Use of (RW)data in assessing the quality, safety, and efficacy of the medicines

Carla Torre

FACULDADE DE FARMÁCIA
UNIVERSIDADE DE LISBOA

Disclosure

- The views expressed in this presentation are my personal views and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency (EMA) or any of its committees or working parties/groups I am affiliated with.

- I declare having no conflict of interest.

A single story of a *continuum* of tales in regulatory decision making

REVIEW

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 109 NUMBER 5 | May 2021

Randomized Controlled Trials Versus Real World Evidence: Neither Magic Nor Myth

Hans-Georg Eichler[1,2,*], Francesco Pignatti[1], Brigitte Schwarzer-Daum[2,3], Ana Hidalgo-Simon[1], Irmgard Eichler[1], Peter Arlett[1,4], Anthony Humphreys[1], Spiros Vamvakas[1], Nikolai Brun[5] and Guido Rasi[1,6]

Compared with drugs from the blockbuster era, recently authorized drugs and those expected in the future present a heterogenous mix of chemicals, biologicals, and cell and gene therapies, a sizable fraction being for rare diseases, and even individualized treatments or individualized combinations. The shift in the nature of products entails secular trends for the definitions of "drugs" and "target population" and for clinical use and evidence generation. We discuss that the lessons learned from evidence generation for 20th century medicines may have limited relevance for 21st century medicines. We explain why the future is not about randomized controlled trials (RCTs) vs. real-world evidence (RWE) but RCTs and RWE—not just for the assessment of safety but also of effectiveness. Finally, we highlight that, in the era of precision medicine, we may not be able to reliably describe some small treatment effects—either by way of RCTs or RWE.

Ready-Made Bouquet, *Rene Magritte* (1956)

1. **The use of RWD to support regulatory decision making is not new (e.g. SAFETY) – different evidentiary role according to decision contexts**

2. **Current landscape: research question drives evidence choice - embraces spectrum of data and methods**

Leads to a driver change: it is NOT about RCT *vs* RWE…
…..BUT RCTs AND RWE…COMPLEMENTARY

Shift in the nature of R&D pipeline: moving from *block*buster to *niche*buster

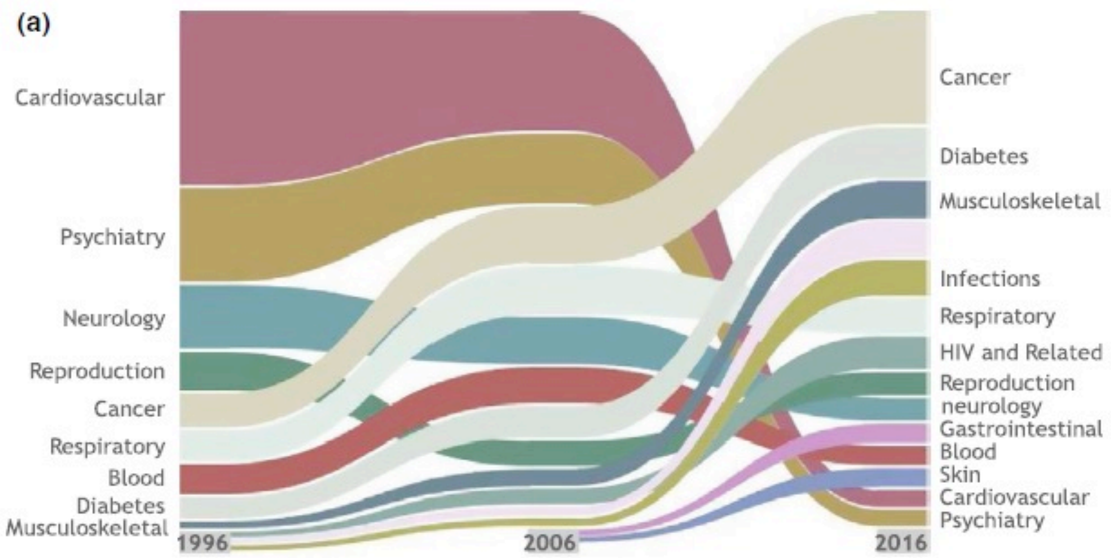
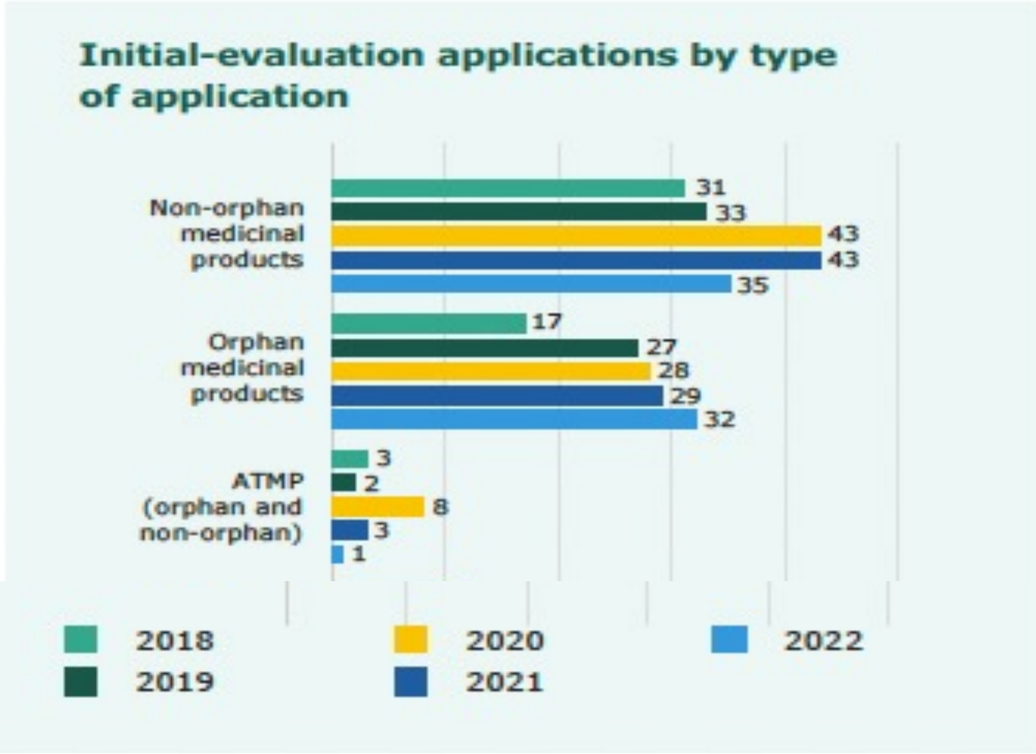


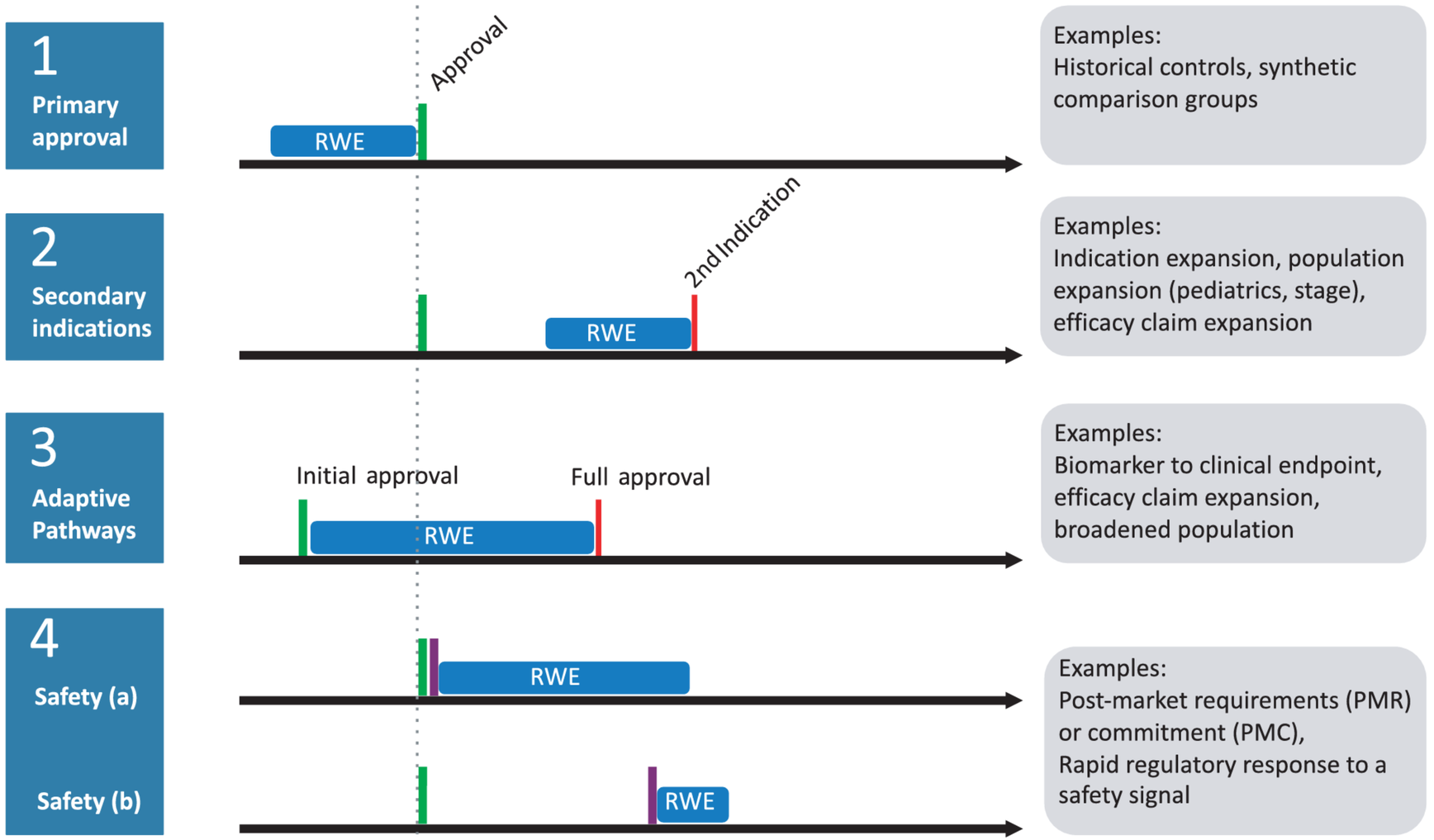
Figure 1 Therapeutic area trends. (a) United States share of revenue by therapeutic area, 1996–2



An increasing number of medicines orphan products/ATMPs for conditions with significant unmet need, face challenges when aligning with the traditional drug development pathway (e.g. traditional RCTs may be *unfeasible*, *unethical*, or less well suited to "precision medicines")

EMA Annual Report, 2022

RWE & Regulatory Decision Making: key use cases



Franklin JM, Glynn RJ, Martin D, Schneeweiss S. Evaluating the Use of Nonrandomized Real-World Data Analyses for Regulatory Decision Making. Clin Pharmacol Ther. 2019

Trends in recent RWD use in EMA/FDA approved medicines

Review | Open Access

Marketing Authorization Applications Made to the European Medicines Agency in 2018–2019: What was the Contribution of Real-World Evidence?

Robert Flynn, Kelly Plueschke, Chantal Quinten, Valerie Strassmann, Ruben G. Duijnhoven, Maria Gordillo-Marañon, Marcia Rueckbeil, Catherine Cohet, Xavier Kurz

First published: 24 October 2021 | https://doi.org/10.1002/cpt.2461 | Citations: 1

> Clin Pharmacol Ther. 2023 Jan;113(1):135-151. doi: 10.1002/cpt.2766. Epub 2022 Nov

Contribution of Real-World Evidence in European Medicines Agency's Regulatory Decision Making

Elisabeth Bakker [1], Kelly Plueschke [2], Carla J Jonker [2 3], Xavier Kurz [2], Viktoriia Starokozhko [1 3], Peter G M Mol [1 3 4]

Affiliations + expand

PMID: 36254408 PMCID: PMC10099093 DOI: 10.1002/cpt.2766

FDA U.S. FOOD & DRUG ADMINISTRATION

Review | Open Access

The Role of Real-World Evidence in FDA-Approved New Drug and Biologics License Applications

Christina A. Purpura, Elizabeth M. Garry, Nicholaas Honig, Abigail Case, Jeremy A. Rassen

First published: 02 November 2021 | https://doi.org/10.1002/cpt.2474 | Citations: 1

Article | Open Access

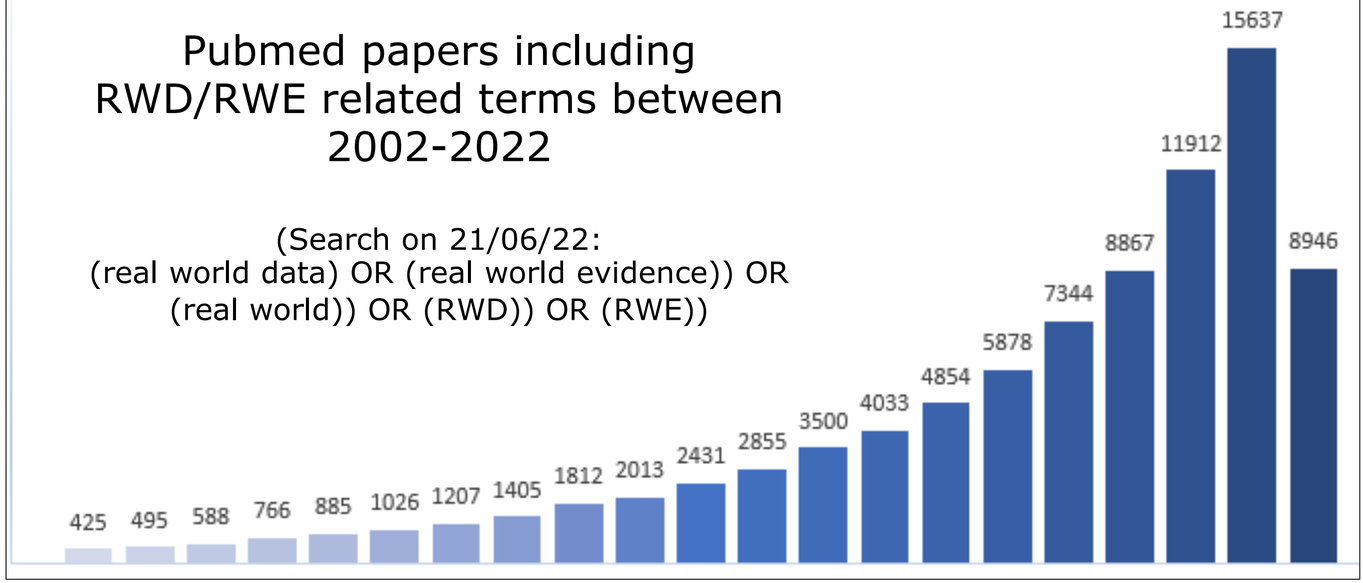
Use of Real-World Data and Evidence in Drug Development of Medicinal Products Centrally Authorized in Europe in 2018–2019

Sini Marika Eskola, Hubertus Gerardus Maria Leufkens, Andrew Bate, Marie Louise De Bruin, Helga Gardarsdottir

First published: 24 October 2021 | https://doi.org/10.1002/cpt.2462

Pubmed papers including RWD/RWE related terms between 2002-2022

(Search on 21/06/22:
(real world data) OR (real world evidence)) OR (real world)) OR (RWD)) OR (RWE))



Courtesy Kelly Plueschke & Carla Jonker, EMA

Trends in recent use in EMA/FDA approved medicines

Part I

	Flynn et al. (2022) What was the Contribution of Real-World Evidence in EU?	Eskola et. al (2022) Use of Real-World Data and Evidence in Drug Development in EU	Purpura et al. (2022) The Role of Real-World Evidence in FDA
Number of products reviewed	158	111	136
Period	Jan 2018 – Dec 2019 (submitted marketing applications, including non-published information)	Jan 2018 – Dec 2019 (approved marketing applications, only published information)	Jan 2019 – June 2021 (approved marketing applications, only published information)
Number of products with RWE included	**63 (39.9%)**	**111 (100%)**	**116 (85.2%)**
Therapeutic area with higher use of RWE	Oncology and anti-infectives	Oncology, hematology and anti-infectives	Oncology and anti-infectives
	High variability in percentages of applications with RWE due to: • Different definitions • Different sources of information (e.g., authorised vs. submitted applications) • Different methods		

Courtesy **Kelly Plueschke & Carla Jonker, EMA**

Trends in recent use in EMA approved medicines

Part II

- Considering variety of purpose for which RWD is used and data sources used, appraisal of RWE still requires a **case-by-case analysis**
- **As RWD is usually considered in the overall evidence package of the applications,** it is **difficult to isolate its exact impact on decision making (e.g. influential, supportive)**
- Strengths were mentioned less often than **limitations**. Some examples:

Strengths	Limitations

• Registries are able to obtain data over several years from a quite significant number of patients with a rare disease
 	
• Appropriateness of:
  • Use of historical controls
  • Study population
  • Follow-up time
  • Measuring time points
	• Missing data
	• Lack of representativeness of e.g.,:
	  • Study population
	  • Study period
	  • Measuring time points
	• Small sample size
	• Lack of an adequate or pre-specified analysis plan
	• Risk of several types of confounding and bias, e.g.:
	  • Selection bias
	  • Publication bias

COVID-19 as a window of opportunity to RWE

son of those outcomes with RWD from patients in studies of the natural history of the condition. Although RWD were less prominent here than in the tacrolimus approval, in both cases, reviewers found the data fit for use and

tions of RWD and RWE and practices related to them. In general, the pandemic has accelerated awareness and adoption of RWD and RWE, but their use was already increasing before the pandemic. In addition, though

more
conduc
tional
vance

The v
those of
ily repre
Food an
versity.

Disclo
are avail

From the
the Offi
Center f
Food and
MD; and
(J.C.).

This art
2022, at

1. Food
work fo
gram. D

Overall, Covid-19 presents an opportunity to leverage RWD to inform clinical and regulatory decisions, but scientific rigor must be maintained.

concluded that the study design addressed the regulatory question and that the study conduct met FDA requirements.[2]

robust RWE has sometimes informed pandemic responses,[5] challenges involved in diagnosing, treating, and reporting on a

The telescope, *Rene Magritte* (1963)

Concato J, Corrigan-Curay J. Real-World Evidence - Where Are We Now? N Engl J Med. 2022

The pandemonium of RWD during a pandemic

American Journal of Epidemiology
© The Author(s) 2021. Published by Oxford University Press on behalf of the Johns Hopkins Bloomberg School of Public Health. All rights reserved. For permissions, please e-mail: journals.permissions@oup.com.
Vol. 190, No. 8
https://doi.org/10.1093/aje/kwab028
Advance Access publication: February 10, 2021

Commentary

Biases in Evaluating the Safety and Effectiveness of Drugs for the Treatment of COVID-19: Designing Real-World Evidence Studies

Christel Renoux, Laurent Azoulay, and Samy Suissa*

* Correspondence to Dr. Samy Suissa, Centre for Clinical Epidemiology, Jewish General Hospital 3755 Cote Ste-Catherine, H4.61, Montreal, Québec, Canada H3T 1E2 (e-mail: samy.suissa@mcgill.ca).

Initially submitted August 12, 2020; accepted for publication February 5, 2021.

Trust

EPIDEMIOLOGY
Articles & Issues · Collections · Multimedia · For Authors · Journal Info

Outline · Download · Cite · Share · Favorites · Permissions

LETTERS

Re: Association of Inpatient Use of Angiotensin-converting Enzyme Inhibitors and Angiotensin II Receptor Blockers with Mortality Among Patients with Hypertension Hospitalized with COVID-19

Rouette, Julie MSc; Suissa, Karine PhD; Azoulay, Laurent PhD
Author Information

Epidemiology 31(6):p e52-e53, November 2020. | *DOI:* 10.1097/EDE.0000000000001250

FREE · Metrics

To the Editor:

We read with interest the study by Zhang et al.,[1] examining the association between inpatient use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) and mortality in patients hospitalized with coronavirus disease 2019 (COVID-19), published in *Circulation Research*. The use of ACEIs or ARBs was associated with an important 58% risk reduction in all-cause

RETRACTED

Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis

Mandeep R Mehra, Sapan S Desai, Frank Ruschitzka, Amit N Patel

Summary

Background Hydroxychloroquine or chloroquine, often in combination with a second-generation m[illegible]ide, are [illegible] widely used for treatment of COVID-19, despite no conclusive evidence of their benefit. Although [illegible]erall[illegible]e when used for approved indications such as autoimmune disease or malaria, the safety and bene[illegible] of treatment regimens are poorly evaluated in COVID-19.

Methods We did a multinational registry analysis of the use of hydroxychloroquine [illegible]oroquine with[illegible]out a macrolide for treatment of COVID-19. The registry comprised data from 671 hospitals in [illegible] continents. We includ patients hospitalised between Dec 20, 2019, and April 14, 2020, with a positive laboratory [illegible]g for SARS-Co Patients who received one of the treatments of interest within 48 h of diagn[illegible] included in [illegible] four treatm groups (chloroquine alone, chloroquine with a macrolide, hydroxychlor[illegible]ine alone, or hydroxychloroquine wi macrolide), and patients who received none of these treatments formed [illegible] control gr[illegible] Patients for whom or the treatments of interest was initiated more than 48 h after diagnosis or [illegible]le they w[illegible]on mechanical ventilat as well as patients who received remdesivir, were excluded. The main outc[illegible] of int[illegible] were in-hospital mort and the occurrence of de-novo ventricular arrhythmias [illegible]ained o[illegible]ed ventricular tachycardi ventricular fibrillation).

Findings 96 032 patients (mean age 53·8 years, 46·3[illegible] women) [illegible]OVID-19 were hospitalised during the s period and met the inclusion criteria. Of the[illegible] patie[illegible]were in the treatment groups (1868 rece chloroquine, 3783 received chloroquine with[illegible]macr[illegible]e, 3016[illegible]eived hydroxychloroquine, and 6221 rece hydroxychloroquine with a macrolide) and [illegible] pati[illegible]to the control group. 10 698 (11·1%) patients die hospital. After controlling for multiple c[illegible]fou[illegible]ctors[illegible], sex, race or ethnicity, body-mass index, underl cardiovascular disease and its risk fac[illegible]diabetes[illegible]erlying lung disease, smoking, immunosuppressed condi and baseline disease severity), w[illegible]compared w[illegible]ortality in the control group (9·3%), hydroxychlorog (18·0%; hazard ratio 1·335, 95%[illegible]·2–1·457), hydr[illegible]chloroquine with a macrolide (23·8%; 1·447, 1·368–1·5 chloroquine (16·4%; 1·365, 1·318–1·531), [illegible]chloroquine with a macrolide (22·2%; 1·368, 1·273–1·469) were independently associated [illegible] an increased [illegible] of in-hospital mortality. Compared with the control group (0· hydroxychloroquine (6[illegible]·2·36[illegible]·935–2·900), hydroxychloroquine with a macrolide (8·1%; 5·106, 4·106–5·5 chloroquine (4·3%[illegible]·2[illegible]·0–4·596), and chloroquine with a macrolide (6·5%; 4·011, 3·344–4·812) independently associate[illegible]an inc[illegible]ed risk of de-novo ventricular arrhythmia during hospitalisation.

Interpretati[illegible] We [illegible] unable[illegible]confirm a benefit of hydroxychloroquine or chloroquine, when used alone or a macro[illegible]on in[illegible]ospital outcomes for COVID-19. Each of these drug regimens was associated with decre in-hospit[illegible]eased frequency of ventricular arrhythmias when used for treatment of COVID-1

Funding William[illegible]ey Distinguished Chair in Advanced Cardiovascular Medicine at Brigham and Women's Hosp

Introduction

The absence of an effective treatment against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has led clinicians to redirect drugs that are [illegible] drugs have been shown in laboratory conditions to [illegible] antiviral properties as well as immunomodula effects.[illegible] However, the use of this class of drugs COVID-19 is based on a small number of anec

Published Online June 4, 2020 https://doi.org/10.1016/S0140-6736(20)31324-6

Retraction—Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis

After publication of our *Lancet* Article,[1] several concerns were raised with respect to the veracity of the data and analyses conducted by Surgisphere Corporation and its founder and our co-author, Sapan Desai, in our publication. We launched an independent third-party peer review of Surgisphere with the consent of Sapan Desai to evaluate the origination of the database elements, to confirm the completeness of the database, and to replicate the analyses presented in the paper.

Our independent peer reviewers informed us that Surgisphere would not transfer the full dataset, client contracts, and the full ISO audit report to their servers for analysis as such transfer would violate client agreements and confidentiality requirements. As such, our reviewers were not able to conduct an independent and private peer review and therefore notified us of their withdrawal from the peer-review process.

We always aspire to perform our research in accordance with the highest ethical and professional guidelines. We can never forget the responsibility we have as researchers to scrupulously ensure that we rely on data sources that adhere to our high standards. Based on this development, we can no longer vouch for the veracity of the primary data sources. Due to this unfortunate development, the authors request that the paper be retracted.

We all [illegible] in good fai[illegible] the COVID-[illegible] you, the edi[illegible] embarrassm[illegible] caused.

MBM reports pers[illegible] Triple Gene, Mesoi[illegible] NupulseCV, FineH[illegible] committee memb[illegible] consulting, and le[illegible] to the University c[illegible] to these trials or o[illegible] personal fees fror[illegible] fees from Zoll, per[illegible] grants and person[illegible] fees from BMS, pe[illegible] personal fees fror[illegible] from Bayer, perso[illegible] Ingelheim, other f[illegible] competing interes[illegible]

*Mandeep R M[illegible]
mmehra@bwh[illegible]

Brigham and Wor[illegible] School, Boston, M[illegible] Hospital Zurich, Z[illegible] Engineering, Unive[illegible] Research Institute,[illegible]

1 Mehra MR, D[illegible] chloroquine[illegible] a multinational registry analysis. *Lancet* 2020; published online June 2. https://doi.org/10.1016/S0140-6736(20)31180-6.

Retraction: Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2007621.

TO THE EDITOR: Because all the authors were not granted access to the raw data and the raw data could not be made available to a third-party

Timothy D. Henry, M.D.
Christ Hospital
Cincinnati, OH
[illegible] N. Patel, M.D.
[illegible]ity of Utah
[illegible]ce City, UT

[illegible]ter was published on June 4, 2020, at NEJM.org.

News in focus

COVID-19 RETRACTIONS RAISE CONCERNS ABOUT DATA OVERSIGHT

Studies relied on health-record analyses from firm that declined to share its raw data for an audit.

By Heidi Ledford and Richard Van Noorden

Two weeks after a high-profile paper in *The Lancet*[1] reported that the anti-malarial drug hydroxychloroquine [illegible]

in South America, says Carlos Chaccour of the Barcelona Institute for Global Health in Spain, who is running a clinical trial of ivermectin and had raised questions about the preprint's data.

Researchers testing hydroxychloroquine in clinical trials are worried that the *Lancet* findings might make it harder for them to complete their research, despite the fact that the paper has been retracted. "We're hearing that people just aren't interested in hydroxychloroquine," says David Smith, an infectious-disease specialist at the University of California, San Diego, who is helping to run a trial of the drug in people with COVID-19 who have not been hospitalized.

Most data on hydroxychloroquine in COVID-19 have come from *in vitro* studies or small clinical trials. On 5 June, however, researchers working on a large randomized

Nature 588, 553 (2020)

The Treachery of Images, *Rene Magritte (1929)*

The value of RWE during a pandemic

Received: 12 July 2022 | Revised: 23 September 2022 | Accepted: 6 November 2022

DOI: 10.1111/bcp.15611

ORIGINAL ARTICLE

COVID-19-related medicine utilization study in pregnancy: The COVI-PREG cohort

Guillaume Favre[1] | Eva Gerbier[1,2] | Emeline Maisonneuve[1,2] | Léo Pomar[1,3] | Ursula Winterfeld[4] | Karine Lepigeon[1] | Kitty W. M. Bloemenkamp[5] | Odette de Bruin[5,6] | Hurley Eimir[7] | Hedvig Nordeng[7] | Satu J. Siiskonen[8] | Miriam C. J. M. Sturkenboom[6] | David Baud[1] | Alice Panchaud[2,9] | the COVI-PREG and CONSIGN group

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-022-29159-x OPEN

Check for updates

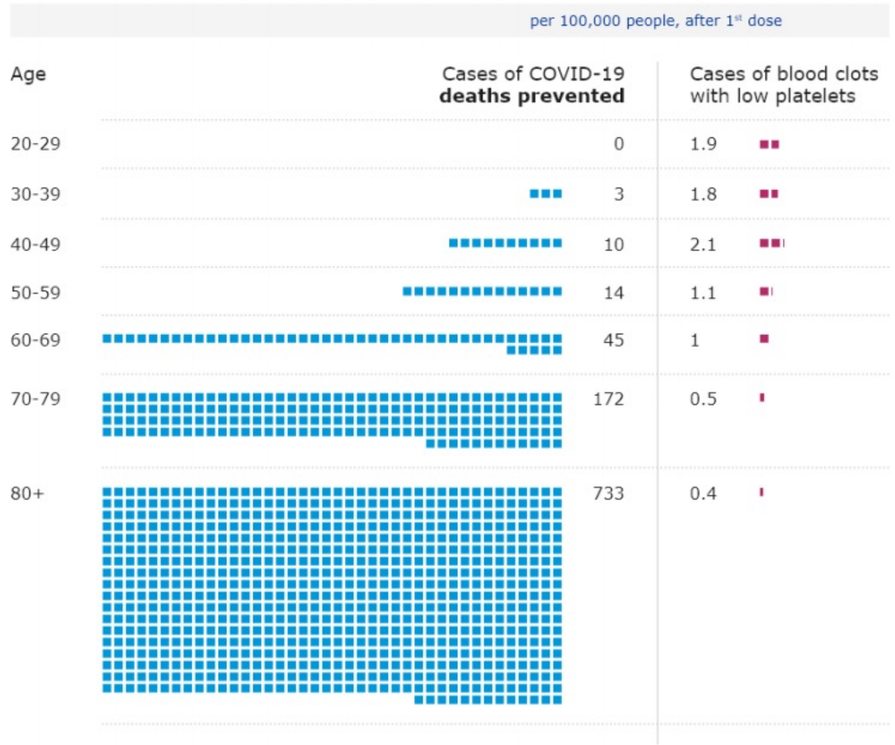
Comparative effectiveness of the BNT162b2 and ChAdOx1 vaccines against Covid-19 in people over 50

Junqing Xie[1], Shuo Feng[2], Xintong Li[1], Ester Gea-Mallorquí[3], Albert Prats-Uribe[1] & Dani Prieto-Alhambra[1]✉

Pandemic shows new ways of working

4. COVID-19 deaths prevented with Vaxzevria compared with unusual blood clots with low platelets

High infection rate*



* "High" exposure: using virus circulation for January 2021 (incidence 886/100,000 population)

RWD for regulatory decision making – real-world challenges, solutions and opportunities

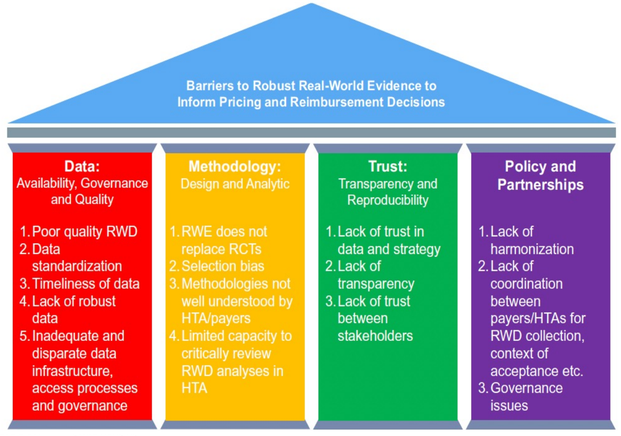
Real-world data and real-world evidence in regulatory decision making

CIOMS Working Group report
Draft, 6 June 2023

CIOMS

Can we use existing guidance to support the development of robust real-world evidence for health technology assessment/payer decision-making?

Gorana Capkun[1*], Sorcha Corry[2], Oonagh Dowling[1], Fatemeh Asad Zadeh Vosta Kolaei[1], Shweta Takyar[1], Cláudia Furtado[3], Páll Jónsson[4], Diane Kleinermans[5], Laurie Lambert[6], Anja Schiel[7] and Karen Facey[8]



Capkun et al, International Journal of Technology Assessment in Health Care, 2022

Real-World Evidence in EU Medicines Regulation: Enabling Use and Establishing Value

Peter Arlett[1,*], Jesper Kjær[2], Karl Broich[3] and Emer Cooke[1]

We outline our vision that 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. We are working to deliver this vision through collaboration where we leverage the best that different stakeholders can bring. This vision will support the development and use of better medicines for patients.

Arlett et al, Clin Pharmacol Ther. 2022

PERSPECTIVES

Real-World Data for Regulatory Decision Making: Challenges and Possible Solutions for Europe

Alison Cave[1,*], Xavier Kurz[1] and Peter Arlett[1]

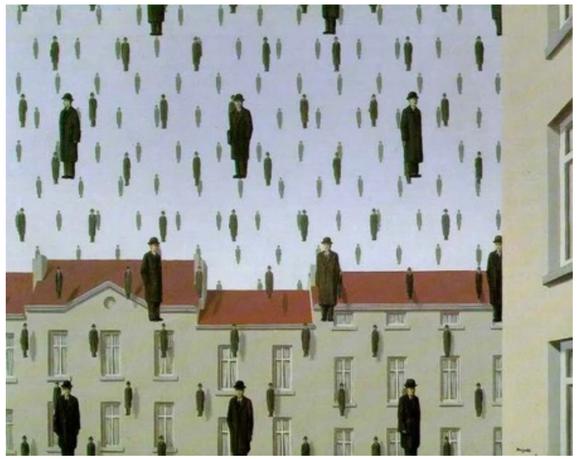
Real-world data (RWD) offers the possibility to derive novel insights on the use and performance of medicines in everyday clinical use, complementing rather than competing with evidence from randomized control trials. While Europe is rich in healthcare data, its heterogeneous nature brings operational, technical, and methodological challenges. We present a number of potential solutions to address the full spectrum of regulatory use cases and emphasize the importance of early planning of data collection.

Arlett et al, Clin Pharmacol Ther. 2019

HMA Heads of Medicines Agencies

EMA EUROPEAN MEDICINES AGENCY

I. DATA



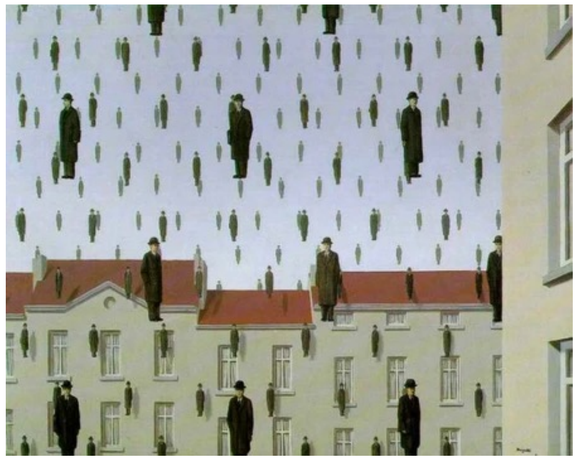
Golconda, *Rene Magritte* (1953)

Availability, Governance & Quality

- **Heterogeneity of RWD types** (e.g. EHR, claims, registries, patient-generated data) and **level care settings** (e.g. primary, secondary, tertiary) and **characteristics** (e.g. purpose, population coverage, data elements/coding terminology)
- **Different levels of data quality**: **dimensions** (validity, completeness, timeliness, etc – exposure, outcomes, confounders), **quality assurance** and **control procedures**
- **Variety of models of governance, data sharing and access** (different landscape of national/regional laws and regulation)
- **Reliable RWE is built on using fit-for-purpose RWD: ensure the data speak to the question at hand and are high quality**

Availability, Governance & Quality

I. DATA



Golconda, *Rene Magritte* (1953)

Data Quality framework

- High-level Data Quality **principles and definitions** applying **to all data types**;
- Data Quality **dimensions** (completeness, uniqueness, timeliness, validity);
- Data Quality **standards** (= metadata) (integration with ISO standards)
- Collaboration with the joint action '**Towards A European Health Data Space – TEHDAS**' focused on technical and scientific aspects of data quality

Data discoverability

- Criteria for RW databases selection
- Common set of metadata for describing and identifying RWD sources
- Public catalogues of European RWD sources and of observational studies
- List of metadata for Real World Data catalogues

II. METHODOLOGY

Philosopher's lamp, *Rene Magritte* (1936)

- **Analytical Integrity: appropriateness of study designs decisions** and **data analyses**; original purpose of data collection often are not for research
- **Compliance** with **best methodological standards** (e.g. ENCePP guide on methodological standards for PhEpi, EMA GVP, tools to address critical elements that influence the validity of findings from observational studies/methodological quality, risk of bias – e.g. ROBINS).

II. METHODOLOGY

Philosopher's lamp, *Rene Magritte* (1936)

THE LEGACY OF UNBREAKABLE PRINCIPLES

Databases should not distract us from sound methodological and clinical thinking.

Brian L. Strom, Bordeaux ICPE meeting (2004)

III. TRUST

The lovers, *Rene Magritte* (1928)

Improving **Transparency** to build societal **Trust**

- Compliance with methodological standards - **detailed description of study design**, **data collection**, **methods** and **analyses** that are **transparent**, **auditable**, and **reproducible**.

- **Pre-registration of protocols** in publicly available repositories/databases (*e.g.* EU PAS Register), **protocol templates/harmonization** (*e.g.* HARPER), SAP, **transparent reporting** and **responsible communication of results** are key components of establishing reliable RWE for regulatory decision-making.

IV. POLICY & GOVERNANCE ENVIRNOMENT

The Therapist, *Rene Magritte* (1937)

- Importance of **strengthening international collaboration on activities** to enable the use of RWE in regulatory decision-making.

ICMRA - 4 focus areas for regulatory cooperation

- Harmonisation of terminologies for RWD and RWE
- Regulatory convergence on RWD and RWE guidance and best practice
- Readiness to address public health challenges and emerging health threats
- Transparency

- **Early dialogue** and **frequent interactions with regulators** is key (e.g., awareness of opportunities & limitations in the planning, design and review phases of RWE generation)
- **Roadmap of EMA comprehensive guidance** on the use of **RWE to support regulatory decision-making**.
- **Capacity and trust building**, continuous **training** and **engagement** with all stakeholders → **Patients/HCP are key**.


LISBOA
UNIVERSIDADE
DE LISBOA


FACULDADE DE
FARMÁCIA
Universidade de Lisboa