Routine Health Care Data as a resource for Post-Approval Safety and Effectiveness Assessment of Medicines

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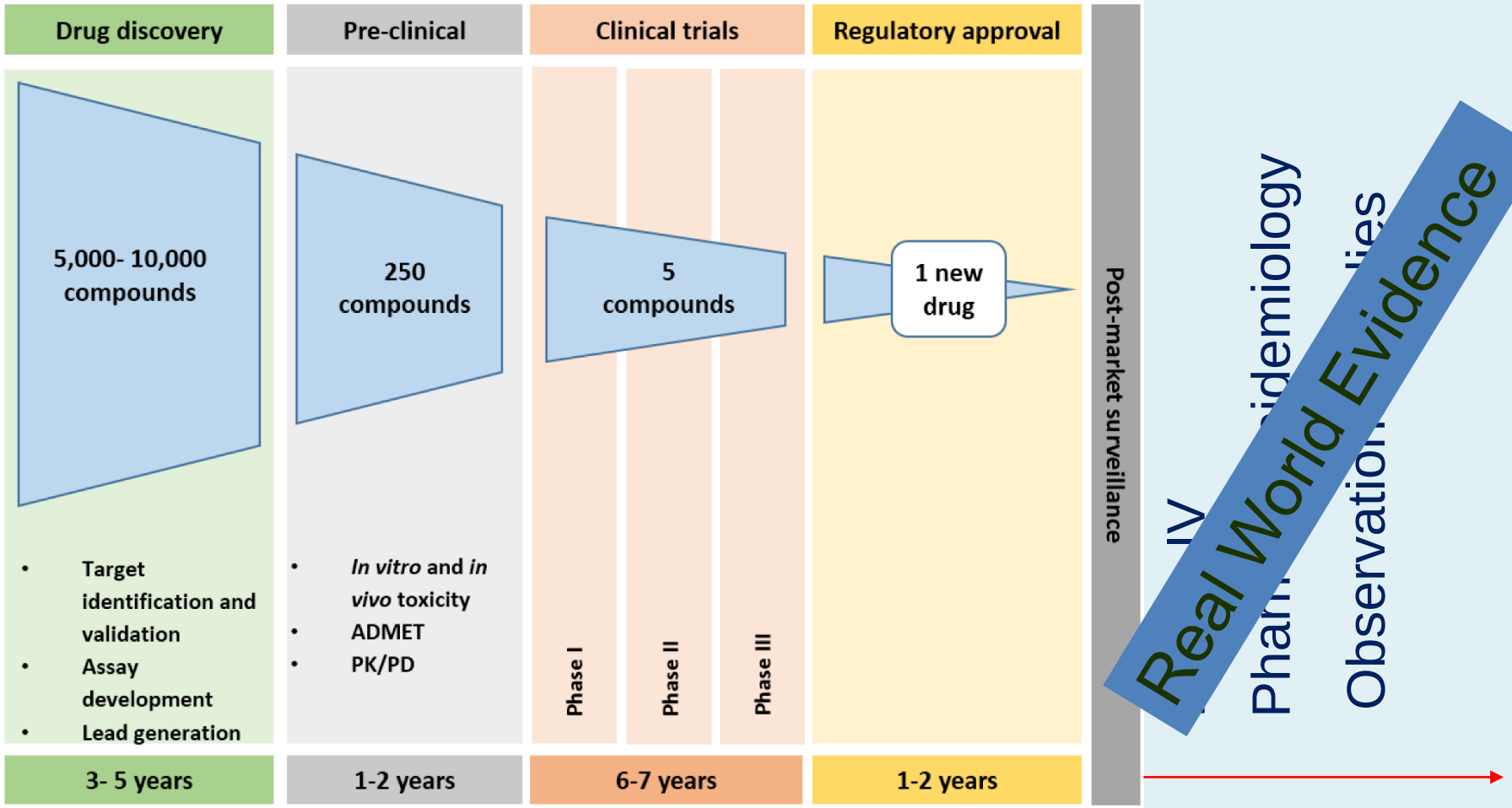
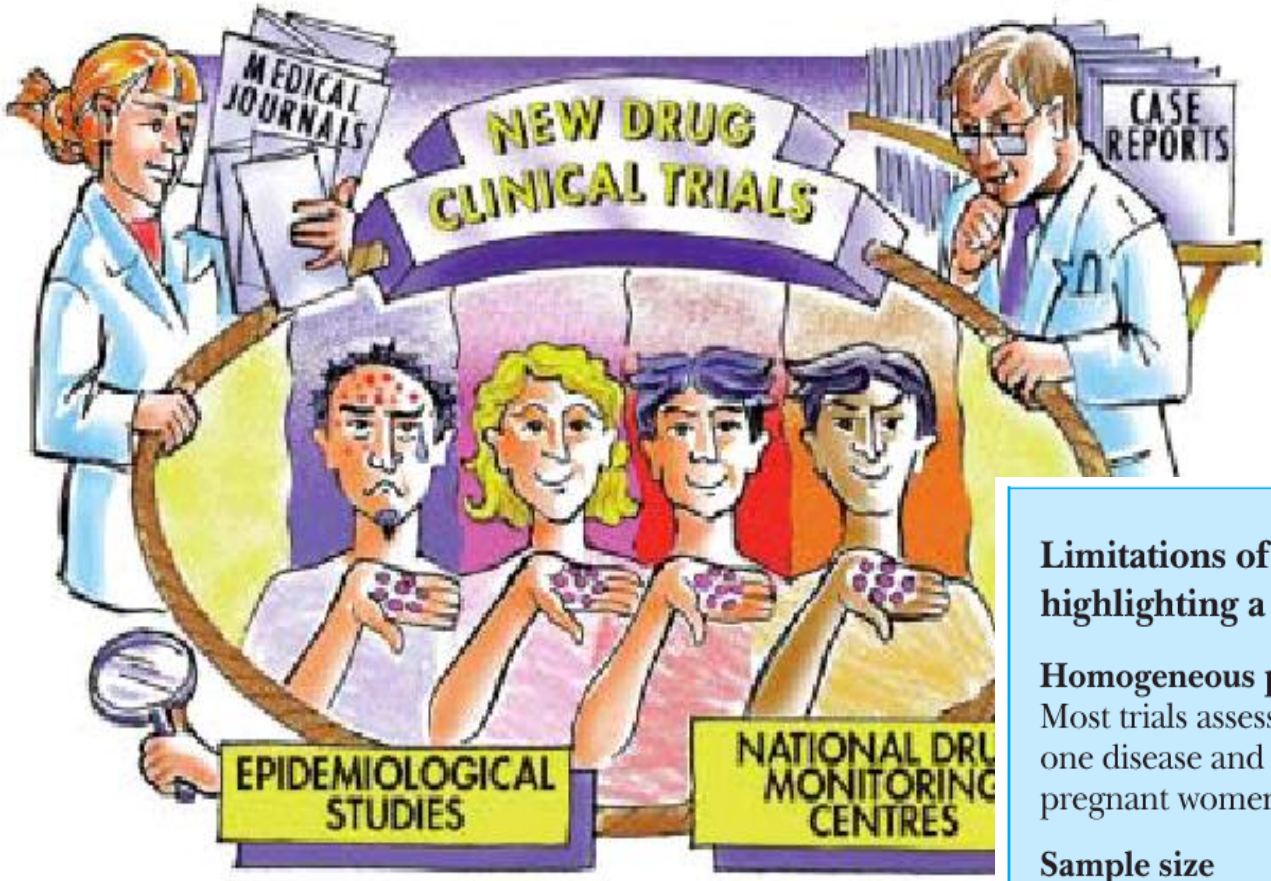
Contents

- Drug development post-approval
- Methodological challenges of observational post-approval studies
- Effectiveness versus efficacy (Real World Evidence)
- Challenges and solutions for multi-country, mult-database studies
- Applications of Real World EHR data during Sars-Cov-2 Pandemic

Drug development does not stop after approval



Proteomes **2016**, *4*, 28; doi:10.3390/proteomes4030028



Limitations of most clinical trials in highlighting a drug's safety

Homogeneous populations
Most trials assess relatively healthy patients with only one disease and mostly exclude specific groups such as pregnant women, children, and elderly people

Sample size
Small sample size (up to 1000 patients) reduces the chance of finding rare adverse effects

Limited duration
Trials of short duration preclude the discovery of long term consequences such as cancer

Inability to predict the real world
Drug interactions can be substantial in a population as patients may take drugs concomitantly, a situation that can almost never be predicted from clinical trials

Stricker BHCh, Psaty BM. Br Med J 2004; 329:44-7.

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PLoS MEDICINE

Essay

Observational Research, Randomised Trials, and Two Views of Medical Science

Jan P. Vandenbroucke

Box 1. Hierarchy of Study Designs for Intended Effects of Therapy

1. Randomised controlled trials
2. Prospective follow-up studies
3. Retrospective follow-up studies
4. Case-control studies
5. Anecdotal: case report and series

Box 2. Hierarchy of Study Designs for Discovery and Explanation

1. Anecdotal: case reports and series, findings in data, literature
2. Case-control studies
3. Retrospective follow-up studies
4. Prospective follow-up studies
5. Randomised controlled trials

Systematic evaluation of the

The centralised Santeon Farmadatabase does not contain any patient-specific data that could pose a risk to patients' privacy. The only personal data included in the database are gender, year and month of birth. These items are allowed for storage without a formal approval from the Dutch Data Protection Authority and an informed consent from the patient is not required.[3 4] The latter is under the condition that all hospitals have an operational opt-out procedure for patients who do not want their data to be used for scientific research. Patients who have opted out are actively filtered during the data uploading process. During

Figure 1 The locations of the Santeon hospitals in the Netherlands.

Systematic evaluation of the efficacy–effectiveness gap of systemic treatments in metastatic nonsmall cell lung cancer

Christine M. Cramer-van der Welle [1], Bas J.M. Peters[2], Franz M.N.H. Schramel[3], Olaf H. Klungel[4], Harry J.M. Groen[5] and Ewoudt M.W. van de Garde[2,4], for the Santeon NSCLC Study Group[6]

TABLE 2 Number of patients, real-world outcomes and reference outcome per regimen

	Patients (real-world) n	Median OS (real-world) months	Median OS (clinical trials) months [reference]
Cisplatin-pemetrexed	347	8.90#	10.19 [14–17]
Cisplatin-gemcitabine	214	7.90#	9.88 [16–43]
Carboplatin-pemetrexed	213	6.51#	10.18 [44–48]
Carboplatin-gemcitabine	171	6.67#	8.75 [42–44, 49–59]
Bevacizumab-carboplatin-paclitaxel	73	8.18#	12.57 [14, 47, 60, 61]
Carboplatin-docetaxel	45	4.93#	9.52 [45, 62–65]
Gefitinib (in EGFR-positive patients)	35	21.19#	24.90 [66–71]
Erlotinib (in EGFR-positive patients)	24	14.32#	22.01 [72, 73]
Total	1122	8.02#	10.84

OS: overall survival; EGFR: epidermal growth factor receptor. #: significantly different from median OS clinical trials.

TABLE 3 Completion of treatment plan in first-line chemotherapy, and subsequent lines of chemotherapy

	Completion of ⩾4 cycles		Subsequent line of chemotherapy	
	Real world	Clinical trials % (n references)	Real world	Clinical trials % (n references)
Cisplatin-pemetrexed	209 (60)	72 (2)	123 (35)	50 (2)
Cisplatin-gemcitabine	129 (60)	44 (19)	79 (37)	43 (10)
Carboplatin-pemetrexed	109 (51)	69 (4)	56 (26)	41 (4)
Carboplatin-gemcitabine	76 (44)	58 (13)	56 (33)	21 (5)
Bevacizumab-carboplatin-paclitaxel	52 (71)	70 (2)	29 (40)	54 (3)
Carboplatin-docetaxel	22 (49)	52 (4)	19 (42)	33 (4)
Gefitinib (in EGFR-positive patients)	13.4 months[#]	7.0 months[#] (3)	16 (46)	66 (5)
Erlotinib (in EGFR-positive patients)	9.6 months[#,¶]	10.5 months[#] (2)	9 (38)	57 (1)
Overall	56%	61%	34%	46%

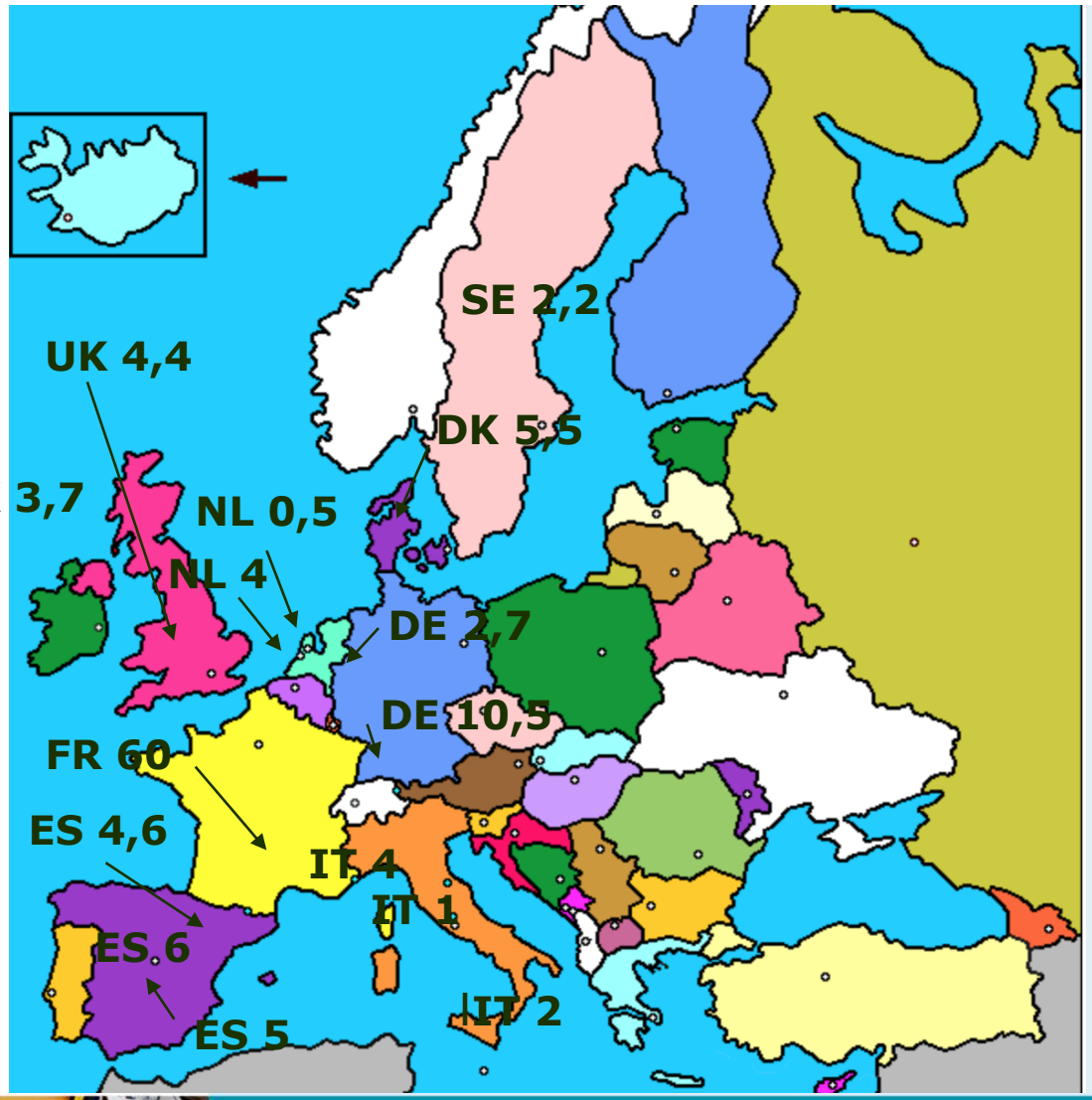
Data are presented as n (%), unless otherwise stated. EGFR: epidermal growth factor receptor. [#]: mean duration of treatment in months; [¶]: n=1 missing.

Rationale for Multi Database studies

- Increased sample size
  - Precise estimates for rare exposures/outcomes
  - Subgroup effects
  - Short time window (early months following approval)

- Reproducibility
  - Conceptual replication:
    - Different Data <> Same Methods
    - Same Data <> Different Methods
    - Different Data <> Different Methods

EU PE&PV research network
>115 M subjects (cumulative)



Characteristics of selected EU healthcare databases

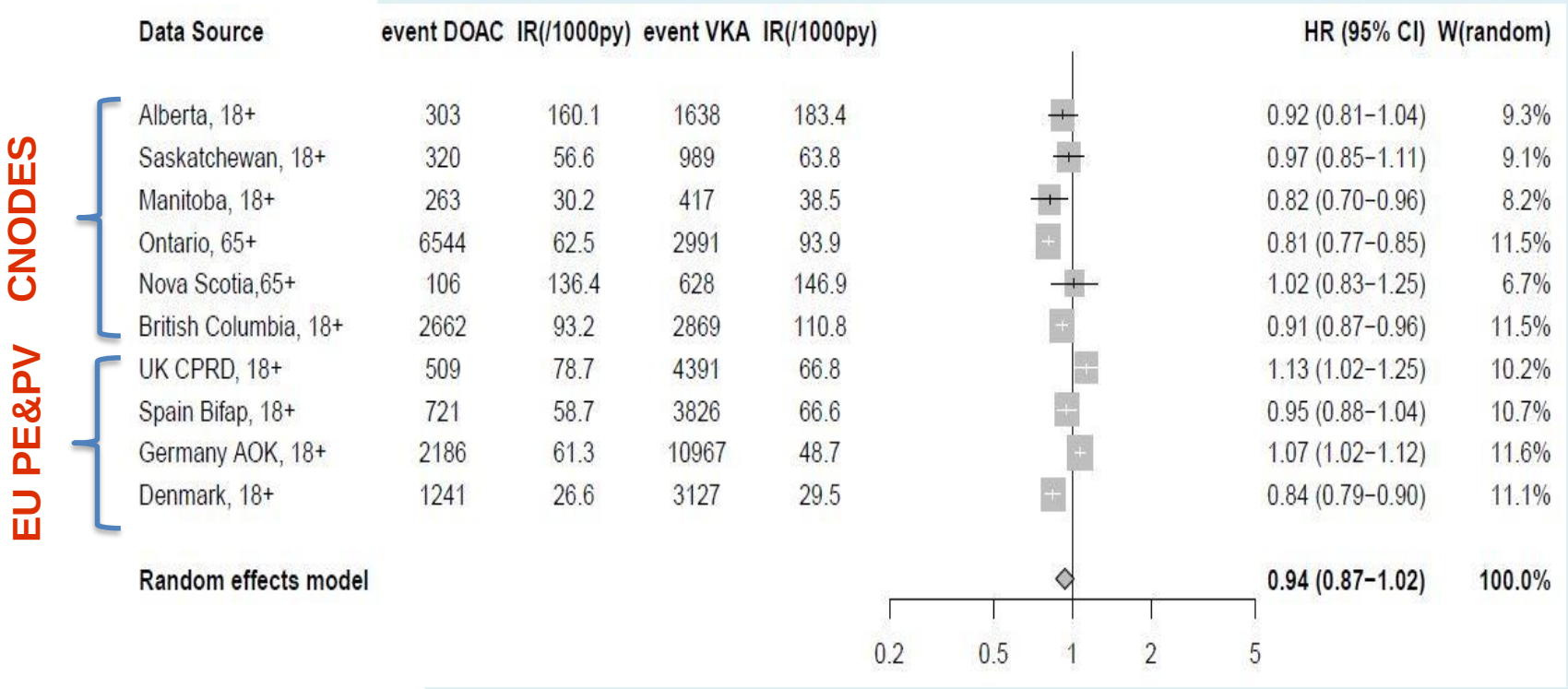
Database	Country	Cumulative population (2008)	Data source	Coding diagnoses	Free text	Coding drugs	Recording of drug use
BIFAP	ES	7.5 M	GP	ICPC-2, ICD-9	Spanish	ATC	Prescribing
SIDIAP	ES	7.0 M	GP	ICD-10	No	ATC	Prescribing
ARS	IT	4.0 M	Hospital claims/death	ICD-10	No		Dispensing
Health Search Italy	IT	1.0 M		ICD-9-CM	Italian		
CPRD	UK	12.5 M	GP	READ	English	BNF	Prescribing
THIN	UK	7.8 M	GP	READ	English	BNF	Prescribing
IPCI AHC	NL NL	0.75 M 0.26 M	GP GP/Pharmacy	ICPC ICPC	Dutch Dutch	ATC ATC	Prescribing Prescribing + dispensing
PHARMO	NL	3 M	Pharmacy/Hospital/Laboratory/GP	ICD-9-CM, ICPC	Dutch	ATC	Prescribing /dispensing
The Danish national registries	DK	5.2 M	Hospital/ Pharmacy/death	ICD-8/9/10	No	ATC	Dispensing
Bavarian Claims	DE	10.5 M	Claims	ICD-10-GM	No	ATC	Dispensing
AOK Nordwest	DE	2.7 M	Claims	ICD-10-GM	No	ATC	Dispensing
EGB	FR	0,7/60 M	Claims	ICD-10	No	ATC	Dispensing

Common protocol, Distributed Data Network

EU PE&PV, CNODES

- No sharing of individual patient data
- Overall results are collected for meta-analysis
- Allows optimization for individual database
- Common protocol with sufficient detail implemented at single site
- Blinding of site-specific results

DOACs and risk of major bleeding



EU PE&PV Network; EMA Framework service contract (nr. EMA/2015/27/PH)

Collaboration between EMA/Health Canada/UU/CNODES

Van den Ham, Souverein PC, Klungel OH, et al. Submitted

Different Strategies to Execute Multi-Database Studies for Medicines Surveillance in Real-World Setting: A Reflection on the European Model

Rona Gini[1,*], Miriam C. J. Sturkenboom[2], Janet Sultana[3], Alison Cave[4], Annalisa Landi[5,6], Alexandra Pacurariu[4], Giuseppe Roberto[1], Tania Schink[7], Gianmario Candore[4], Jim Slattery[4], and Gianluca Trifirò[8] on behalf of the Working Group 3 of ENCePP (Inventory of EU data sources and methodological approaches for multisource studies)

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 108 NUMBER 2 | August 2020

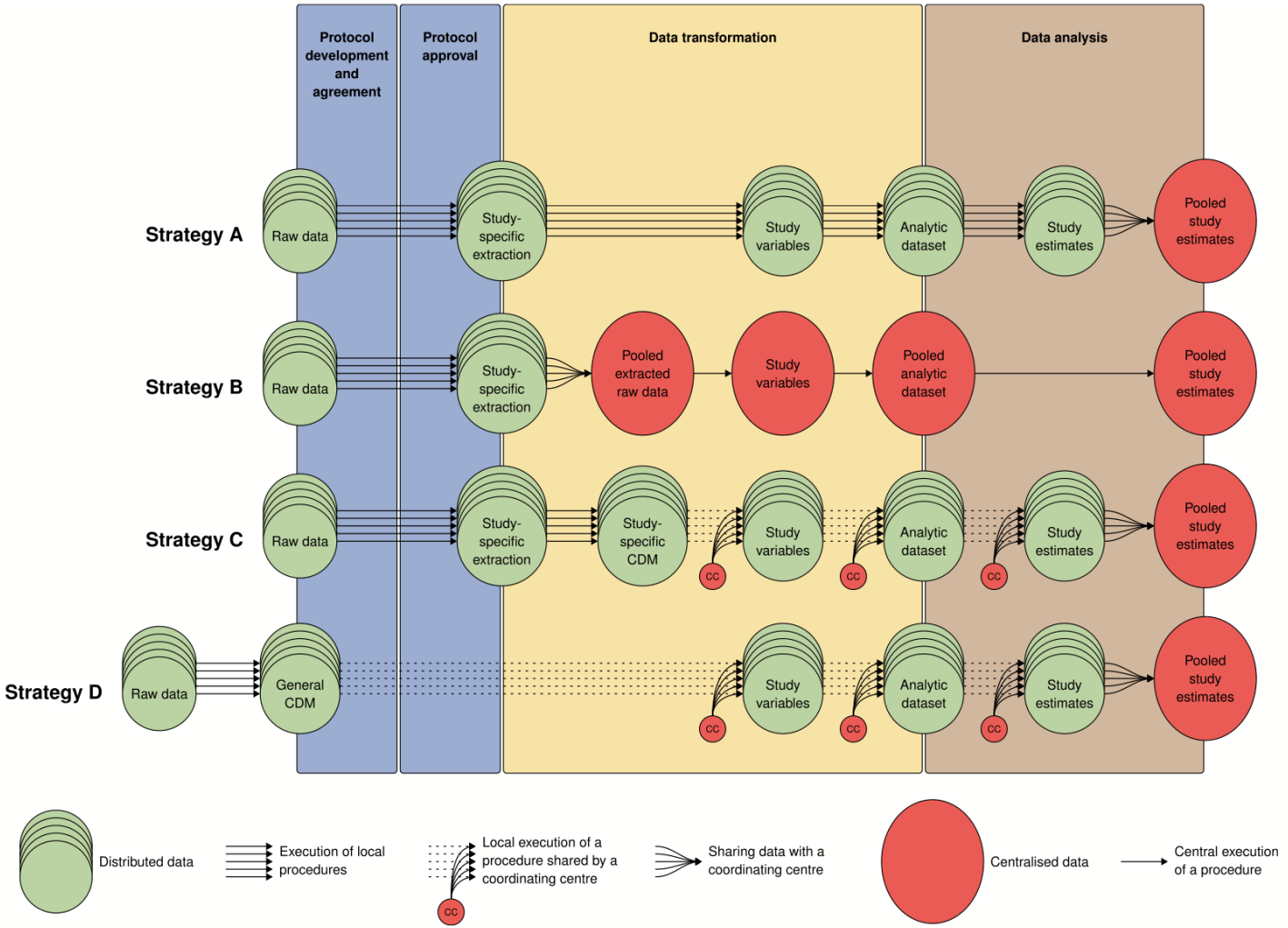


Figure 1 Graphical representation of the four strategies. For simplicity, we did not graphically represent the possibility that in strategies A, C, and D analytic datasets or an aggregated version thereof may be shared. It is intended that the data transformation of raw data into the general CDM in strategy D happens independently of a specific study. CDM, common data model.

CNODES: the Canadian Network for Observational Drug Effect Studies

Samy Suissa, David Henry, Patricia Caetano, Colin R. Dormuth, Pierre Ernst, Brenda Hemmelgarn, Jacques LeLorier, Adrian Levy, Patricia J. Martens, J. Michael Paterson, Robert W. Platt, Ingrid Sketris, Gary Teare; for the Canadian Network for Observational Drug Effect Studies (CNODES)

Open Medicine 2012;6(4)e134

The FDA Sentinel Initiative — An Evolving National Resource

Richard Platt, M.D., Jeffrey S. Brown, Ph.D., Melissa Robb, M.S., Mark McClellan, M.D., Ph.D., Robert Ball, M.D., M.P.H., Michael D. Nguyen, M.D., and Rachel E. Sherman, M.D., M.P.H.

N ENGL J MED 379;22 NEJM.ORG NOVEMBER 29, 2018

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2013; **22**: 700–704
Published online 8 May 2013 in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.3439

COMMENTARY

The Asian Pharmacoepidemiology Network (AsPEN): promoting multi-national collaboration for pharmacoepidemiologic research in Asia

AsPEN collaborators[†], Morten Andersen[1,12,13], Ulf Bergman[1,12,13], Nam-Kyong Choi[2,14], Tobias Gerhard[3,15], Cecilia Huang[3,15], Jessica Jalbert[4], Michio Kimura[5], Tomomi Kimura[5], Kiyoshi Kubota[6], Edward Chia-Cheng Lai[7], Nobuhiro Ooba[6], Byung-Joo Park[8,9]*, Nicole Pratt[10], Elizabeth E. Roughead[10], Tsugumichi Sato[6], Soko Setoguchi[11], Ju-Young Shin[9], Anders Sundström[1,12,13] and Yea-Huei Kao Yang[7]

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EMA commissions independent research to prepare for real-world monitoring of COVID-19 vaccines

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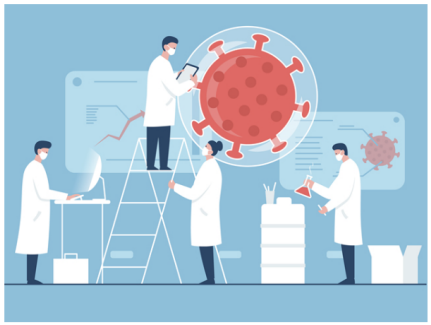
Press release 27/05/2020



EMA is engaging early with researchers to ensure that a European infrastructure will be in place to effectively monitor COVID-19 vaccines in the real world, once these are authorised in the European Union. The Agency has signed a contract with Utrecht University as coordinator of the EU Pharmacoepidemiology and Pharmacovigilance Research Network, a public-academic partnership of 22 European research centres, to conduct preparatory research into data sources and methods that can be used to monitor the safety, effectiveness and coverage of COVID-19 vaccines in clinical practice. The ACCESS (vACcine Covid-19 monitoring readinESS) project will be led by the University Medical Center Utrecht (UMCU) and Utrecht University.

Prof. dr. Miriam Sturkenboom, prof. dr. OH Klungel

Utrecht University

Pharmacoepidemiology & Clinical Pharmacology

EHR Data to calculate background rates of >20 AESI (adverse events of special interest)

Country	Organization	Name Data source	Active population	Type of data source
Germany	BIPS	GePaRD	16 million	Health insurance
Netherlands	PHARMO	PHARMO	6 million	Record linkage
Denmark	Aarhus University	Danish Registries	5.8 million	Record linkage
Spain	AEMPS	BIFAP	8 million	GP Medical records
Spain-Valencia	FISABIO	FISABIO	5 million	Record linkage
Spain-Catalunya	IDIAP-Jordi Gol	SIDIAP	5.7 million	Record linkage
Italy	SoSeTe	PEDIANET	0.3 million	Pediatric medical record
	ARS	ARS data	5 million	Record linkage
United Kingdom	University Utrecht	CPRD	13 million	GP medical record
Norway	University Oslo	Norwegian registries	5.3 million*	Record linkage
France	University of Bordeaux BPE	SNDS	69 million	Health insurance
Total			138.6 million	

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Many hypotheses/rumours on specific medicines during pandemic

…. and risk of infection

….. and prognosis.

Ibuprofen, hydroxychloroquine, ACE inhibitors, Angiotensin II type 1 receptor antagonists, statins….

Need for **urgent** and **reliable** evidence

Received: 14 April 2020 | Revised: 28 April 2020 | Accepted: 2 May 2020

DOI: 10.1002/pds.5029

REVIEW

WILEY

Considerations for pharmacoepidemiological analyses in the SARS-CoV-2 pandemic

Anton Pottegård[1] | Xavier Kurz[2] | Nicholas Moore[3] | Christian F. Christiansen[4] | Olaf Klungel[1,5]

This commentary received endorsement from the International Society for Pharmacoepidemiology (ISPE).

Pharmacoepidemiol Drug Saf. 2020;1–7.

Spain - Madrid

Use of renin–angiotensin–aldosterone system inhibitors and risk of COVID-19 requiring admission to hospital: a case-population study

*Francisco J de Abajo, Sara Rodríguez-Martín, Victoria Lerma, Gina Mejía-Abril, Mónica Aguilar, Amelia García-Luque, Leonor Laredo, Olga Laosa, Gustavo A Centeno-Soto, Maria Ángeles Gálvez, Miguel Puerro, Esperanza González-Rojano, Laura Pedraza, Itziar de Pablo, Francisco Abad-Santos, Leocadio Rodríguez-Mañas, Miguel Gil, Aurelio Tobías, Antonio Rodríguez-Miguel, Diego Rodríguez-Puyol, on behalf of the MED-ACE2-COVID19 study group**

Summary

Background Concerns have been raised about the possibility that inhibitors of the renin–angiotensin–aldosterone system (RAAS) could predispose individuals to severe COVID-19; however, epidemiological evidence is lacking. We report the results of a case-population study done in Madrid, Spain, since the outbreak of COVID-19.

Lancet 2020; 395: 1705–14

Published Online
May 14, 2020
https://doi.org/10.1016/

Interpretation RAAS inhibitors do not increase the risk of COVID-19 requiring admission to hospital, including fatal cases and those admitted to intensive care units, and should not be discontinued to prevent a severe case of COVID-19.

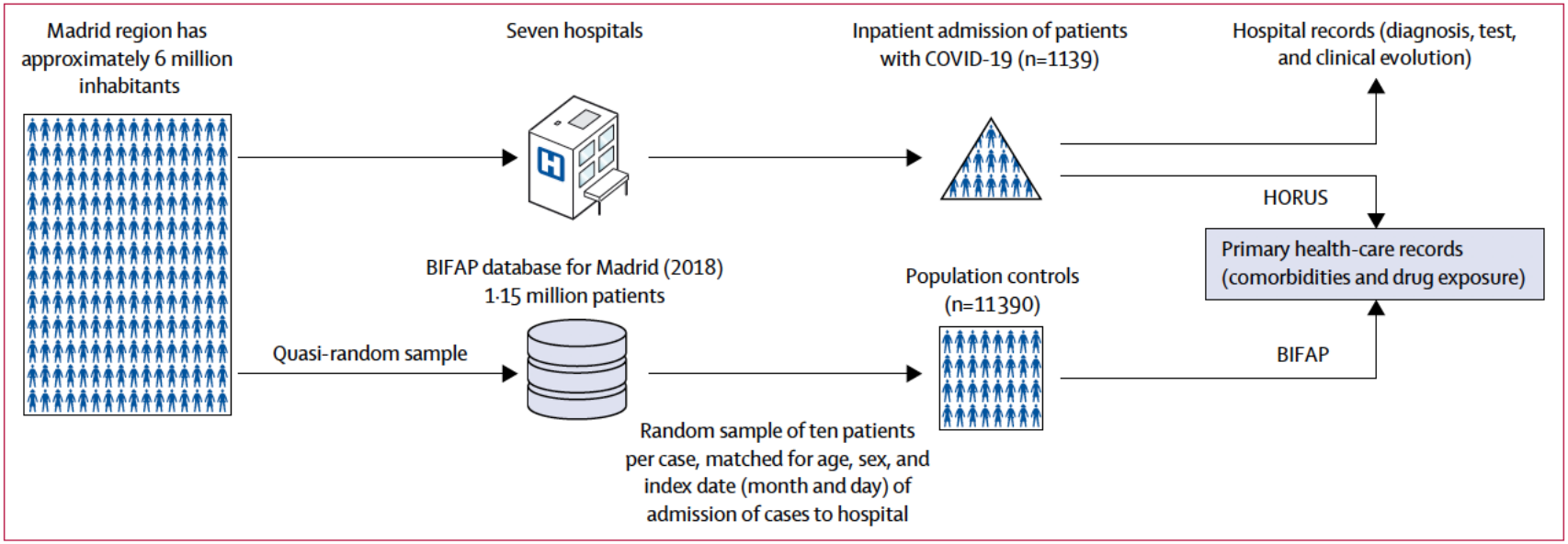

Figure 1: **Case-population study design**

COVID-19 cases requiring admission to hospital were selected consecutively from seven hospitals in Madrid, Spain. Data were collected for ten individuals per case who were matched for age, sex, and index date (day and month) of hospital admission of cases (matched controls) from the 2018 Madrid region database of BIFAP, a national primary health-care database. Drug exposure and comorbidities before the index date (2020 for cases and 2018 for controls) were collected from primary health-care records of the NHS in Madrid: for cases through HORUS (an online platform to access primary-care clinical records from any health-care centre of the NHS in Madrid) and for controls through BIFAP. BIFAP=Base de datos para la Investigación Farmacoepidemiológica en Atención Primaria. NHS=National Health System.

Denmark

JAMA | Original Investigation

Association of Angiotensin-Converting Enzyme Inhibitor or Angiotensin Receptor Blocker Use With COVID-19 Diagnosis and Mortality

Emil L. Fosbøl, MD, PhD; Jawad H. Butt, MD; Lauge Østergaard, MD; Charlotte Andersson, MD, PhD; Christian Selmer, MD, PhD; Kristian Kragholm, MD, PhD; Morten Schou, MD, PhD; Matthew Phelps, MSc; Gunnar H. Gislason, MD, PhD; Thomas A. Gerds, Dr rer nat; Christian Torp-Pedersen, MD, DMSc; Lars Køber, MD, DMSc

Editor's Note page 177

IMPORTANCE It has been hypothe
(ACEIs)/angiotensin receptor bloc
coronavirus disease 2019 (COVID-
functional receptor of the virus, ar

CONCLUSIONS AND RELEVANCE
with COVID-19 diagnosis among
disease among patients diagnos
discontinuation of ACEI/ARB me
COVID-19 pandemic.

upplemental

doi:10.1001/jama.2020.11301
20.

Data Sources

Data from Danish national administrative registries were linked on an individual level by the use of a unique personal identifier. By such linkage, data were obtained on civil status, hospitalizations, procedures, and prescription fills. The Danish health care system is administered by the state, and all hospitalizations since 1978 are registered (using *International Classification of Diseases, Eighth Revision* [*ICD-8*] coding of diagnoses from 1978-1994 and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* [*ICD-10*] thereafter), all procedures since 1996 are registered, and all prescription fills since 1995 are registered. The Danish registries are validated, previously described in detail, and are of high quality and completeness.[15,16]

& Clinical Pharmacology

Multi-country EU

In June, EMA contracted the company IQVIA with a project to build a framework for the conduct of **multicentre cohort studies on the use of medicines in COVID-19 patients**. This project will include the identification of large national cohorts of COVID-19 patients and appropriate comparator groups, the development of a study protocol template for multinational studies as well as the establishment of a collaborative framework for researchers. The project will be carried out in collaboration with the European Health Data & Evidence Network (EHDEN) consortium, which was established under the Innovative Medicines Initiative and includes the Erasmus Medical Centre in Rotterdam and the University of Oxford as project lead and research coordinator, respectively.*

Conclusions

- Routine Electronic Health Care Data are Essential for Post-approval Safety and Effectiveness assessment of medicines
  - Complementary to RCTs
    - Safety (rare events, long term effects)
    - Effectiveness in Real World
- Valid design, analysis and data
- EU Models for Multi-Database studies established and described
  - Further development and strengthening of infrastructure
- COVID-19 related research on medicines builds on many years of experience in collecting and analyzing of Real World Data
  - Maintain access to data, while preserving privacy