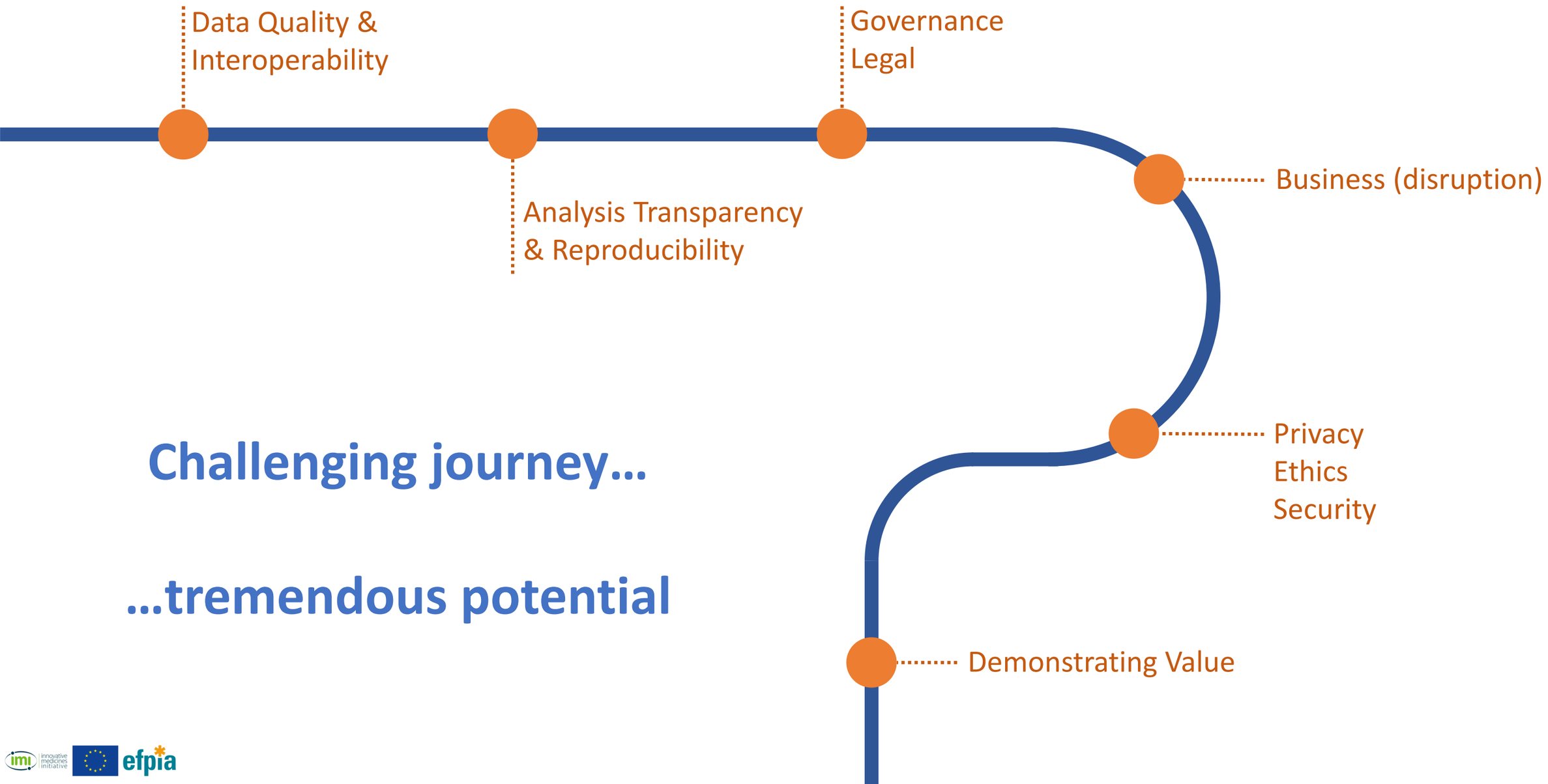
imi innovative medicines initiative

efpia

The presenter declares no conflicts of interest. Views expressed are not those of the presenter's employer or the European Commission

Real World Research is a Challenging Journey



Challenging journey…

…tremendous potential

THE JOURNEY TO REAL WORLD EVIDENCE

Reproducible data flow

Documented manipulations and procedures.

Automated, end-to-end analysis code.

Common Data Model & standardised vocabulary

Two-step process: standardisation before analysis.

ETL & source code separated from analysis.

Re-use of data & analysis.

EHDEN CONSORTIUM

Start date: 1 Nov 2018
End date: 30 Apr 2024
Duration: 66 months

23 partners

Almost €29 million

Universities, public bodies and research organisations

Erasmus MC Universitair Medisch Centrum Rotterdam — **Academic coordinator**

Uppsala Monitoring Centre

universidade de aveiro

NICE National Institute for Health and Care Excellence

Tartu Ülikool 1632 Universitas Tartuensis

University of Oxford

SME & Mid-sized companies

SYNAPSE Research Management Partners

ODYSSEUS Data Services Inc

thehyve

Non-profit organisations

EPF European Patients Forum

ICHOM

EFPIA & Associated partners

Janssen Pharmaceutical Companies of Johnson & Johnson — **EFPIA Lead**

Bayer

Celgene

Pfizer

Lilly

abbvie

AstraZeneca

Boehringer Ingelheim

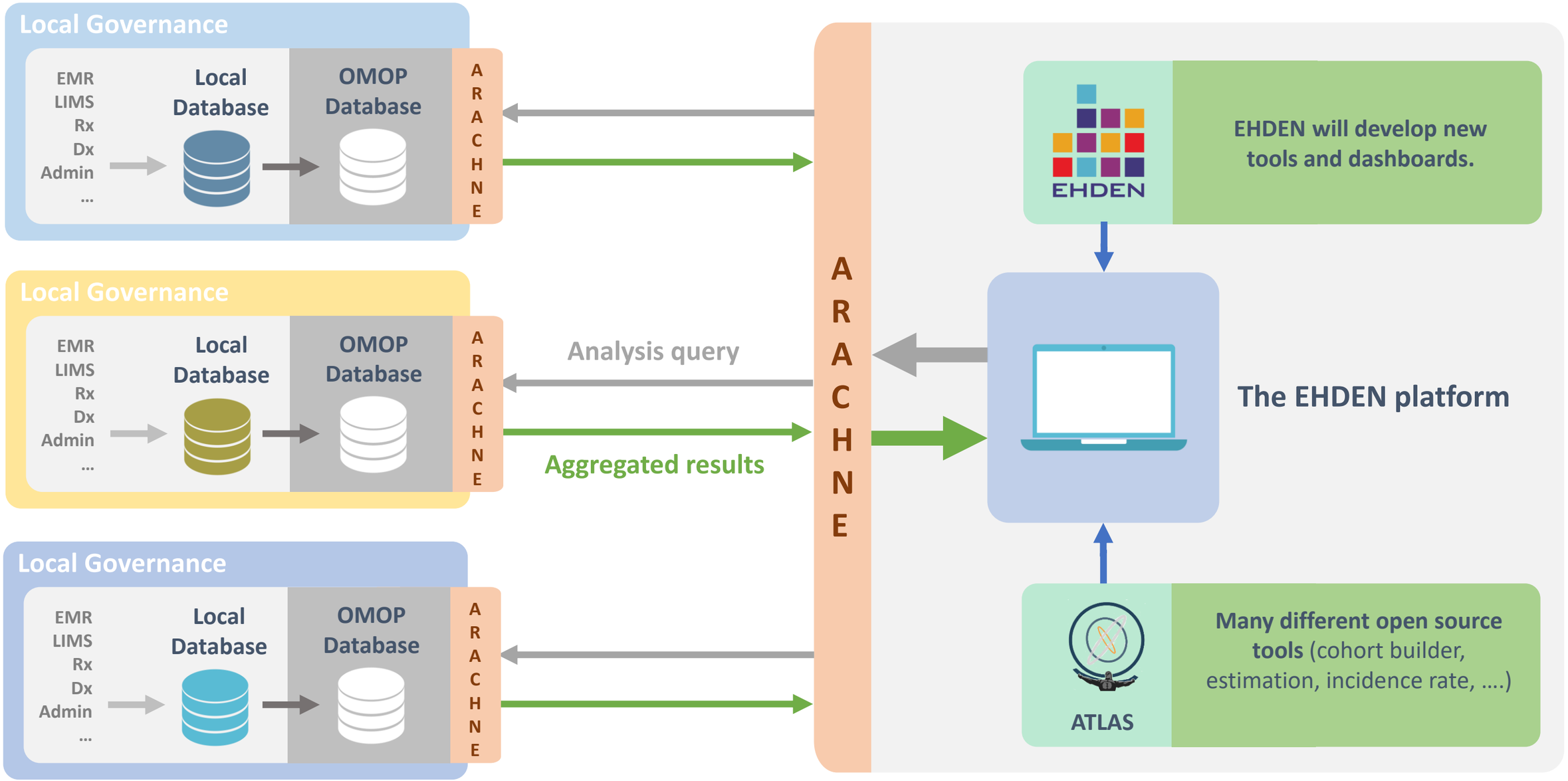
Sanofi

UCB

Novartis

Servier

The EHDEN Federated Data Network



Benefits of a Federated Data Network

- Data remains under the **control** of the data owner.
- Locally required **legal** and **ethical** approvals apply.
- No patient-level data leaves the owner's site; only aggregated counts, thereby ensuring patient **privacy.**
- **GDPR** – *'Privacy by Design'.*
- **Analysis** is "brought to the data" rather than creating a central data repository.
- Use of **common data model** allows for efficient search/analysis across multiple data sets.
- Requires close **collaboration** with data owners, which builds **trust**.

On the other Hand

Trusted Research Environments/Data lakes

- Allow individual patient level data analysis
- Avoiding potential loss of information in the mapping process
- Linkage of databases and pooling of data from different sources

Today's Panel

Prof. Daniel Prieto-Alhambera
Prof. of Device and Pharmaco-epidemiology
University of Oxford, UK

Dr Alex Asiimwe
Head of Open Innovation Partnerships
Bayer AG,
Berlin, Germany

Dr Alan Lamb
Scientific Adviser
NICE, UK

Using Federated Networks to generate RWE

Why not now?

Dani Prieto-Alhambra, MD PhD
Prof of Pharmaco-epidemiology
Oxford University

AGENDA

- Why RWD and Open Science?
- The EHDEN-OHDSI COVID-19 experience
- Characterisation
- Causal inference

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Why RWE?


Systematic Reviews
Randomized Controlled Trials
Cohort Studies
Case-Control Studies
Case Series, Case Reports
Editorials, Expert Opinion

Why ‘real world’ data?
1.RCTs are not always possible …

Hazard

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

BMJ 2003

What this study adds

No randomised controlled trials of parachute use have been undertaken

The basis for parachute use is purely observational, and its apparent efficacy could potentially be explained by a “healthy cohort” effect

The medicalisation of free fall

It is often said that doctors are interfering monsters obsessed with disease and power, who will not be satisfied until they control every aspect of our lives (*Journal*

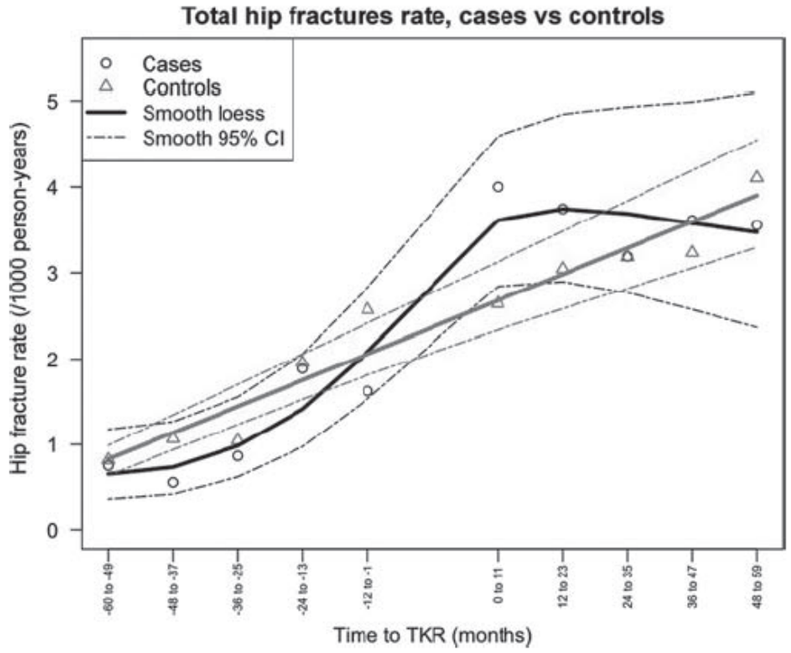
 # OF RCTs = 0

Why ‘real world’ data?

2.The data is out there … and this enables replication studies

Changes in hip fracture rate before and after total knee replacement due to osteoarthritis: a population-based cohort study

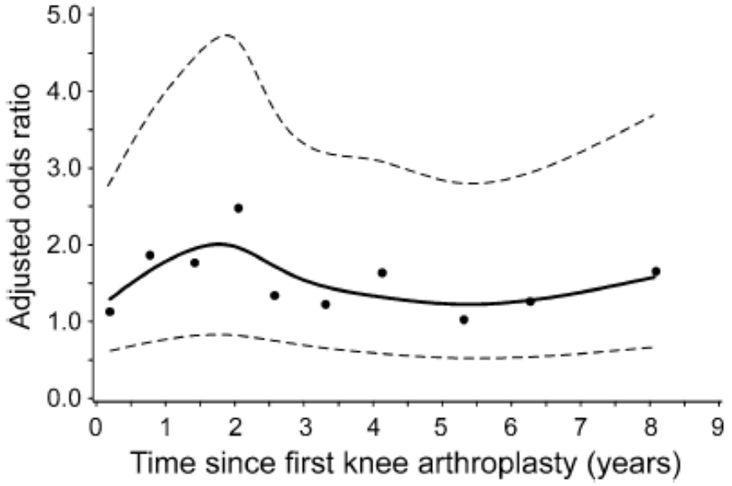
Daniel Prieto-Alhambra,[1–3] M Kassim Javaid,[1] Joe Maskell,[1,4] Andrew Judge,[1] Michael Nevitt,[5] Cyrus Cooper,[1,4] Nigel K Arden[1,4]



Prieto-Alhambra D et al. Ann Rheum Dis 2011

Knee Arthroplasty and Risk of Hip Fracture: A Population-Based, Case–Control Study

Arief Lalmohamed · Frans Opdam · Nigel K. Arden · Daniel Prieto-Alhambra · Tjeerd van Staa · Hubertus G. M. Leufkens · Frank de Vries



Prieto-Alhambra D et al. CTI 2012

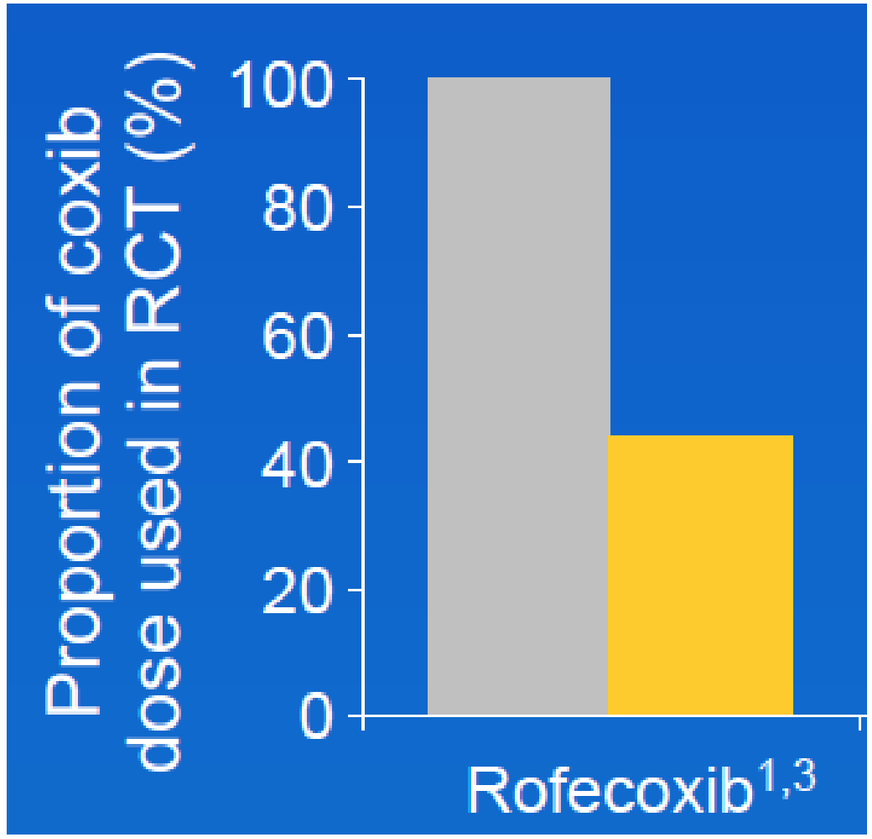
Why ‘real world’ data?
3.Generalizability

Table 1 Comparison of the exclusion criteria in the FIT trial with the incident users of alendronate in the SIDIAP and DHR database

FIT exclusion criteria[a]	Operational definition/ICD-10 Codes	Incident users of Alendronate[d]	
		SIDIAP $N = 14{,}316$ (%)	DHR $N = 21{,}214$ (%)
Men	Sex according to administrative data	3818 (26.7 %)	3885 (18.3 %)
Age <55 years old	Age at first ALD dispensation	1844 (12.9 %)	1654 (7.8 %)
Age >80 years old	Age at first ALD dispensation	2347 (16.4 %)	5275 (24.9 %)

C Reyes et al. Osteoporos Int 2014

Why ‘real world’ data?
4.Efficacy vs Effectiveness …



Adherence in RCT (Vigor study) vs “real life”

Rofecoxib users in CPRD

[TV Staa PLoS One ‘09]

5.Not saying always… but do not say NEVER

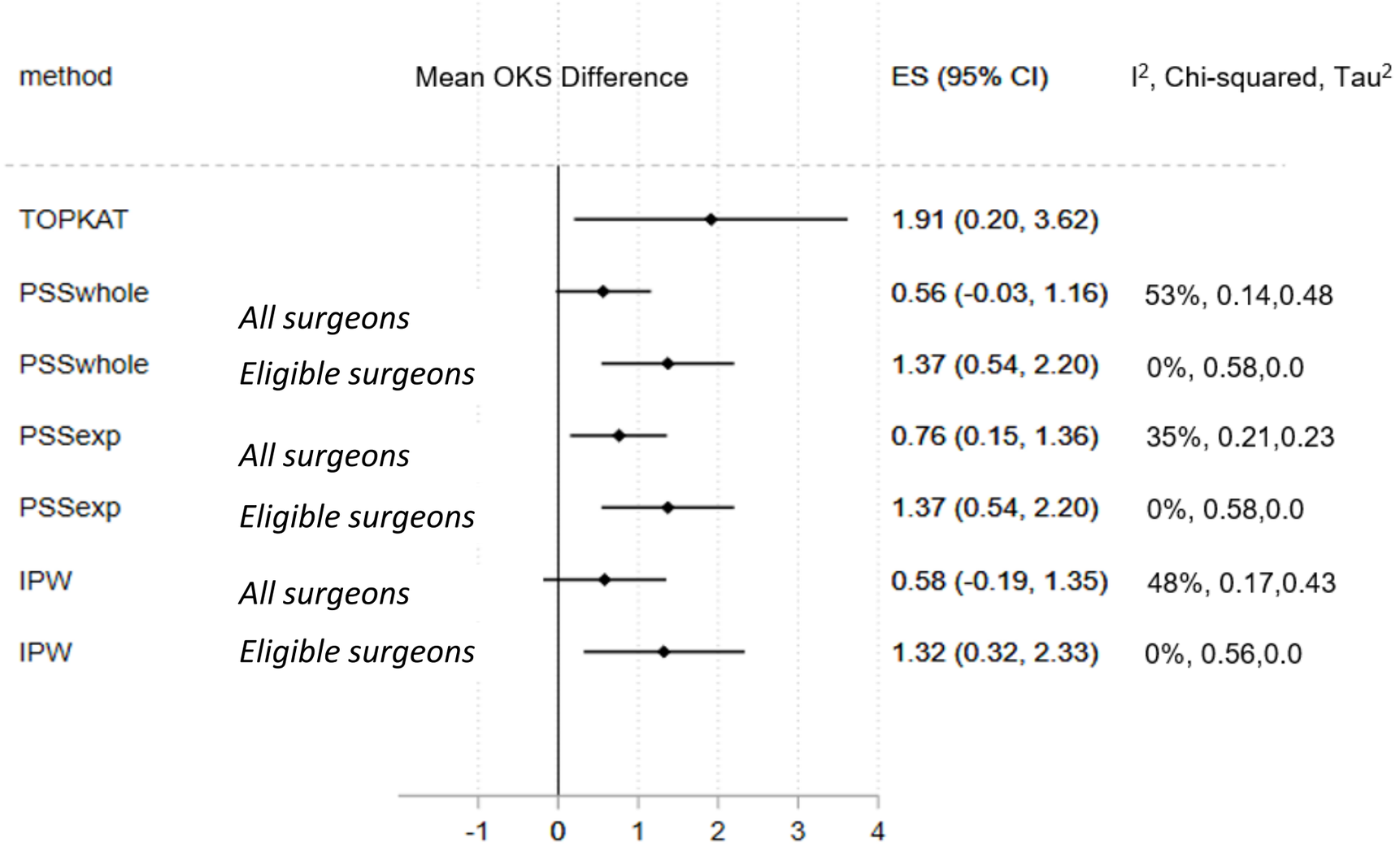
- RWE can replicate RCTs …
  - *When the right data is available*
  - *When the right expertise is in place*
  - *When the best methods (for a given RQ) are applied*

UTMoST
Risk-benefit and costs of unicompartmental knee replacement for patients with multiple co-morbidities
NIHR | National Institute for Health Research

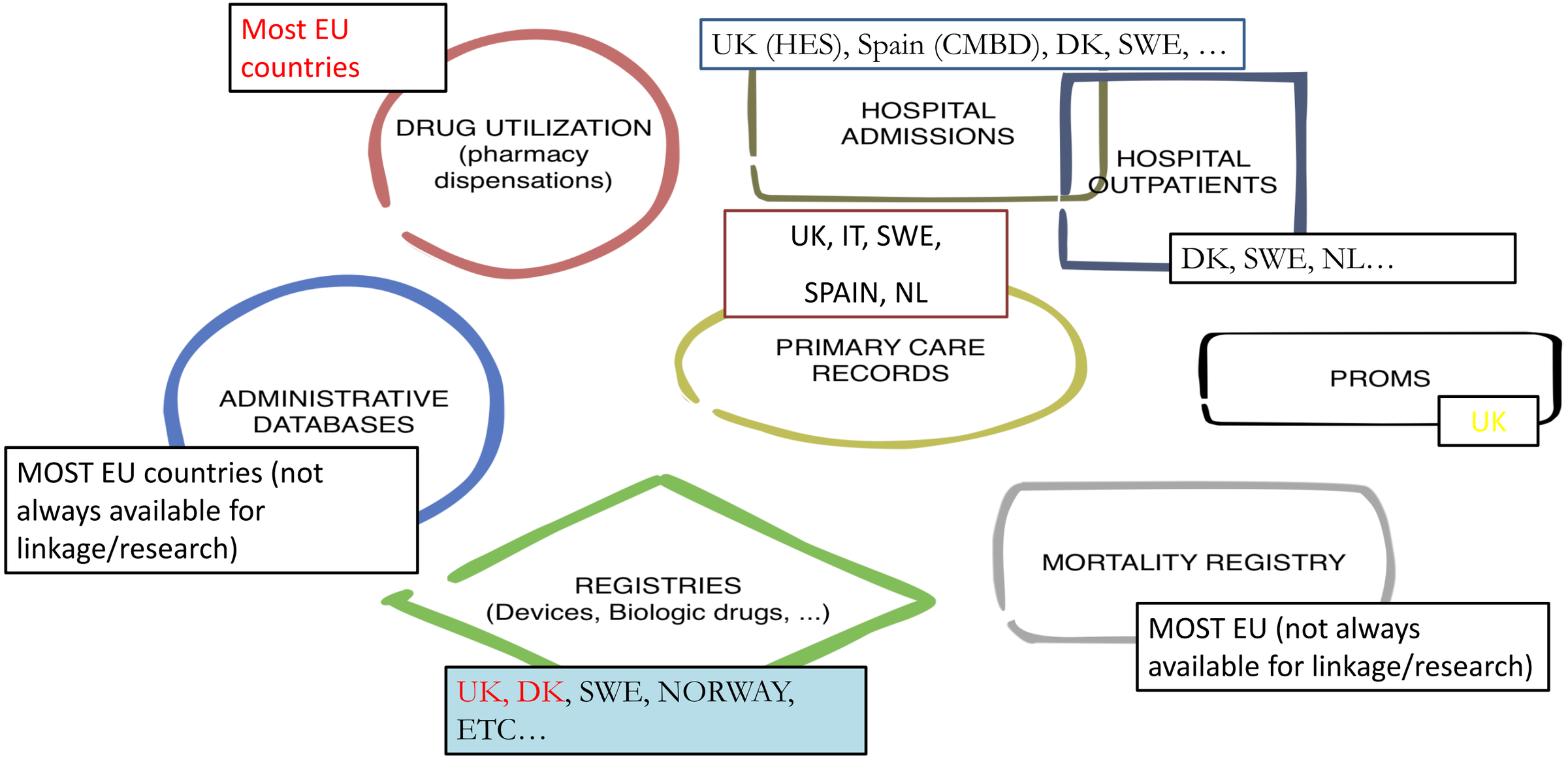
UTMOST

Risk-benefit and costs of unicompartmental (compared to total) knee replacement for patients with multiple co-morbidities: a non-randomised study, and different novel approaches to minimise confounding.

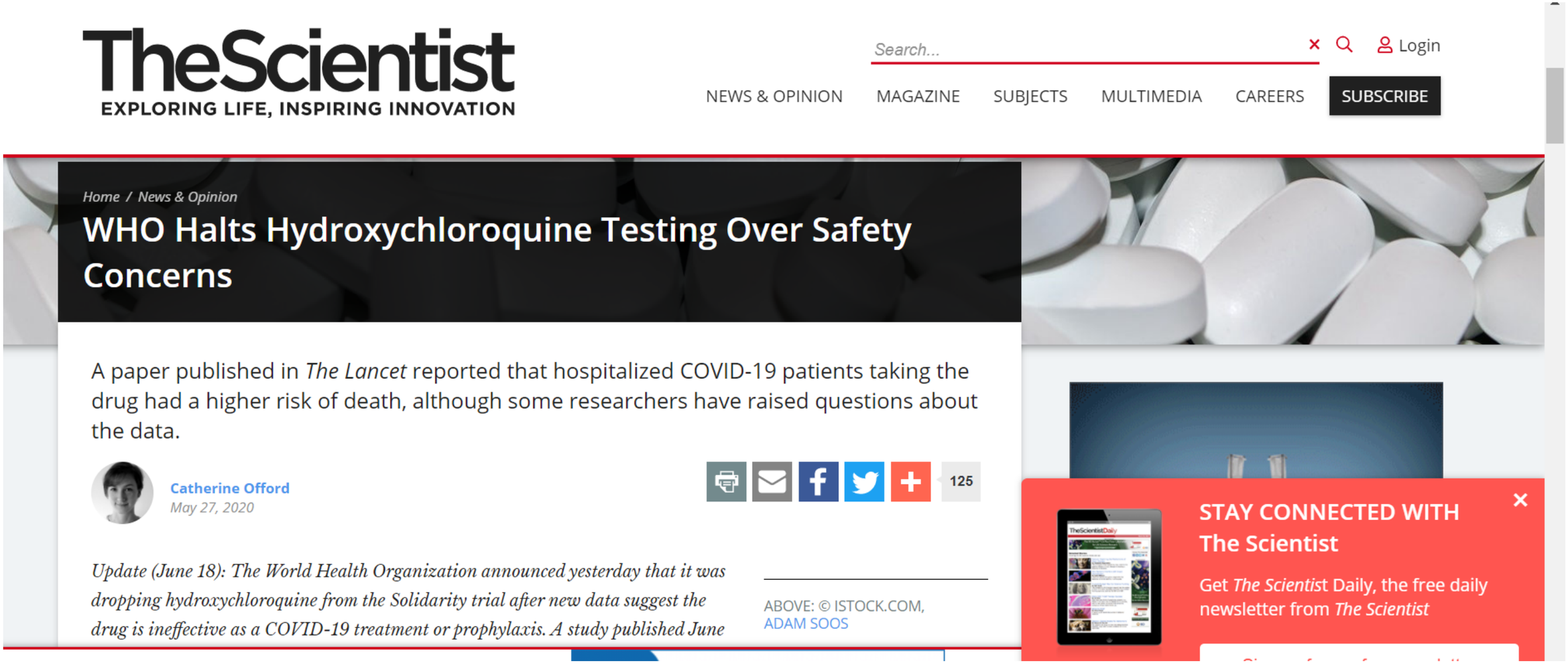
Propensity Score analyses vs TOPKAT (RCT)- OKS
Sensitivity analysis restricted to 'eligible' surgeons



THE EU: BREADTH OF DATA FOR RESEARCH



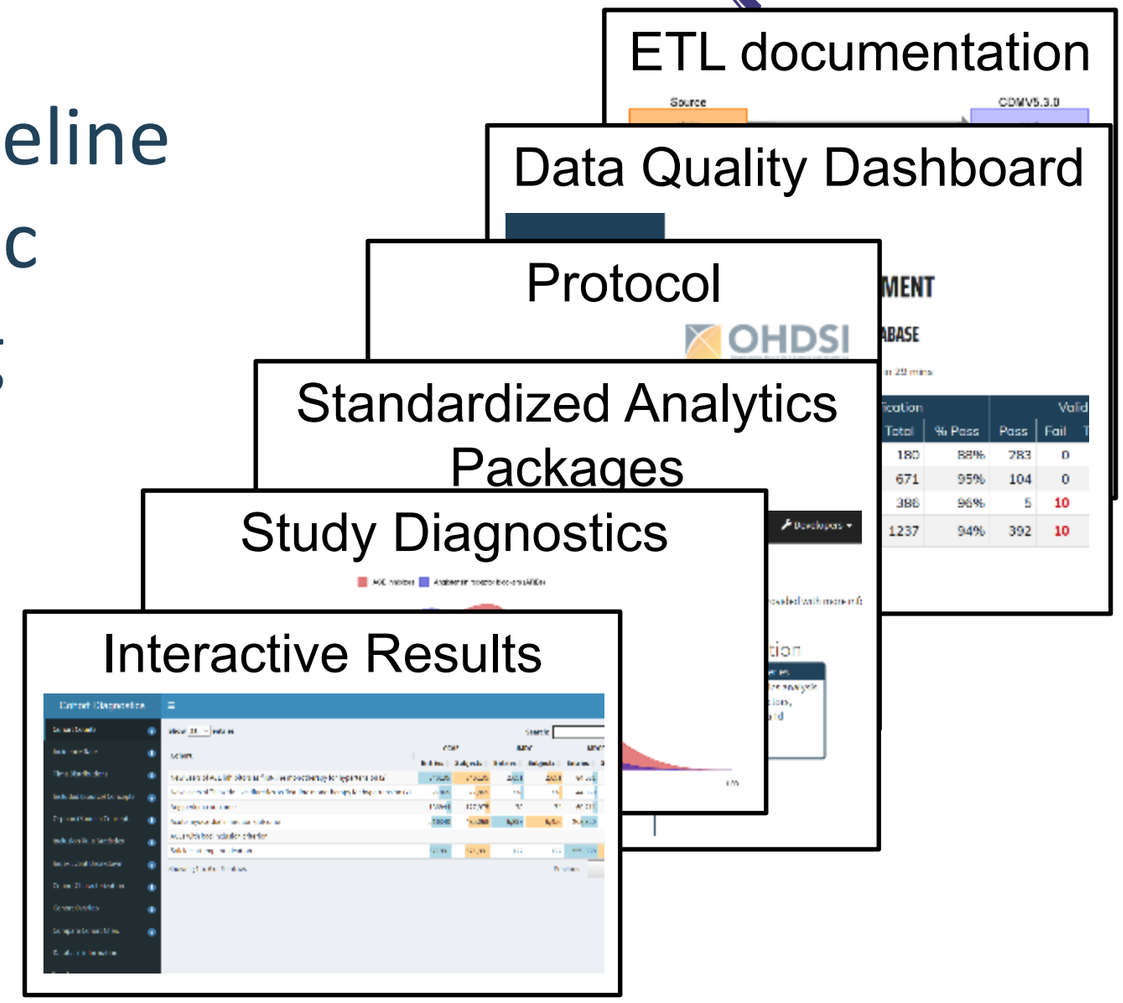
OPEN SCIENCE:
Not Only About The Data…



How can Open Science help?

- All artifacts of our analytics pipeline are made available to the public
- In doing so, we are encouraging others to do the same

- Transparency is key to
  - **Reproducibility**
  - **Interpretability**
  - **Trustworthiness**



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- The EHDEN-OHDSI COVID-19 experience
- Characterisation
- Causal inference

EHDEN
EUROPEAN HEALTH DATA & EVIDENCE NETWORK

What have we done?

In only **88** hours, we did:

- Convene **351** participants from **30** countries
- Hold **12** Global Huddles, **>100** collaborator calls, **>13,000** chat messages
- Engage **15** concurrent channels
- Review **>10,000** publications
- Draft **9** study protocols
- Release **13** study packages
- Design **355** cohort definitions
- Assemble a distributed data network with **37** partners signed on to execute studies

https://www.ohdsi.org/covid-19-updates/

4 things that we did in 4 days that nobody had ever done before

- First large-scale characterization of COVID patients in Europe, US and Asia
- First prediction model externally validated on COVID patients to inform shielding strategies
- Largest study ever conducted on the safety of hydroxychloroquine…
- And a MASSIVE NETWORK for research

Methods

The power of a community

USA

Columbia University Irving Medical Center (CUIMC, February to December 2020)

IQVIA Hospital CDM (February to October 2020)

STAnford medicine Research data Repository (STARR-OMOP from February to May 2020)

Premier (from February to August 2020)

Optum-EHR (February to October 2020)

Tufts Medical Center Clinical Academic Research Enterprise Trust (TRDW, February to May 2020)

Department of Veterans Affairs (VA-OMOP, February to June 2020).

South Korea

Health Insurance Review and Assessment (HIRA, February to April 2020)

China

Nanfang Hospital and Southern Medical University
(NFHCRD database, January to April 2020)

Spain

HM Hospitales
(March to April 2020)

Hospital del Mar
(February to August 2020)

EHDEN-OHDSI COVID-19 RWE Collaboration

OHDSI
OBSERVATIONAL HEALTH DATA SCIENCES AND INFORMATICS

EUROPE (9)		
CPRD (EHR)	3,864	NR
IQVIA DA Germany (EHR)	11,500	NR
HM Hospitales (Hospital Billing)	NR	2,544
Hospital del Mar (EHR)	NR	2,686
Integrated Primary Care Information (EHR)	3,306	60
IQVIA LPD France (EHR)	23,592	NR
IQVIA LPD Italy (EHR)	4,816	NR
Information System for Research in Primary Care (SIDIAP) (EHR)	124,305	18,369
SIDIAP-H (EHR Hospital linkage)	43,441	7,197

- > 4.5 m tested+
- > 1.2 m hospitalized
- 9 EU countries
- 13 US, 3 Asian nodes

USA (13)		
Columbia University Irving Medical Center (EHR)	10,437	3,439
Department of Veterans Affairs (EHR)	57,937	10,951
HealthVerity (Claims with diagnostic testing)	587,683	22,887
IQVIA Open Claims (Claims)	2,875,812	533,997
IQVIA Hospital Charge Data (Hospital Billing)	153,477	57,062
Optum EHR (EHR)	217,772	36,717
Optum SES (EHR with socio-economic data)	7,863	4,336
Oregon Health & Sciences University (EHR)	11,187	627
Premier (Hospital Billing)	417,650	156,187
Stanford University (EHR)	4,788	744
Tufts Medical Center (EHR)	1,250	326
University of Colorado Anschutz Medical Campus-Health Data Compass(EHR)	9,481	1,874
University of Washington School of Medicine (EHR)	3,245	733

ASIA-PACIFIC (3)		
Health Insurance Review & Assessment Service (Claims)	NR	7,599
Daegu Catholic University Medical Center (EHR)	559	46
Nanfang Hospital (EHR)	403	304

KEY

Persons diagnosed with COVID-19 or lab confirmed tested positive (no prior observation required)

Persons hospitalized with diagnosed with COVID-19 or lab confirmed tested positive (no prior observation required)

NR = Not Reported

Kostka K et al. ResearchSquare

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Hacking COVID-19 and its management globally in 2020

https://www.bmj.com/content/373/bmj.n1038

ARTICLE

https://doi.org/10.1038/s41467-020-18849-z OPEN

Deep phenotyping of 34,128 adult patients hospitalised with COVID-19 in an international network study

Edward Burn et al.#

https://www.nature.com/articles/s41467-020-18849-z

RESEARCH

OPEN ACCESS

Check for updates

Use of repurposed and adjuvant drugs in hospital patients with covid-19: multinational network cohort study

Albert Prats-Uribe,[1] Anthony G Sena,[2,3] Lana Yin Hui Lai,[4] Waheed-Ul-Rahman Ahmed,[5,6] Heba Alghoul,[7] Osaid Alser,[8] Thamir M Alshammari,[9] Carlos Areia,[10] William Carter,[11] Paula Casajust,[12] Dalia Dawoud,[13,14] Asieh Golozar,[15,16] Jitendra Jonnagaddala,[17] Paras P Mehta,[18] Mengchun Gong,[19] Daniel R Morales,[20,21] Fredrik Nyberg,[22] Jose D Posada,[23] Martina Recalde,[24,25] Elena Roel,[24,25] Karishma Shah,[5] Nigam H Shah,[23] Lisa M Schilling,[11] Vignesh Subbian,[26] David Vizcaya,[27] Lin Zhang,[28,29] Ying Zhang,[19] Hong Zhu,[30] Li Liu,[30] Jaehyeong Cho,[31] Kristine E Lynch,[32] Michael E Matheny,[33,34] Seng Chan You,[35] Peter R Rijnbeek,[3] George Hripcsak,[36] Jennifer CE Lane,[5] Edward Burn,[1,24] Christian Reich,[37] Marc A Suchard,[38] Talita Duarte-Salles,[24] Kristin Kostka,[37,39] Patrick B Ryan,[2,40] Daniel Prieto-Alhambra[1]

For numbered affiliations see end of the article.

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Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2021;373:n1038 http://dx.doi.org/10.1136/bmj.n1038

ABSTRACT

OBJECTIVE

To investigate the use of repurposed and adjuvant drugs in patients admitted to hospital with covid-19 across three continents.

DESIGN

Multinational network cohort study.

SETTING

in Spain), azithromycin (from 15 (4.9%) in China to 1473 (57.9%) in Spain), combined lopinavir and ritonavir (from 156 (<2%) in the VA-OMOP US to 2,652 (34.9%) in South Korea and 1285 (50.5%) in Spain), and umifenovir (0% in the US, South Korea, and Spain and 238 (78.3%) in China). Use of adjunctive drugs varied greatly, with the five most used treatments being enoxaparin, fluoroquinolones, ceftriaxone, vitamin D, and corticosteroids. Hydroxychloroquine

Open collaboration requires FULL transparency in every step of the research process

- Protocol and analysis source code freely available and directly downloadable: https://github.com/ohdsi-studies/Covid19HospitalizationCharacterization
- Phenotype definitions are both human-readable and computer-executable using ATLAS against any OMOP CDM: https://atlas.ohdsi.org/
- Manuscript posted on Medrxiv while awaiting peer-review: https://www.medrxiv.org/content/10.1101/2020.04.22.20074336v1
- All analysis results available for public exploration through interactive R shiny application: http://evidence.ohdsi.org/Covid19CharacterizationHospitalization/

KEY FINDINGS

- 34,128 participants from 3 continents:
  - North America (US) 8,362
  - Asia (South Korea) 7,341
  - Europe (Spain) 18,425

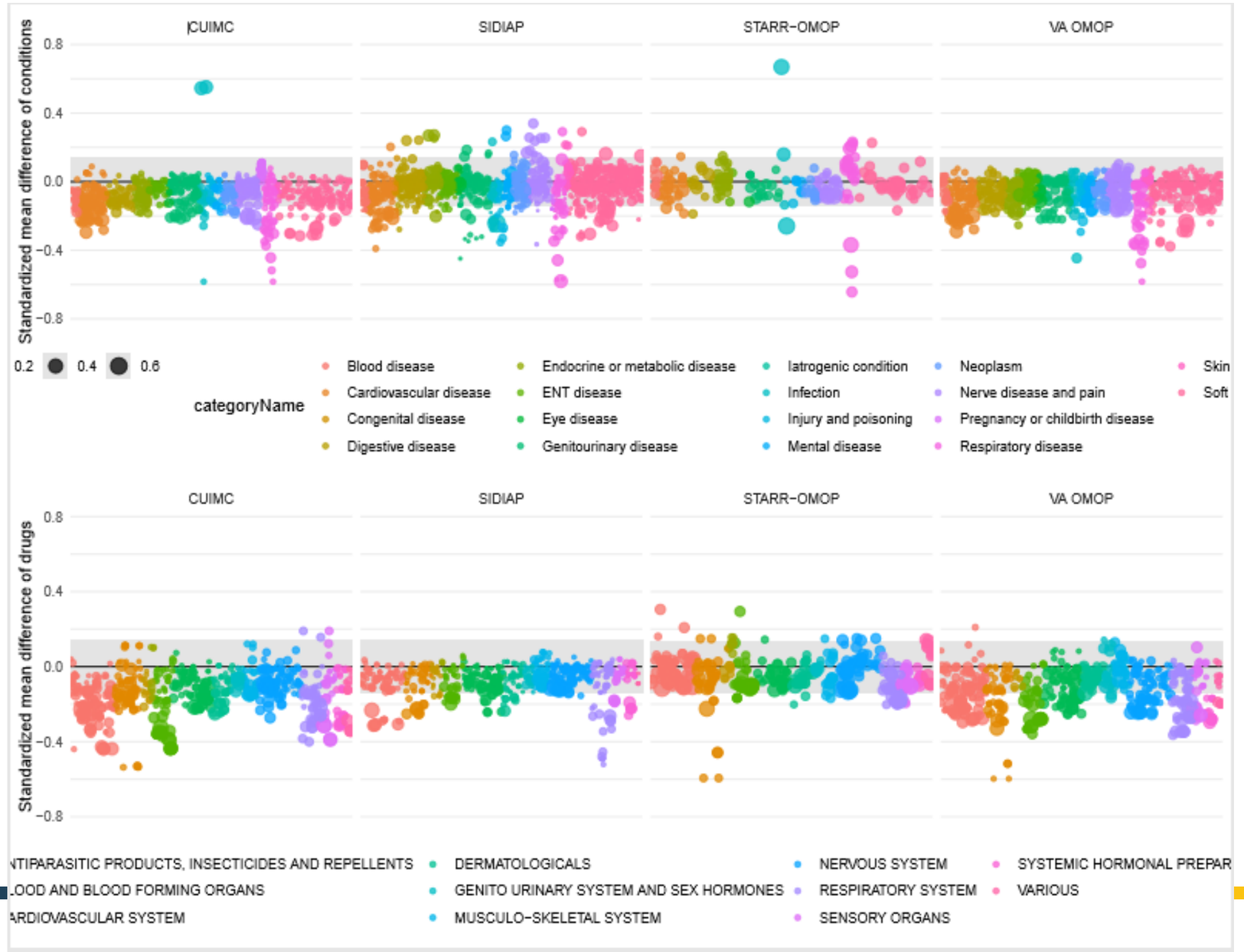
- 81,596 influenza ‘controls’ as benchmark

- 4,811 to 11,643 features extracted and summarised in an interactive web app

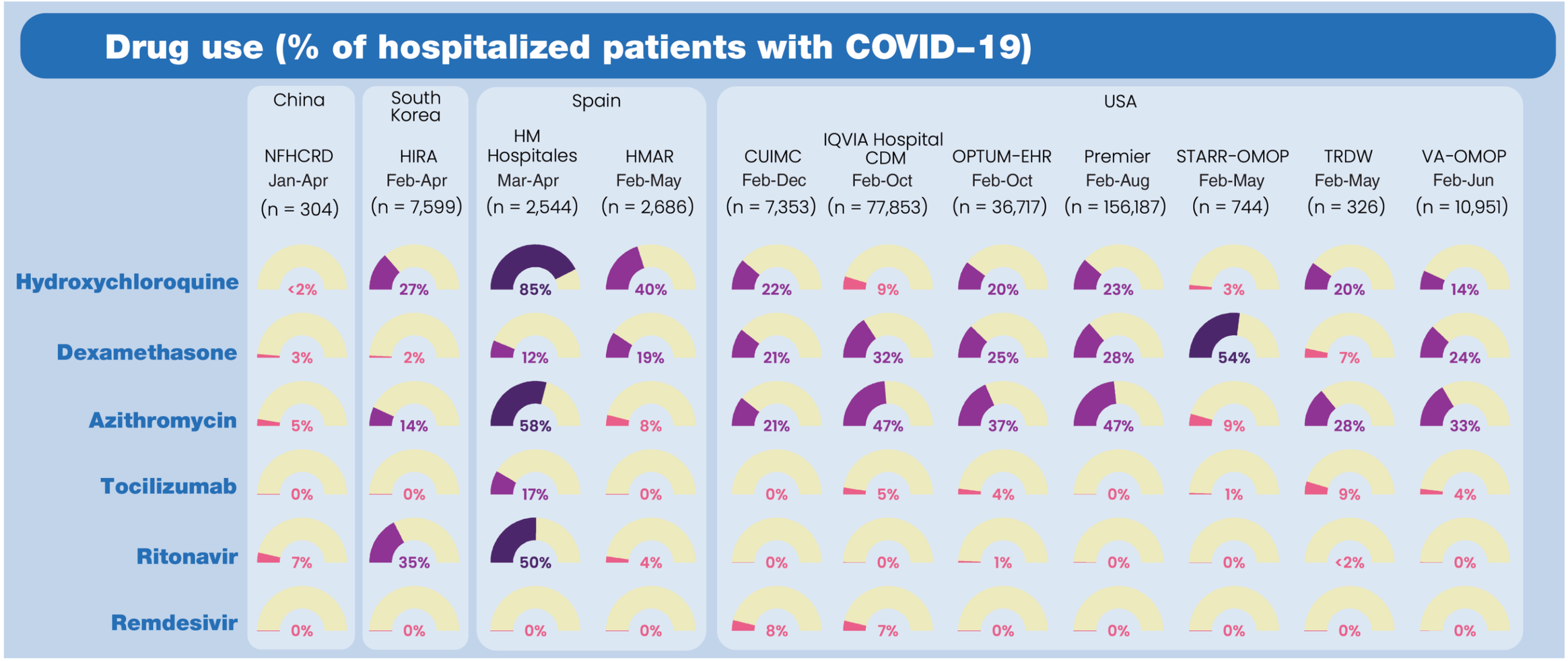
- Preprint available in MedRXiv on 22nd April 2020

KEY FINDINGS (2)

- COVID is no flu
- Healthier
- Less drug usage
- Exceptions incl. obesity OR diabetes



Drug Utilisation within 30d of hosp.



A Prats-Uribe et al. BMJ 2021 [in press]

The rise and fall of HCQ … -> before trials

February 2020
4 February Wang et al - Remdesivir and chloroquine effectively inhibit covid-19 in vitro

March 2020
9 March Yao et al - Hydroxychloroquine shows superior in vitro activity to chloroquine
19 March President Trump promotes hydroxychloroquine in press conference
20 March Gautret et al - Open-label non-randomized clinical trial shows effectiveness
28 March US Food and Drug Administration issues an emergency use authorisation
31 March Chen et al - Preprint of a randomised controlled trial suggests that hydroxychloroquine reduces time to clinical recovery

April 2020
10 April Lane et al - Observational data shows that azithromycin combined with hydroxychloroquine may increase cardiovascular mortality
24 April FDA and European Medicines Agency caution against the use of hydroxychloroquine owing to potential heart rhythm problems

May 2020
7 May Geleris et al - Lack of effectiveness of hydroxychloroquine on observational data
28 May WHO halts hydroxychloroquine arm of Solidarity trial

June 2020
8 June Recovery trial press note shows that hydroxychloroquine has no effect on covid-19
15 June FDA revokes emergency use ruling for hydroxychloroquine

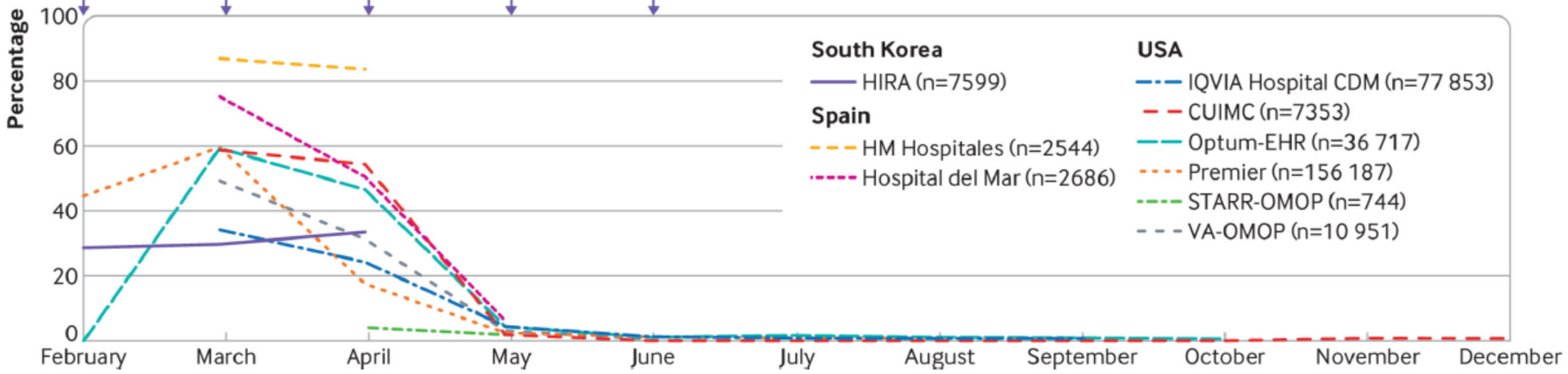


Fig 4 | Time trends in hydroxychloroquine use on days 0 to 30 after hospital admission in patients with a positive test result for or diagnosis of covid-19 by month. CUIMC=Columbia University Irving Medical Center; HIRA=Health Insurance Review and Assessment; OMOP=Observational Medical Outcomes Partnership; Optum-EHR=Optum deidentified electronic health record dataset; STARR=STAnford medicine Research data Repository; TRDW=Tufts Research Data Warehouse; VA=Veterans Affairs

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- Why RWD and Open Science?
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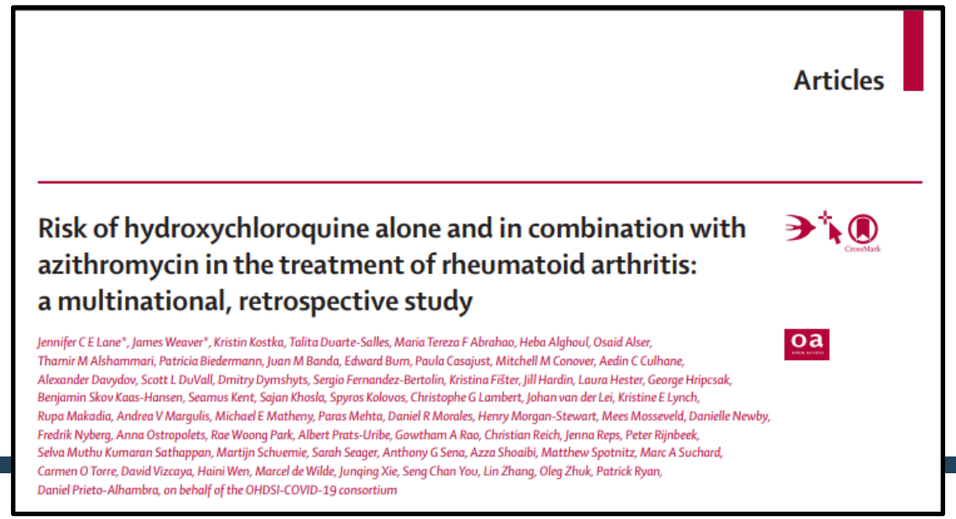
- Causal inference

1. ~~Safety~~ Risks of HCQ ± AZM

a multinational, network cohort and self-controlled case series study



Articles

Risk of hydroxychloroquine alone and in combination with azithromycin in the treatment of rheumatoid arthritis: a multinational, retrospective study

Jennifer C E Lane, James Weaver*, Kristin Kostka, Talita Duarte-Salles, Maria Tereza F Abrahao, Heba Alghoul, Osaid Alser, Thamir M Alshammari, Patricia Biedermann, Juan M Banda, Edward Burn, Paula Casajust, Mitchell M Conover, Aedin C Culhane, Alexander Davydov, Scott L DuVall, Dmitry Dymshyts, Sergio Fernandez-Bertolin, Kristina Fišter, Jill Hardin, Laura Hester, George Hripcsak, Benjamin Skov Kaas-Hansen, Seamus Kent, Sajan Khosla, Spyros Kolovos, Christophe G Lambert, Johan van der Lei, Kristine E Lynch, Rupa Makadia, Andrea V Margulis, Michael E Matheny, Paras Mehta, Daniel R Morales, Henry Morgan-Stewart, Mees Mosseveld, Danielle Newby, Fredrik Nyberg, Anna Ostropolets, Rae Woong Park, Albert Prats-Uribe, Gowtham A Rao, Christian Reich, Jenna Reps, Peter Rijnbeek, Selva Muthu Kumaran Sathappan, Martijn Schuemie, Sarah Seager, Anthony G Sena, Azza Shoaibi, Matthew Spotnitz, Marc A Suchard, Carmen O Torre, David Vizcaya, Haini Wen, Marcel de Wilde, Junqing Xie, Seng Chan You, Lin Zhang, Oleg Zhuk, Patrick Ryan, Daniel Prieto-Alhambra, on behalf of the OHDSI-COVID-19 consortium*

Primum non nocere (First, do no harm)

Hydroxychloroquine …

- Cheap, generic drug
- Indicated for RA, SLE and malaria prophylaxis
- Relatively safe, but:
  - Retinal toxicity
  - QT lengthening

- “In vitro” activity vs SARSCov2
- Great publicity …

Coronavirus: Trump says he is taking unproven drug hydroxychloroquine

19 May 2020 Share

Coronavirus pandemic

Aim/s

We had historical data from >900,000 previous users of HCQ for other indications (RA) to learn:

- What is the risk of serious adverse events (leading to hospital admission) associated with HCQ (vs SSZ as active comparator)?
- What is the risk of serious adverse events associated with the addition of AZM (vs AMX as active comparator) amongst users of HCQ?

Methods

Data source/s: Routine data (electronic medical records and claims) from Germany, Japan, Spain, S Korea, US, and the UK

Design: Comparative cohort analysis (+ SCCS, not covered today)

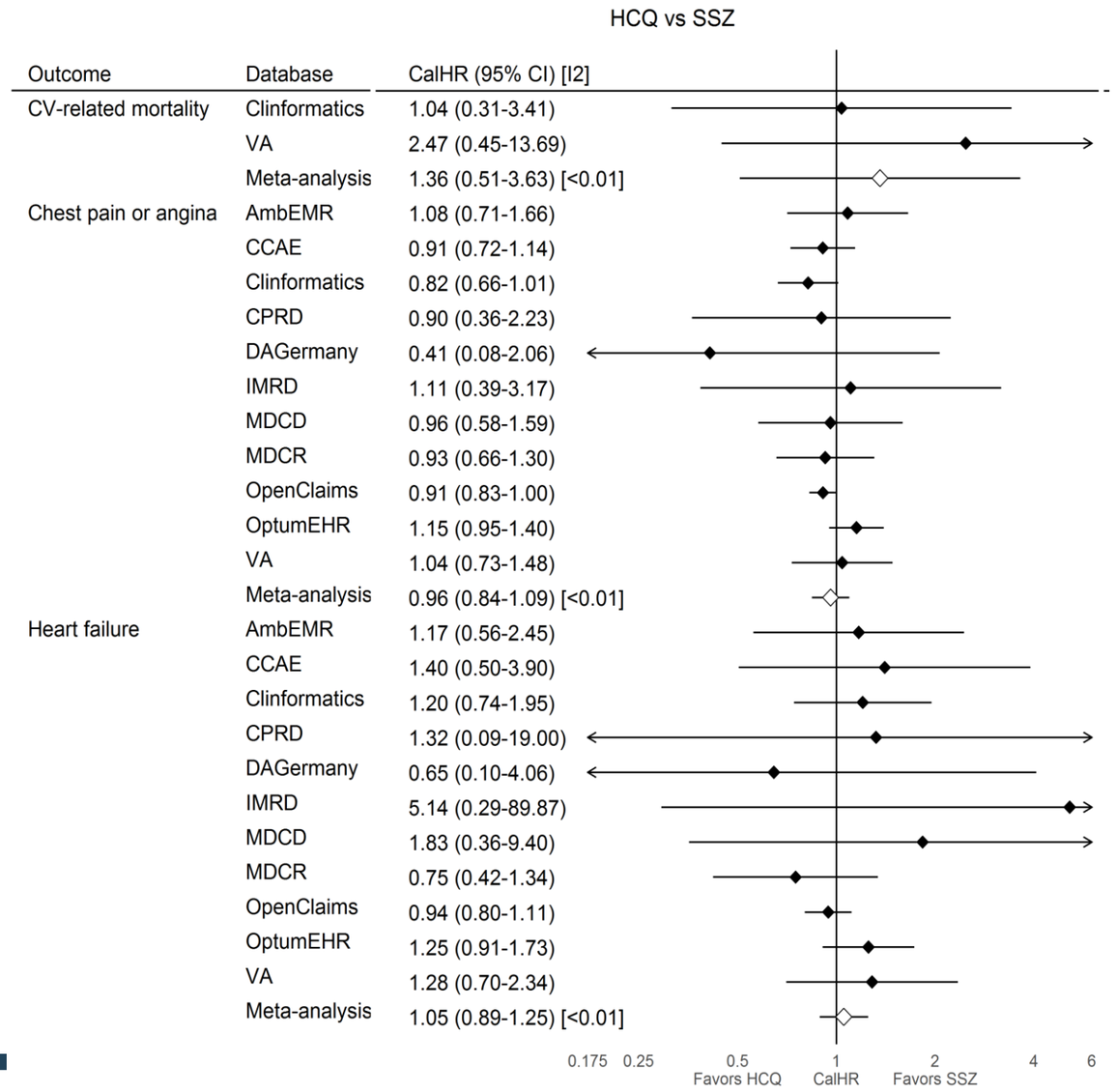
Participants:

- Age 18+ , 1+ years of data ‘visibility’
- Diagnosis of Rheumatoid Arthritis + use of one of the study drugs/ combinations

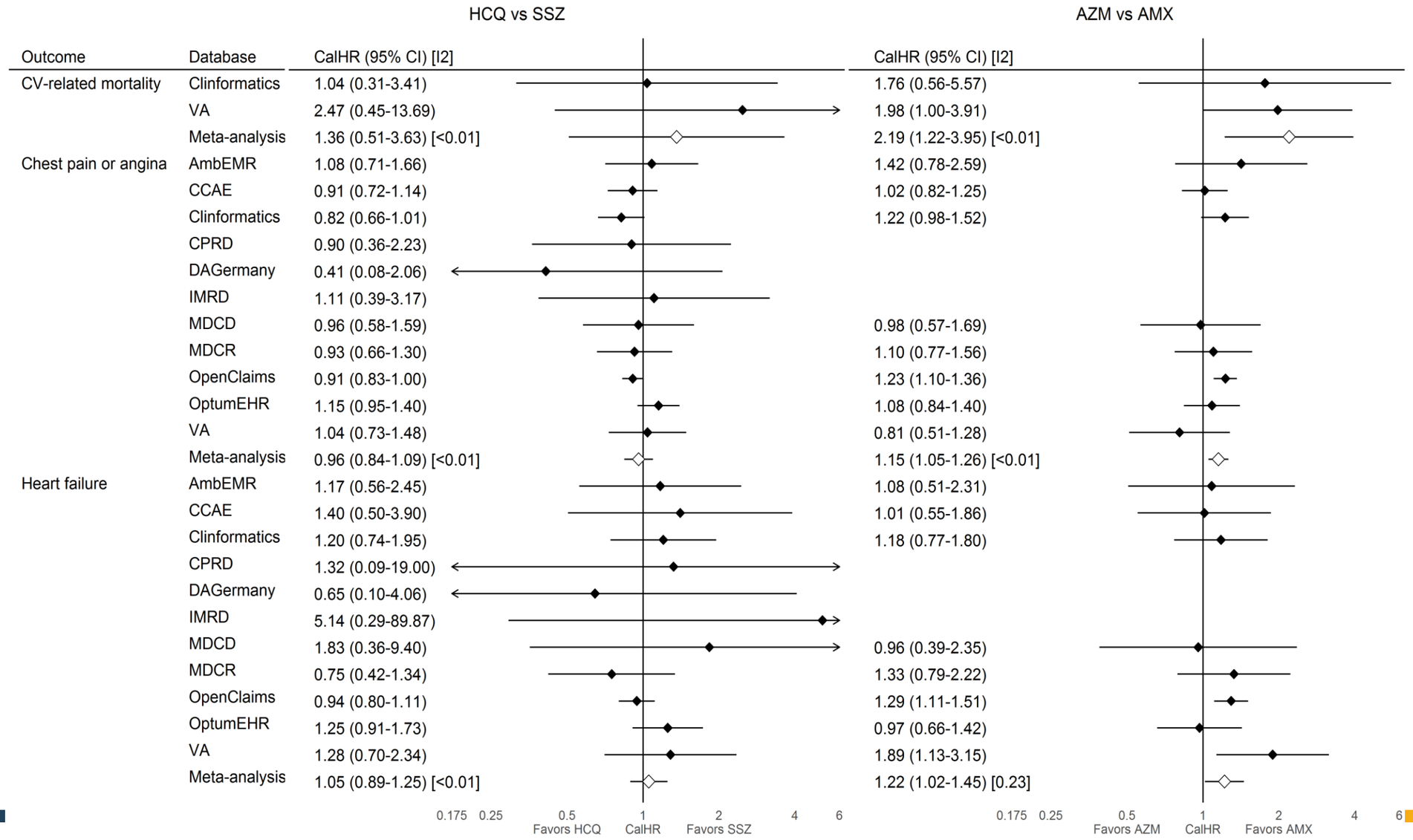
Patient counts

Data source	HCQ	SSZ
AmbEMR	57,140	15,268
CCAE	65,935	22,173
Clinformatics	50,698	17,221
CPRD	9,114	11,388
DAGermany	3,884	5,045
IMRD	8,843	8,452
MDCD	7,982	2,177
MDCR	15,690	5,150
OpenClaims	617,628	182,776
OptumEHR	76,844	21,549
VA	31,824	14,276
Meta-analysis	***945,582***	***305,475***

Short-term (30-day) main event/s safety

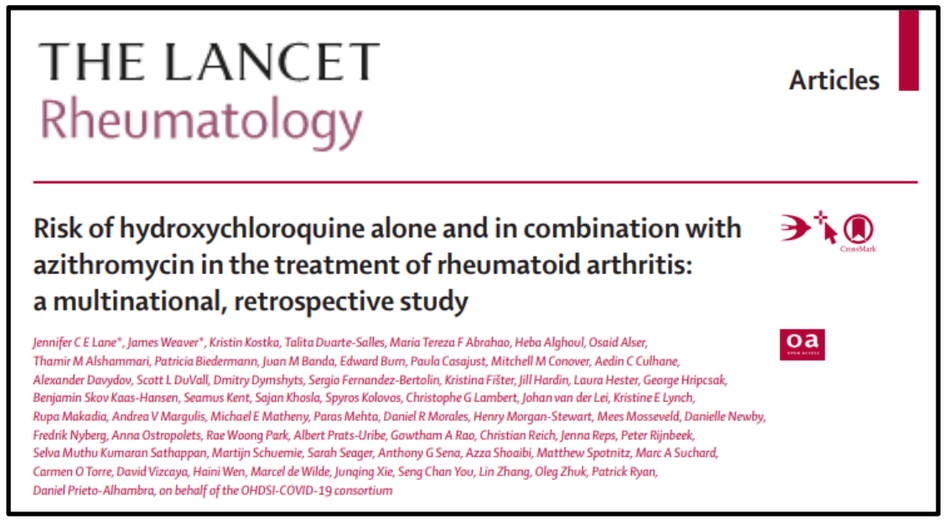


Short-term (30-day) main event/s



SUMMARY

- Findings:
  - In history use in RA population, HCQ alone is generally safe but in combination with AZ it shows a doubling of risk of 30-day cardiovascular mortality.



THE LANCET
Rheumatology

Articles

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Jennifer C E Lane, James Weaver*, Kristin Kostka, Talita Duarte-Salles, Maria Tereza F Abrahao, Heba Alghoul, Osaid Alser, Thamir M Alshammari, Patricia Biedermann, Juan M Banda, Edward Burn, Paula Casajust, Mitchell M Conover, Aedin C Culhane, Alexander Davydov, Scott L DuVall, Dmitry Dymshyts, Sergio Fernandez-Bertolin, Kristina Fišter, Jill Hardin, Laura Hester, George Hripcsak, Benjamin Skov Kaas-Hansen, Seamus Kent, Sajan Khosla, Spyros Kolovos, Christophe G Lambert, Johan van der Lei, Kristine E Lynch, Rupa Makadia, Andrea V Margulis, Michael E Matheny, Paras Mehta, Daniel R Morales, Henry Morgan-Stewart, Mees Mosseveld, Danielle Newby, Fredrik Nyberg, Anna Ostropolets, Rae Woong Park, Albert Prats-Uribe, Gowtham A Rao, Christian Reich, Jenna Reps, Peter Rijnbeek, Selva Muthu Kumaran Sathappan, Martijn Schuemie, Sarah Seager, Anthony G Sena, Azza Shoaibi, Matthew Spotnitz, Marc A Suchard, Carmen O Torre, David Vizcaya, Haini Wen, Marcel de Wilde, Junqing Xie, Seng Chan You, Lin Zhang, Oleg Zhuk, Patrick Ryan, Daniel Prieto-Alhambra, on behalf of the OHDSI-COVID-19 consortium*

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Medicines | Human regulatory | Veterinary regulatory | Committees | News & events | Partners & networks

COVID-19: reminder of risk of serious side effects with chloroquine and hydroxychloroquine Share

News 23/04/2020

Chloroquine and hydroxychloroquine are known to potentially cause heart rhythm problems, and these could be exacerbated if treatment is combined with other medicines, such as the antibiotic azithromycin, that have similar effects on the heart.

Recent studies[1,2] have reported serious, in some cases fatal, heart rhythm problems with chloroquine or hydroxychloroquine, particularly when taken at high doses or in combination with the antibiotic azithromycin.

Questions?

daniel.prietoalhambra@ndorms.ox.ac.uk

The European Network of Excellence for Big Data in Prostate Cancer

Talk title

Session: Using Federated Networks to Generate RWE: Why Not Now?

PIONEER – BD4BO IMI Project

Alex Asiimwe

BAYER AG, EFPIA Lead PIONEER

PIONEER and the BD4BO mission

- **PIONEER** is part of the Innovative Medicine Initiative's (IMI's) "Big Data for Better Outcomes" (BD4BO) programme

- The **BD4BO mission** is to improve health outcomes and healthcare systems in Europe by maximising the potential of Big Data

- **PIONEER aims** to transform the field of prostate cancer care with particular focus on:
    - improving prostate-cancer related outcomes
    - health system efficiency
    - the quality of health and social care across Europe

Big Data for Better Outcomes

THEMES/ENABLERS:

Design sets of standard outcomes and demonstrate value	Increase access to high quality outcomes data	Use data to improve value of HC delivery	Increase patient engagement through digital solutions

DISEASE-SPECIFIC PROJECTS:

- ROADMAP: Alzheimer's disease
- HARMONY: Haematologic malignancies
- BigData@Heart: Cardiovascular diseases
- **PIONEER: Prostate cancer**

CO-ORDINATING PROJECTS:

- DO->IT: Coordination & support actions

OVERARCHING:

- European Health Data Network (EHDEN)

PCa – a major health issue with unmet medical needs

- Prostate Cancer (PCa) is the **second leading cause of cancer death** among men
- Insufficient knowledge on **risk factors** and **patient characteristics**
- Need for **integration of real-world clinical data** into disease classification and care pathways
- Missing standardisation of **PCa-related outcomes**
  - Lack of appropriate **patient stratification**
  - Insufficient **engagement of stakeholders** including patients
  - **Suboptimal care** for prostate cancer patients

PIONEER's primary objective

By applying advanced data analytics, and developing a data-driven platform of unparalleled scale, quality and diversity,

- PIONEER will empower **meaningful improvement in clinical practice, PCa disease-related outcomes, and health-economic outcomes** across the European healthcare landscape

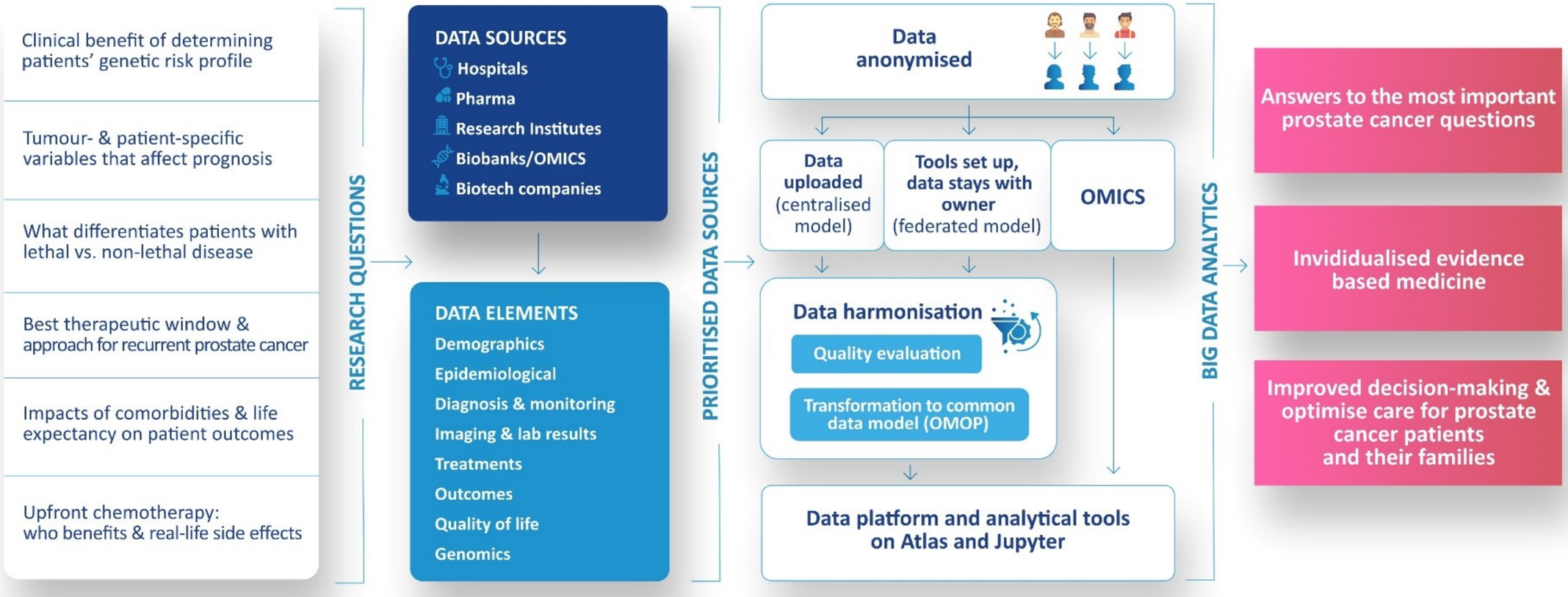
- PIONEER will assemble, standardise, harmonise and analyse high-quality big data from diverse populations of PCa patients across different stages of the disease to provide **evidence-based data for improving decision-making** by key stakeholders

PIONEER

BIG DATA PLATFORM

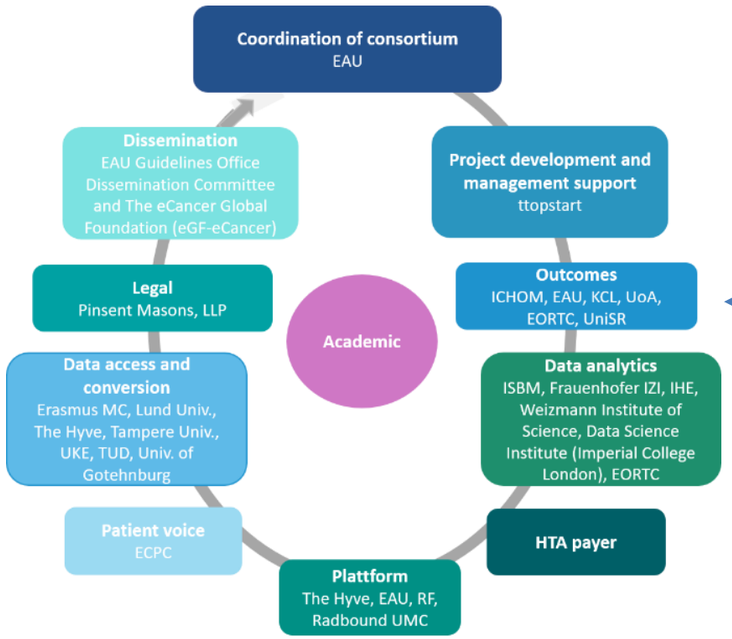
THE EUROPEAN NETWORK OF EXCELLENCE FOR BIG DATA IN PROSTATE CANCER

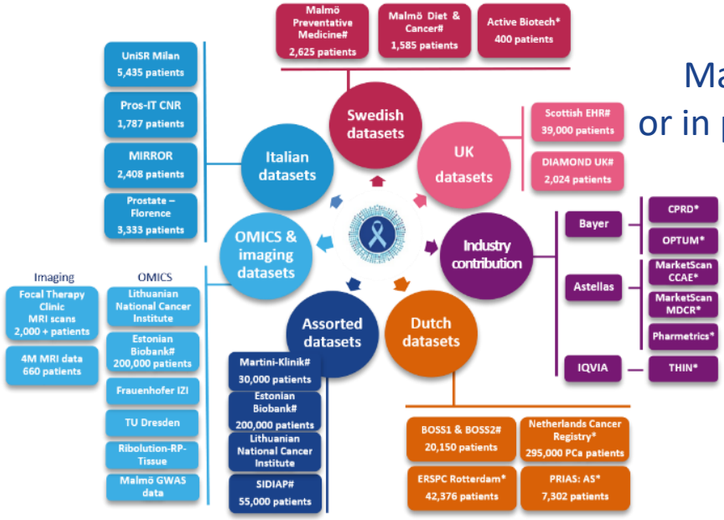
Together we can ensure each individual patient receives the right treatment for them at the right time.

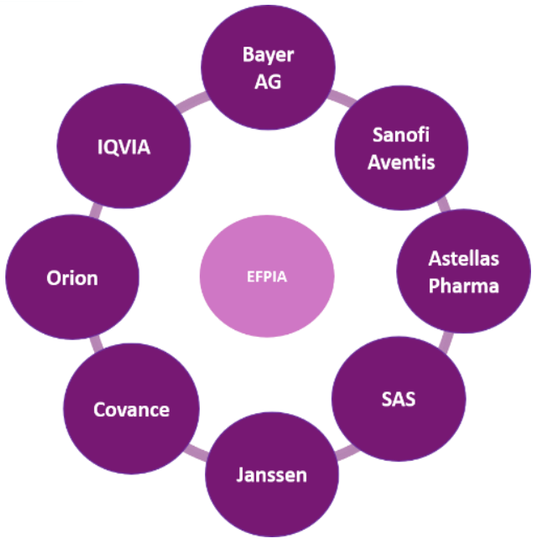


KNOWLEDGE GAPS | DATA SOURCES | BIG DATA PROCESSING | PIONEER OUTCOMES

The PIONEER network of excellence







Mapping completed **(*)**
or in progress/prep phase **(#)**

Adopted from Omar et al.,
Nat. Rev. Urology, 2020. Jun;17(6):351-361.

The PIONEER Study-A-Thon

- PIONEER, in collaboration with IMI2 EHDEN and the OHDSI community conducted a focused five-day meeting (study-a-thon) to generate medical evidence on Prostate Cancer patients undergoing non-interventional management.

- 245 participants
- 4 patients
- 875 team engagements

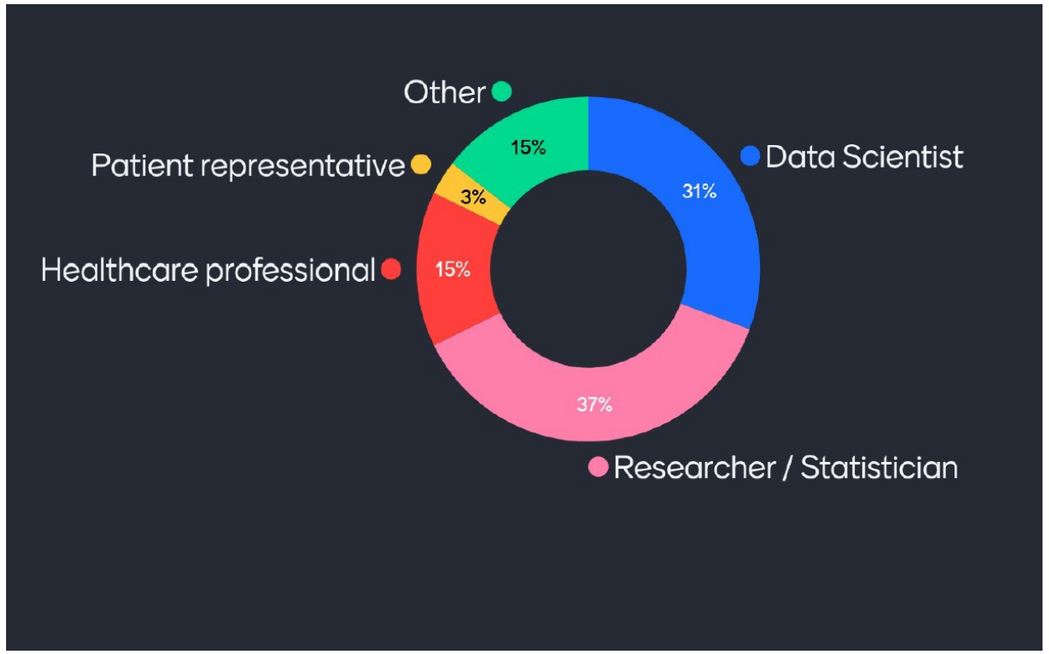
- 20 countries
- 5 time zones
- 5 days

- 4 teams
- 5 cohorts
- 64 phenotypes

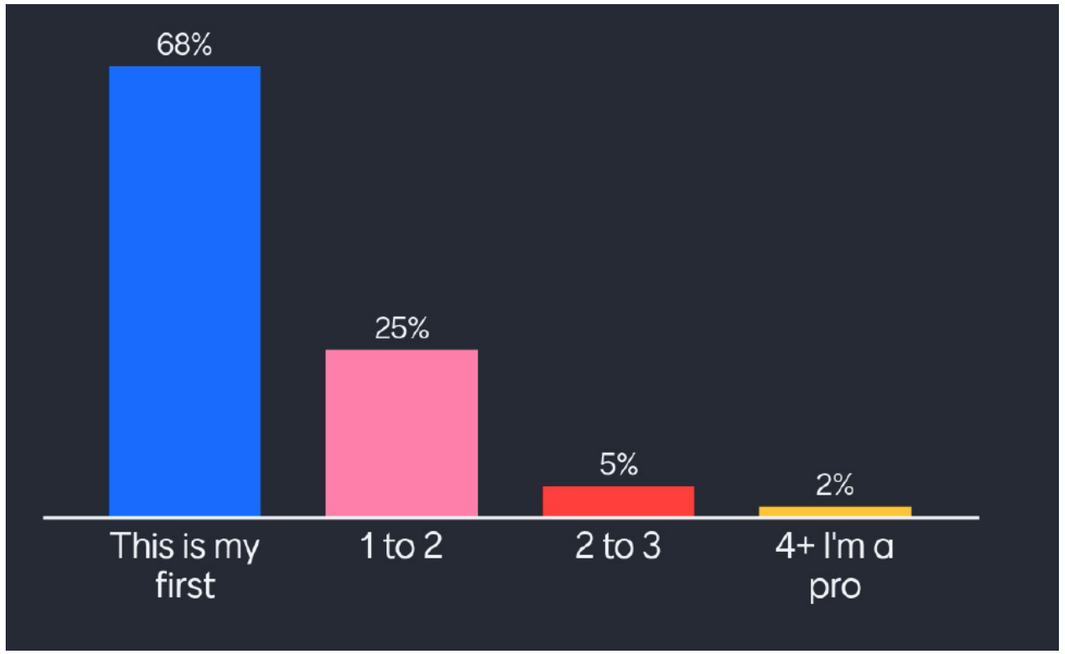
- 17 datasets & counting
- 3 analytics tasks

PIONEER – Study-A-Thon: Group dynamics

What is your background?



How many study-a-thons have you attended?



PIONEER

Studyathon Objectives

To investigates the natural history and outcomes of prostate cancer patients managed with watchful waiting (WW) using an international network of real-world data

Watchful waiting is a conservative management option for prostate cancer patients with a life expectancy < 10 years at time of diagnosis.

Develop and validate risk scores & prediction models that quantify time to death, symptomatic progression and initiation of palliative treatment following WW

With the outcomes of this work we hope to inform shared healthcare decision-making for prostate cancer patients managed by watchful waiting.

PIONEER – Study-A-Thon - Workflow

We prepared in advance: Data; Cohorts; Final draft Protocol(s)

Monday

Introduction day
Split the team in small groups
Start your analysis/article section

Tuesday

Run clinical characterisation
Review cohort diagnostics
Draft patient-level prediction design

Wednesday

Review clinical characterization results
Execute patient-level prediction package

Thursday

Continue clinical characterization analysis
Review patient-level prediction results
Externally validate prediction model

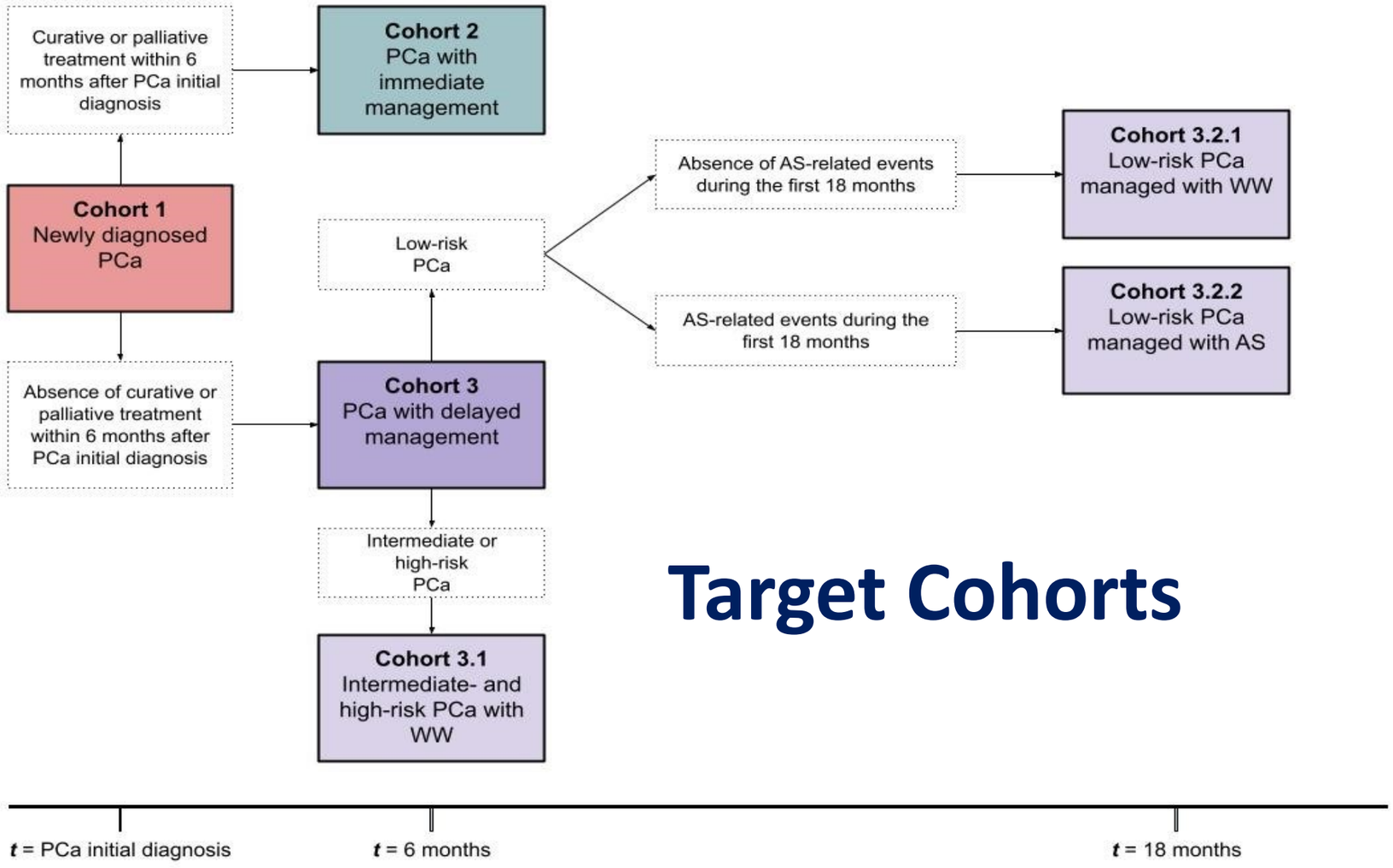
Friday

Review of results
Feedback on studyathon
Plan for completing **publications**

PIONEER – Study-A-Thon – Sub-teams

Sub-teams	Objectives
Clinical characterisation	Describe the demographic and clinical characteristics of patients with prostate cancer under watchful waiting (WW) & estimated clinical outcomes of these patients including those who initiated treatment.
Phenotyping	Define the study phenotypes clearly, unambiguously and accurately to generate meaningfully evidence considering differences/nuances of the databases
Prediction	Develop a prediction model, in the context of WW, that predicts an outcome (symptomatic progression, death, death without symptoms) at a specific moment in time (6, 12, 24 months) based on a combination of patient characteristics.
Data sources & study execution	Identify & recruit appropriate databases to the study; developed the code to run analyses for clinical characterisation and to compile results in an easy-to-install R package

PIONEER



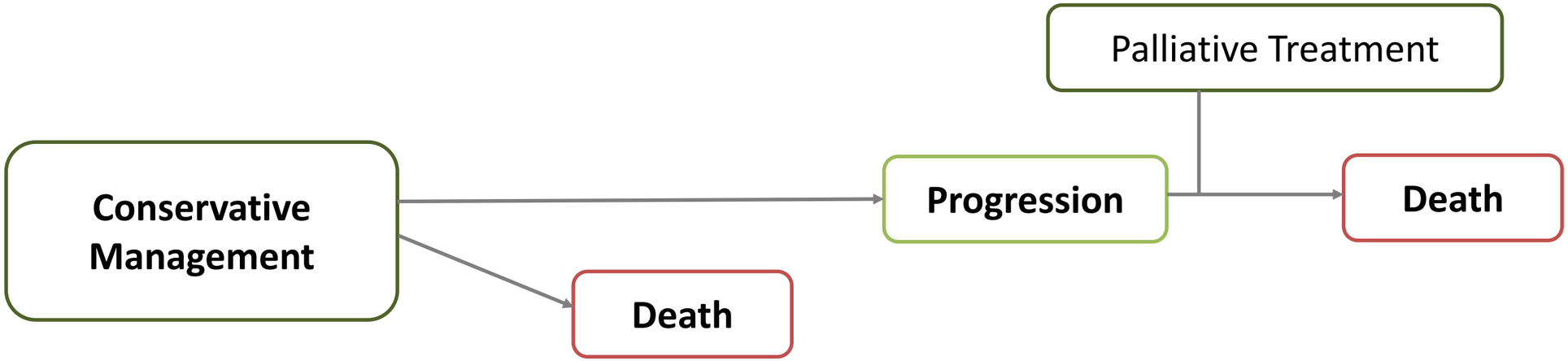
Target Cohorts

PCa = prostate cancer; WW = watchful waiting; AS = active surveillance; t = index date

Outcomes Cohorts

Patients on conservative management experience two main outcomes:

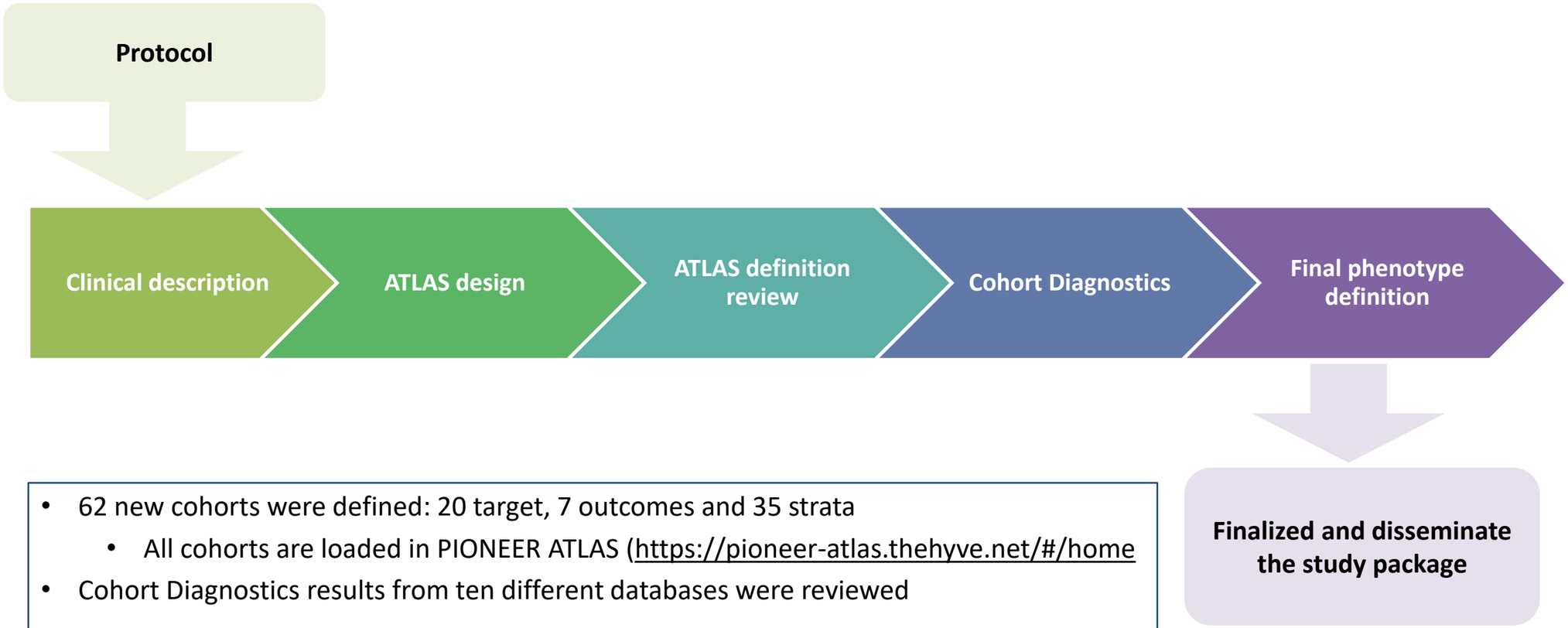
1. Death
2. Progression after which they receive treatment



Characterization Study: describe patients' characteristics and their outcomes

Prediction Study: identify patients likely to experience death before progression

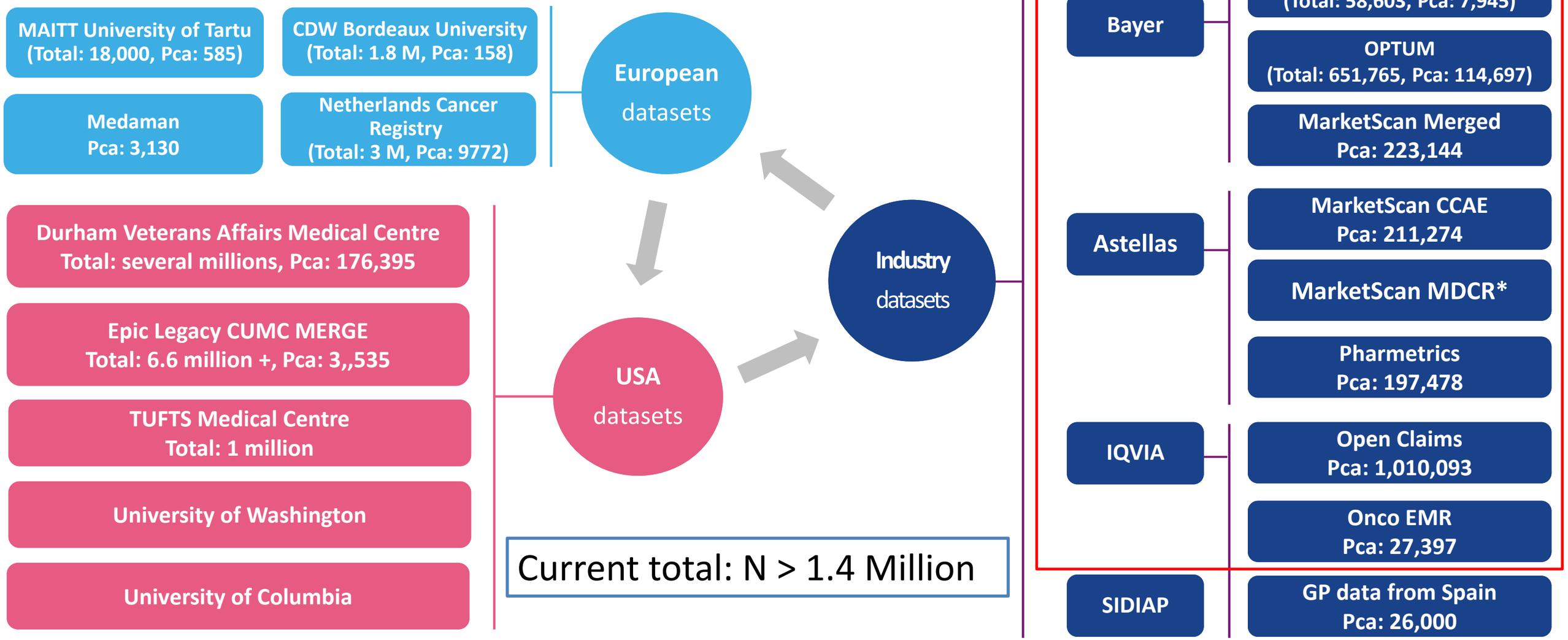
Phenotype-Cohort Development Process



- 62 new cohorts were defined: 20 target, 7 outcomes and 35 strata
  - All cohorts are loaded in PIONEER ATLAS (https://pioneer-atlas.thehyve.net/#/home
- Cohort Diagnostics results from ten different databases were reviewed

Studyathon Data Overview

PIONEER



PIONEER

PIONEER / EHDEN /

- About
- Cohorts
- Cohort Counts
- Cohort Characterization
- Time To Event
- Metrics Distribution
- Compare Cohort Char.
- Database information
- Change Log

Database

CPRD, CUIMC, MAITT, MktSc

Cohort

[PIONEER T1] Newly diagno

Strata

All, with Full 365-day follow

Download

Show 25 entries

Search:

Cohort	Strata	CPRD	CUIMC	MAITT	MktScan	Optum	TMC
		Subjects	Subjects	Subjects	Subjects	Subjects	Subjects
[PIONEER T1] Newly diagnosed PCa	All	6,163	3,736	662	223,144	121,266	315
[PIONEER T1a] Newly diagnosed PCa broad	All	6,163	4,108	668	223,144	122,262	358
[PIONEER T2] PCa treated right away	All	3,377	1,272	394	134,164	67,000	125
[PIONEER T3.1] PCa high/intermediate risk conservative management	All		217	25		1,181	
[PIONEER T3.1a] PCa high/intermediate risk conservative management broad	All		304	27		1,324	19
[PIONEER T3] PCa under conservative management	All	2,311	1,656	161	40,049	27,382	132
[PIONEER T3a] PCa under conservative management broad	All	2,311	1,743	163	40,049	27,525	143
[PIONEER T4.1] Delayed Curative Management	All	69	372	19	14,905	10,795	21
[PIONEER T4.1a] Delayed Curative Management broad	All	69	399	19	14,905	10,810	23
[PIONEER T4.2] Delayed Palliative Management	All	607	283	59	5,293	4,439	
[PIONEER T4.2a] Delayed Palliative Management broad	All	607	352	60	5,293	4,525	14
[PIONEER T5a] Symptom post conservative management broad	All	451	953	31	17,809	16,289	64
[PIONEER T3a sen1] new PCa conservative management sensitivity_1	All	4,640	3,519	456	176,562	97,501	320
[PIONEER T3a sen2] new PCa conservative management sensitivity_2	All	2,904	2,457	253	77,594	47,274	194
[PIONEER T3a sen3] new PCa conservative management sensitivity_3	All	2,155	1,794	162	35,344	25,195	149
[PIONEER T3a sen4] new PCa conservative management sensitivity_4	All	1,993	1,649	148	30,075	21,607	139
[PIONEER T3a sen5] new PCa conservative management sensitivity_5	All	1,749	1,492	119	23,221	16,635	121

Studyathon Goals & Achievements

PIONEER

Cohort diagnostics:
1.4M patients
Shiny app: https://bit.ly/3v6Tnz6

Debugged and functional R package for federated data analytics: bit.ly/3aa1liy

Patient voice included

Prediction models for
- **time to death**
- **symptomatic progression**
- **initiation of palliative treatment**

Communication channels built with EHDEN & OHDSI

Risk scores for risk of death, progression or treatment

Study protocol available on: bit.ly/3vJI7ZK

Characterisation results now on Shiny App: bit.ly/3dTT8QK

PIONEER Study-A-Thon: Patient representatives

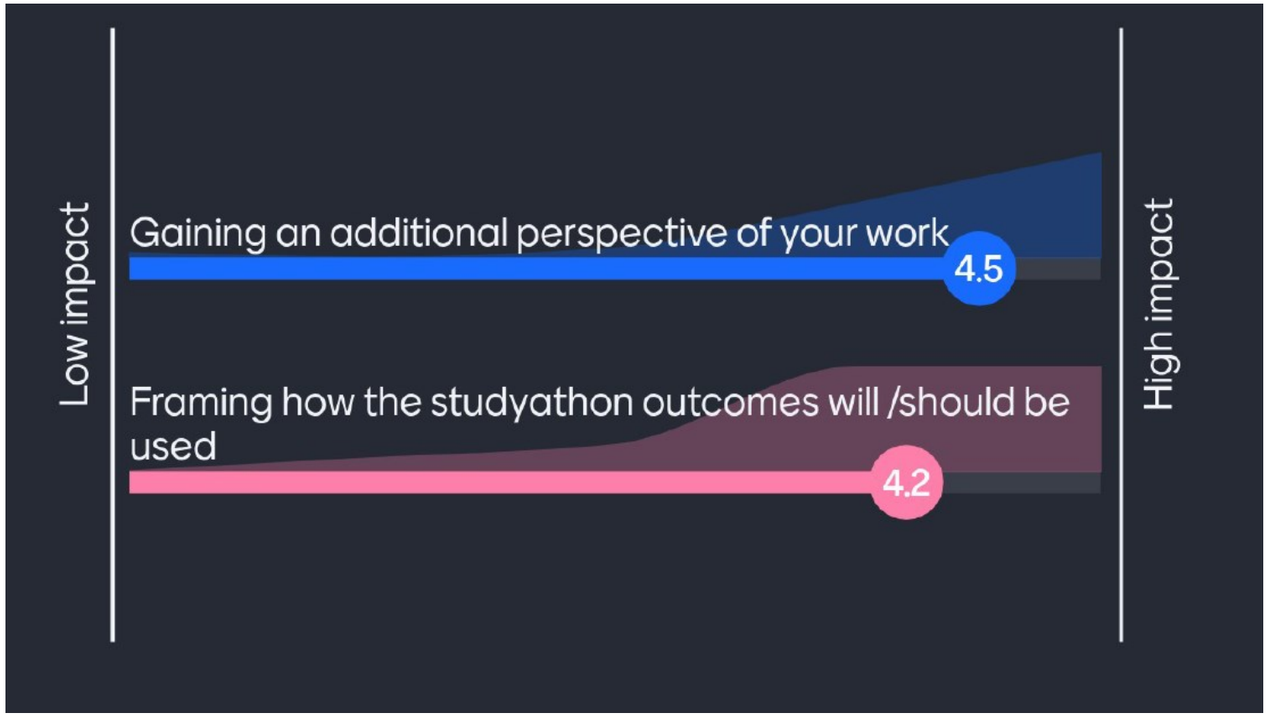
Gary Hooker

Ken Mastris

Robert Greene

Erik Briers

How would you rate the impact of patient participation on the study with regards to:



PIONEER Study-A-Thon: Future Outlook

Study-a-thon is still ongoing!!

- Publications
- Estimations
- Prediction

Importance of patient representatives - key for future studyathons

Next steps

- Future studyathons
  - Different questions & data
- Explore new formats & approaches

Data owners joined the group and keep on joining

Collaborative spirit bringing people & skills together – common goal

The European Network of Excellence for Big Data in Prostate Cancer

Contact us for queries

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Prediction	Ronald Herrera (ronald.herrera@bayer.com)
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EHDEN	Nigel Hughes (nhughes@its.jnj.com)
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RWE for decision making

An HTA perspective

Virtual ISPOR 2021

Alan Lamb – Scientific Adviser

NICE National Institute for Health and Care Excellence

Declarations

Alan Lamb is an employee of NICE and operational lead for WP2 of EHDEN. Views expressed are his own and do not necessarily reflect the views of NICE or the EHDEN consortium.

1

Use of RWE in HTA

How do HTA agencies use evidence from observational studies?

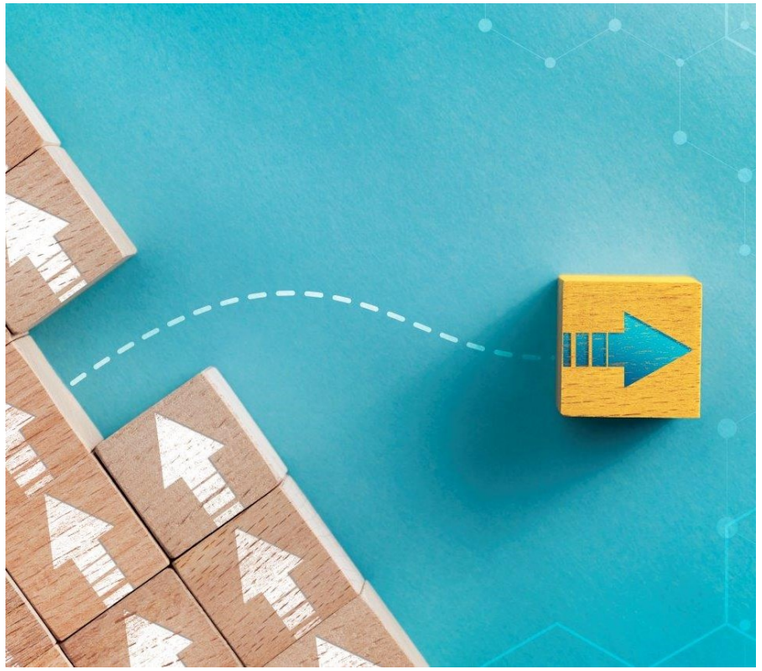
NICE

2

EHDEN and HTA

Reflections from an HTA use case

EHDEN



3

What next?

How will the use of RWE in HTA submissions develop?

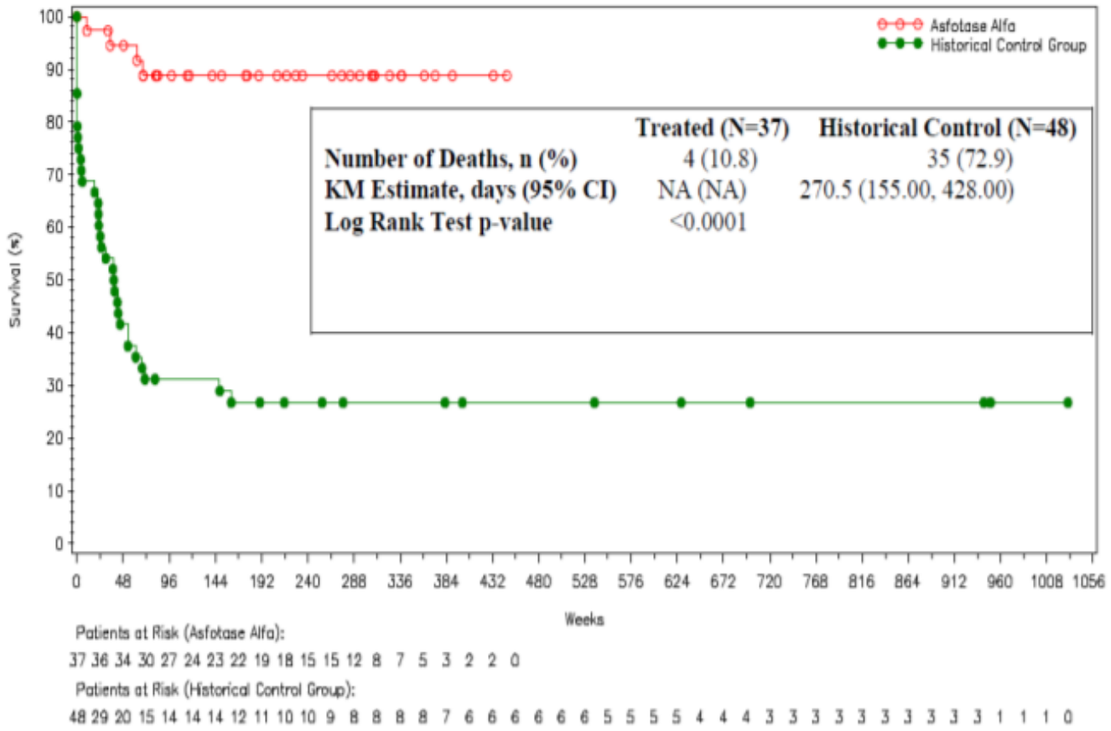
Use of RWE in HTA

External control arms

NICE

Historical control arm for estimating comparative effectiveness

Figure C2: Overall Survival in Perinatal/Infantile-onset HPP Patients Treated with asfotase alfa vs Historical-Control Patients



	Treated (N=37)	Historical Control (N=48)
Number of Deaths, n (%)	4 (10.8)	35 (72.9)
KM Estimate, days (95% CI)	NA (NA)	270.5 (155.00, 428.00)
Log Rank Test p-value	<0.0001	

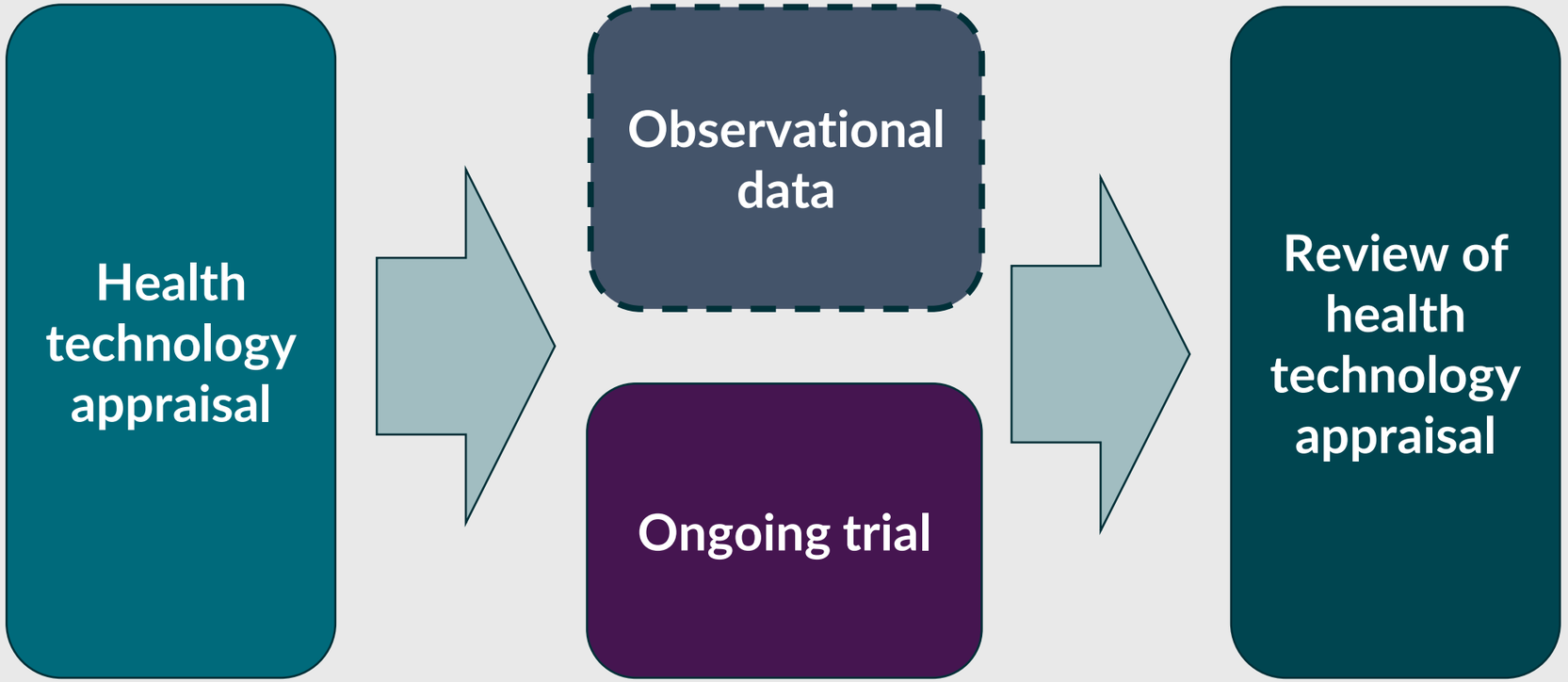
Abbreviations: Confidence Interval (CI); Kaplan-Meier (KM); Not Applicable (NA).
Source:(34,186)

Use of RWE in HTA

Managed access agreements

NICE

Addressing uncertainties in cost effectiveness evidence



Managed access period – Cancer Drug Fund
Data collection – Systemic Anti Cancer Database

EHDEN and HTA

A COPD use case

NICE

Research question

Estimate resource use in patients with COPD by disease severity in the UK and the Netherlands

Databases – mapped to OMOP-CDM

CPRD

INTEGRATED PRIMARY CARE INFORMATION

Methods

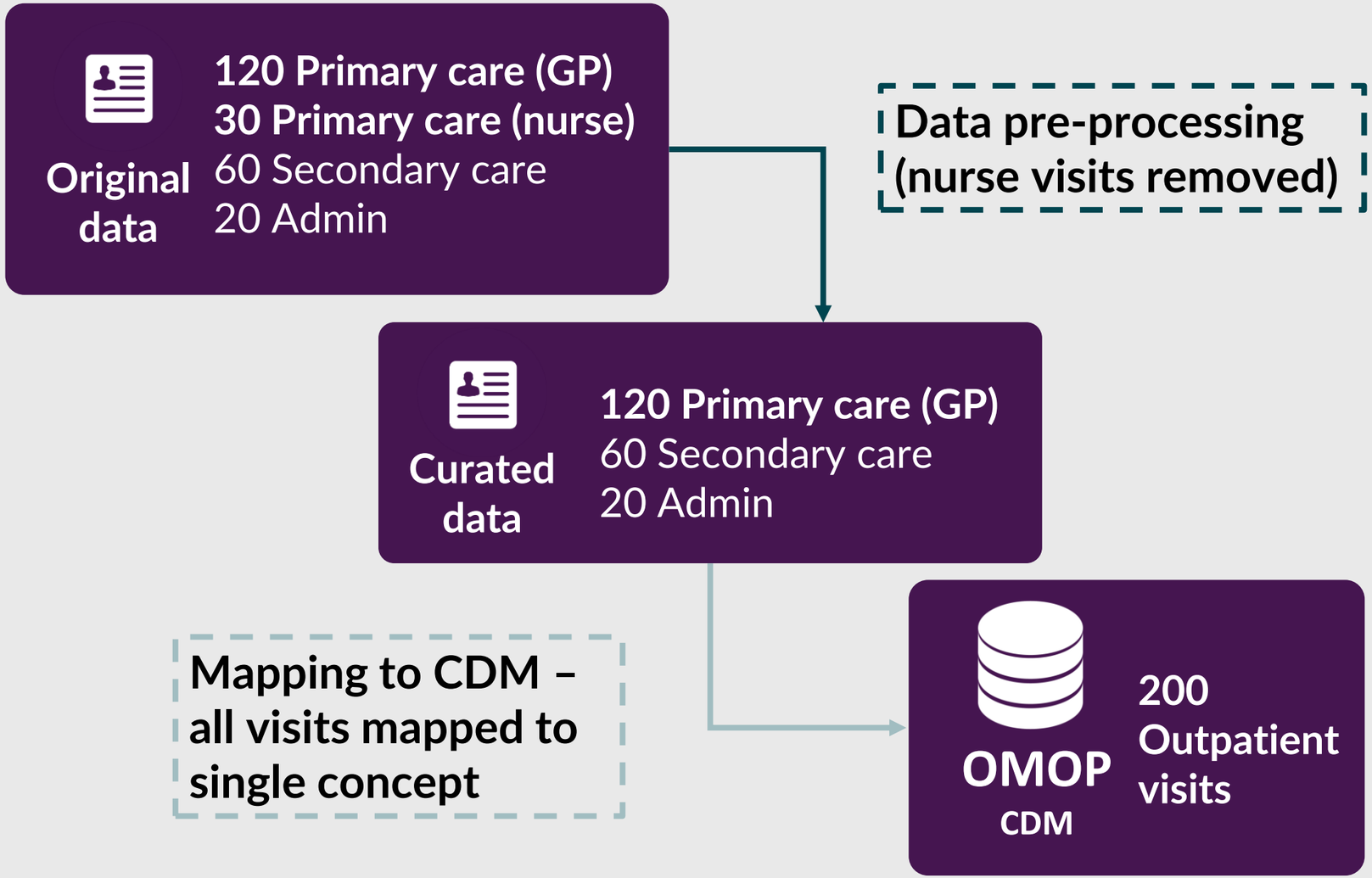
- Characterisation by severity using reported FEV1%
- Estimate resource use by determining annual rates of primary care visits

EHDEN and HTA

A COPD use case – challenges

NICE

Data processing and mapping



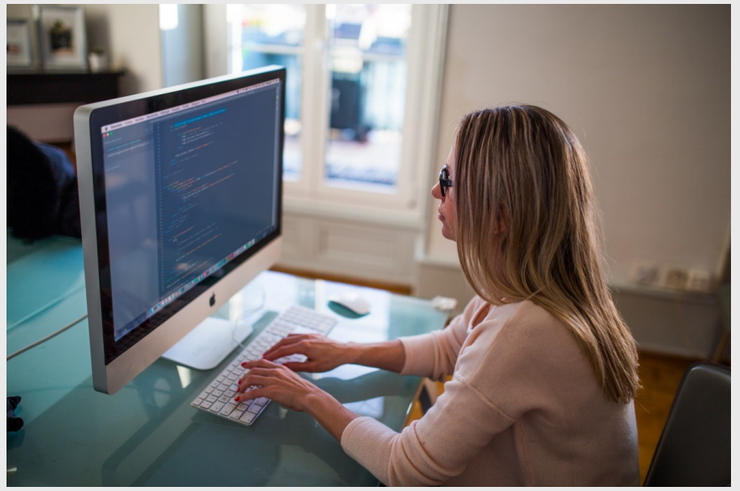
EHDEN and HTA

A COPD use case – challenges

NICE

Tools and dashboards

Current OHDSI tools do not easily support estimation of some common HTA outcomes (eg costs)



Bespoke coding required!

EHDEN and HTA

A COPD use case – addressing the challenges

NICE

Challenges should be surmountable!

Data processing and mapping

- Ensure use of data for HTA purposes is reflected in data processing and mapping processes and ensure HTA experts are involved in the mapping process
- Map visits in a way that reflects specific types of healthcare delivery in different settings (eg distinguishing between primary and secondary care)

Tools and dashboards

Development of analytical tools and dashboards to support common analyses in HTA

Kent, et al. *PharmacoEconomics* **39**, 275–285 (2021)

What might HTA bodies need to have confidence in RWE?

Type of evidence

- Identify data sources using systematic approaches
- Evidence relevant to key model parameters – comparative effectiveness, resource use, quality of life
- Geographically relevant

Data and study quality

- Transparent – pre-registered studies
- Reproducible
- Understanding strengths and limitations of the data source – missingness, etc
- Analysis – risk of bias should be assessed, confounders should be adjusted for where possible and uncertainty should be characterised and quantified if possible

NICE

Polling question . . .

NICE

How confident are you that meaningful evidence can be generated from RWD for HTA purposes?

- Very confident
- Somewhat confident
- Neither confident or unconfident
- Somewhat unconfident
- Very unconfident

NICE National Institute for Health and Care Excellence

Thank you for listening.