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Novel methodologies and Real World Evidence

supporting drug regulatory decision-making

Peter Mol

Principal clinical assessor,
CBG-MEB, Pharmacotherapy group II
Vice-chair EMA Scientific Advice Working Party
Professor, Department of Clinical Pharmacology, UMCG

Today's program

09:00-09:40	Introduction to Day 3. How regulators work and think: the basics (Peter Mol)
09:40-09:45	Q&A
09:45-10:05	Novel regulatory tools & drug development support mechanisms (Peter Mol)
10:05-10:10	Q&A
10:10-10:25	Coffee break
10:25-10:50	Scientific advice (European & national) (Marjon Pasmooij)
10:50-10:55	Q&A
10:55-11:20	Case example – ATMP scientific advice (Viktoriia Starokozhko)
11:20-11:25	Q&A
11:25-11:40	Coffee break
11:40-12:10	Novel methodologies and Real World Evidence supporting drug regulatory decision-making
12:10-12:30	Final Q&A round (Moderator: Marjon Pasmooij)

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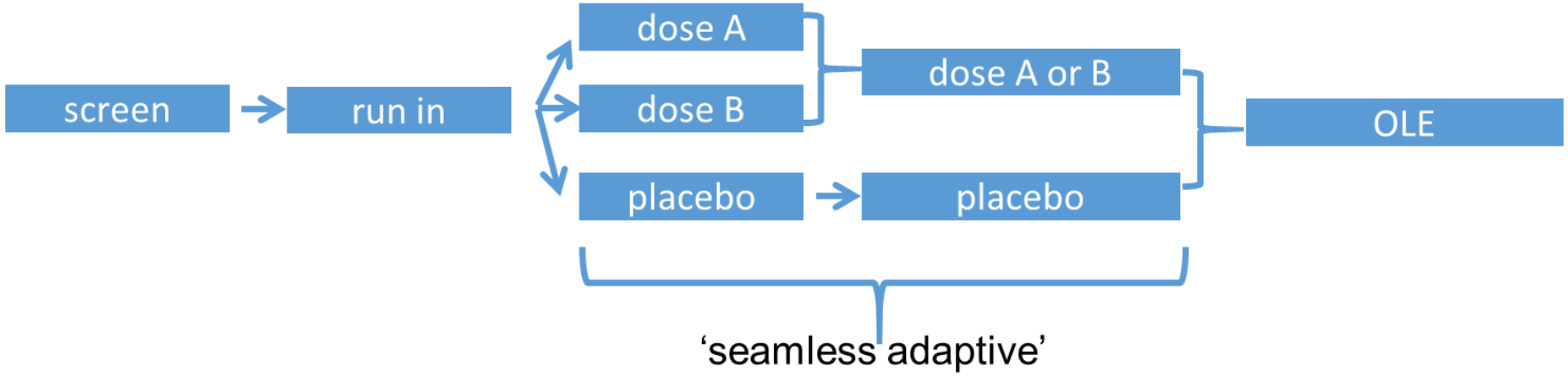
Seamless adaptive design



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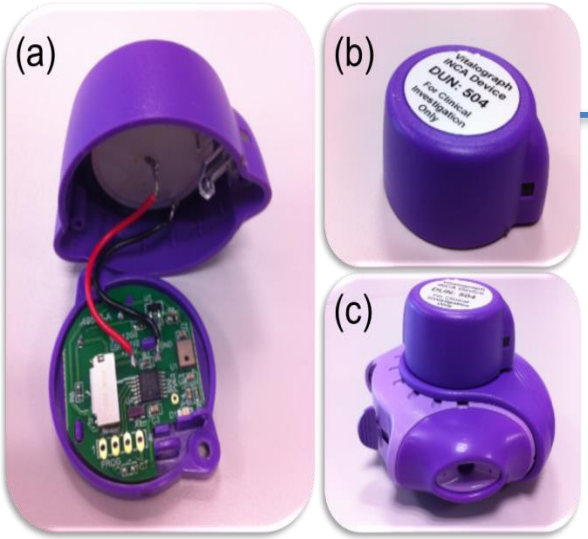
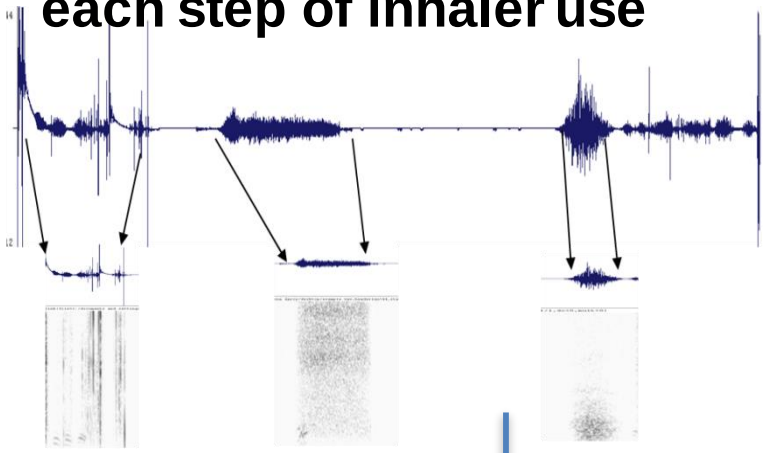
INCA Technology- Objective measurement of inhaler use

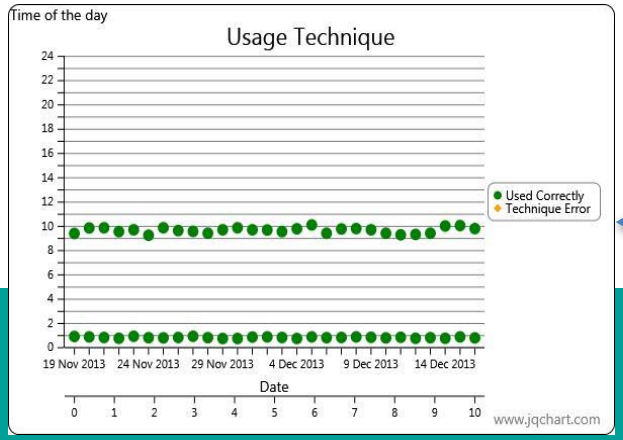
Acoustic recording device attached to inhaler



Patient "uses " inhaler

Device creates audio files of each step of inhaler use

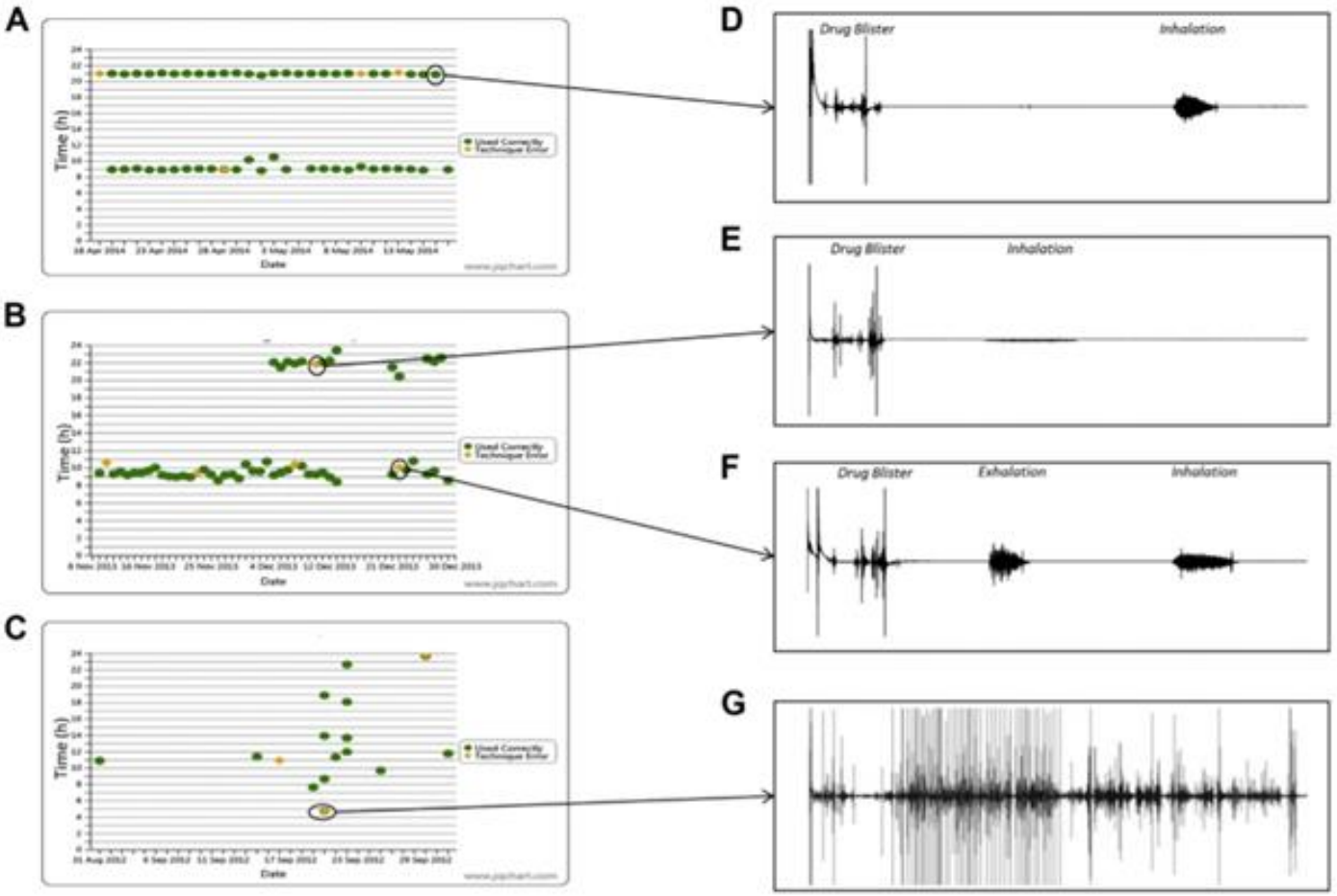




When and how well the inhaler was used

Clinician uses the information to educate the patient

D'Arcy et al. PLoS One. 2014;9(6)



Good

Poor inspiratory effort

Exhale before inhale

Drug dumping

Sulaiman. JACI in P 2016

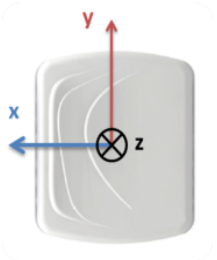
Actimyo monitors real-life activity and decreases variability Duchenne Muscular Dystrophy

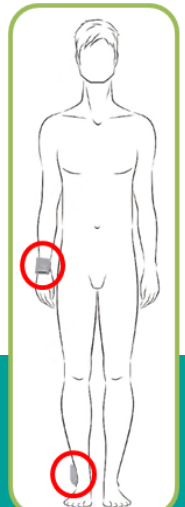
- External motivations can have a significant impact on hospital-based assessments

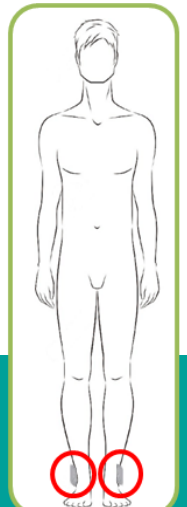
  6MWT = strength + endurance + motivation

  Timed tests = power + physiotherapist's reflex time

- Motion sensors: like ActiMyo contain a magneto-inertial measurement unit





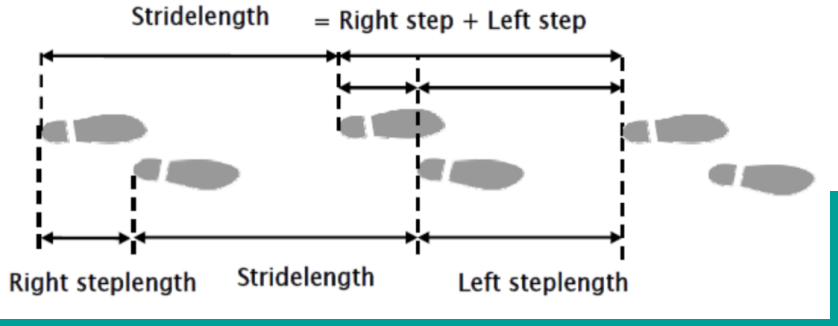


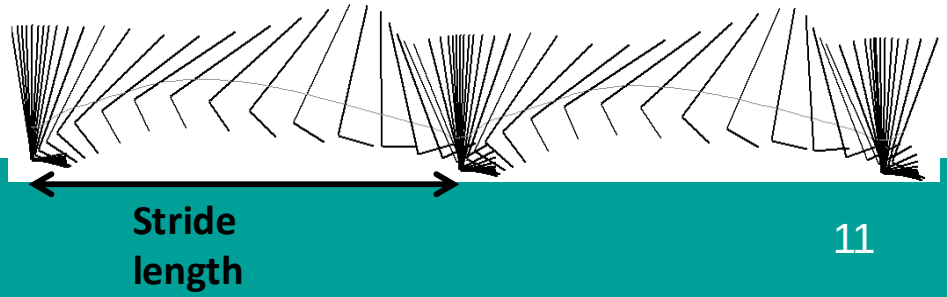
https://www.ema.europa.eu/en/documents/scientific-guideline/qualification-opinion-stride-velocity-95th-centile-secondary-endpoint-duchenne-muscular-dystrophy_en.pdf

Description of Actimyo variables

- Variables derived from the ankle trajectory
  - Stride length: distance between two successive points of floor contact, see figure
  - Stride velocity: stride length divided by its duration
  - Distance walked: sum of all strides taken in the period considered
- Stride length and velocity are presented in quantiles of all strides in a period
  - The median to represent the typical stride
  - The 95th percentile to measure the top performance

THESE DESCRIPTIVE VARIABLES ARE MUCH MORE SENSITIVE TO CHANGE AND RELIABLE THAN CUMULATIVE DATA (NUMBER OF STEPS/DAY)

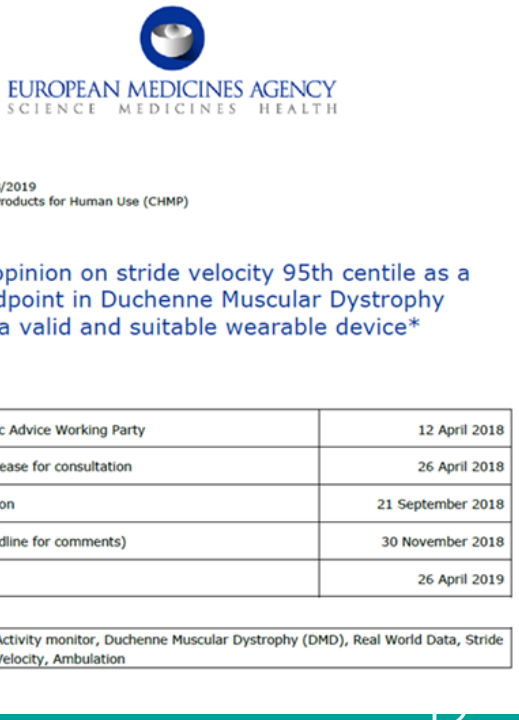




Context of Use

- Stride velocity 95th centile measured at the ankle (SV95C)*
  - Secondary endpoint
  - Baseline performance
  - More robust data needed as PEP

**measured by a valid and suitable wearable device*



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 April 2019
EMA/CHMP/SAWP/178058/2019
Committee for Medicinal Products for Human Use (CHMP)

Qualification opinion on stride velocity 95th centile as a secondary endpoint in Duchenne Muscular Dystrophy measured by a valid and suitable wearable device*

Draft agreed by Scientific Advice Working Party	12 April 2018
Adopted by CHMP for release for consultation	26 April 2018
Start of public consultation	21 September 2018
End of consultation (deadline for comments)	30 November 2018
Adopted by CHMP	26 April 2019

Keywords	Activity monitor, Duchenne Muscular Dystrophy (DMD), Real World Data, Stride Velocity, Ambulation

https://www.ema.europa.eu/en/documents/scientific-guideline/qualification-opinion-stride-velocity-95th-centile-secondary-endpoint-duchenne-muscular-dystrophy_en.pdf

Qualification of Novel Methodologies

- …on the regulatory validity and acceptability of a specific use of a proposed method in R&D context (in non-clinical and clinical studies)
- Voluntary, scientific pathway for innovative methods or drug development tools (e.g. biomarkers) not yet integrated in the drug development and clinical management paradigm
- One procedure with two outcomes:
  - Qualification Advice, OR
  - Qualification Opinion


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

10 November 2014
EMA/CHMP/SAWP/72894/2008
Revision 1: January 2012[1]
Revision 2: January 2014[2]
Revision 3: November 2014[3]
Scientific Advice Working Party of CHMP

Qualification of novel methodologies for drug development: guidance to applicants

Agreed by SAWP	27 February 2008
Adoption by CHMP for release for consultation	24 April 2008
End of consultation (deadline for comments)	30 June 2008
Final Agreed by CHMP	22 January 2009

Long-term benefits from EMA perspective: Speed-up the time to regulatory acceptance of novel approaches and time to new marketing authorisations, improve public health

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004201.pdf

Qualification of Novel Methodologies

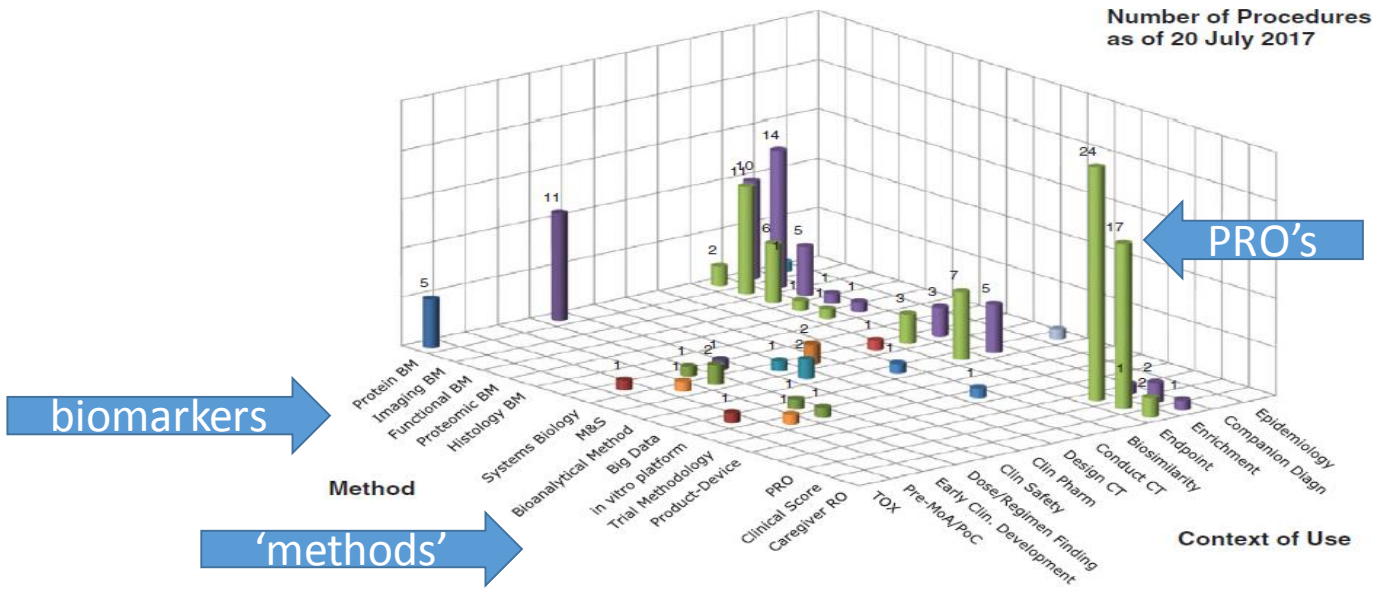


FIGURE 1 Scope of qualification of novel methodologies applications at the European medicines agency. The novel methodology (method) and their intended use (Context of Use) that were submitted to the Scientific Advice Working Party of the European Medicines Agency up to July 20, 2017 are presented in this figure. Figure courtesy of E. Manolis, EMA, London

Mol, P.G. et al. Diabetes Obes Metab. 2018

Regulatory Decision-Making

BIG DATA
REAL WORLD DATA

The place where I come from,
Is a small town
They think so small
They use small words
But not me

Ten recommendations to unlock the potential of big data for public health in the EU

Share

Press release 20/01/2020

The joint Big Data Task Force of EMA and the Heads of Medicines Agencies (HMA) proposes ten priority actions for the European medicines regulatory network to evolve its approach to data use and evidence generation, in order to make best use of big data to support innovation and public health, in a report published today .

Big data are extremely large, rapidly accumulating datasets captured across multiple settings and devices, for example through wearable devices, electronic health records, clinical trials or spontaneous adverse reaction reports. Coupled to rapidly developing technology, big data can complement the evidence from clinical trials and fill knowledge gaps on a medicine, and help to better characterise diseases, treatments and the performance of medicines in individual healthcare systems. The rapidly changing data landscape forces regulators to evolve and change the way they access, manage and analyse data and to keep pace with the rapid advances in science and technology.

"I look forward to working with the European Commission and national competent authorities to see how these concrete proposals can be implemented to better harness the potential of big data. This will help to further strengthen the robustness and quality of the evidence upon which we take decisions on medicines," said Guido Rasi, EMA's Executive Director.

Focus EU regulators

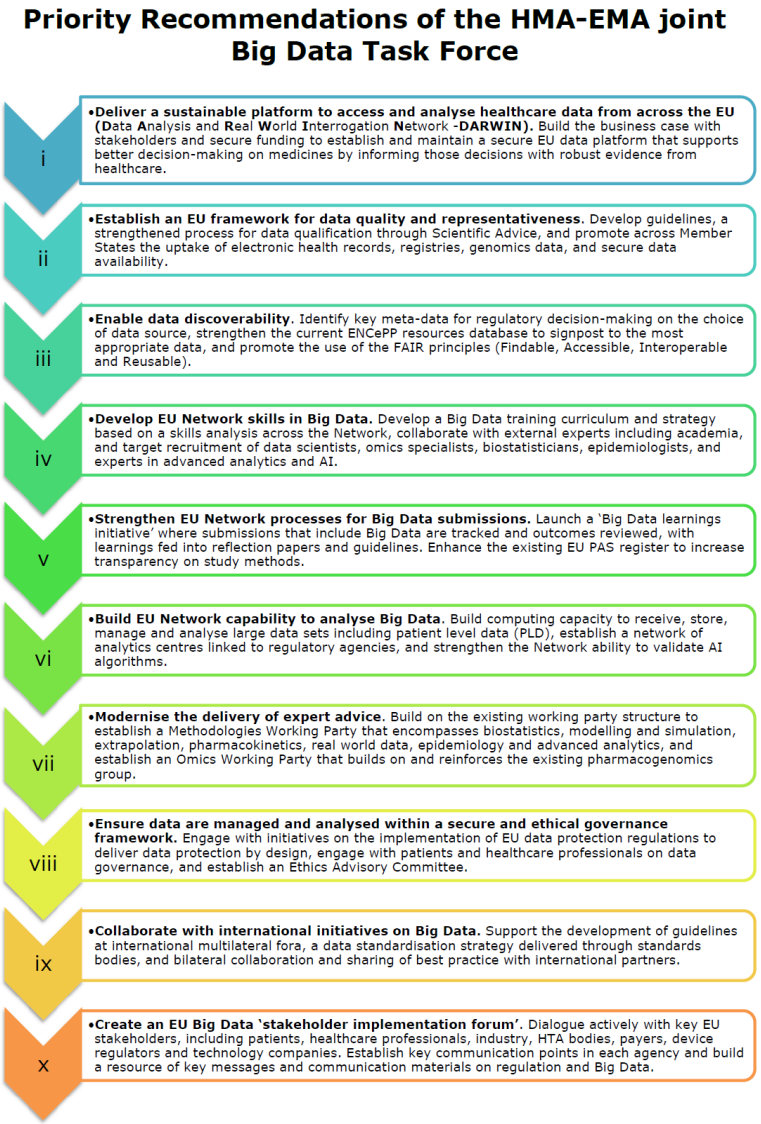
Technical:

- Deliver sustainable platform (DARWIN)
- Network processes Big Data submissions
- Secure & ethical governance

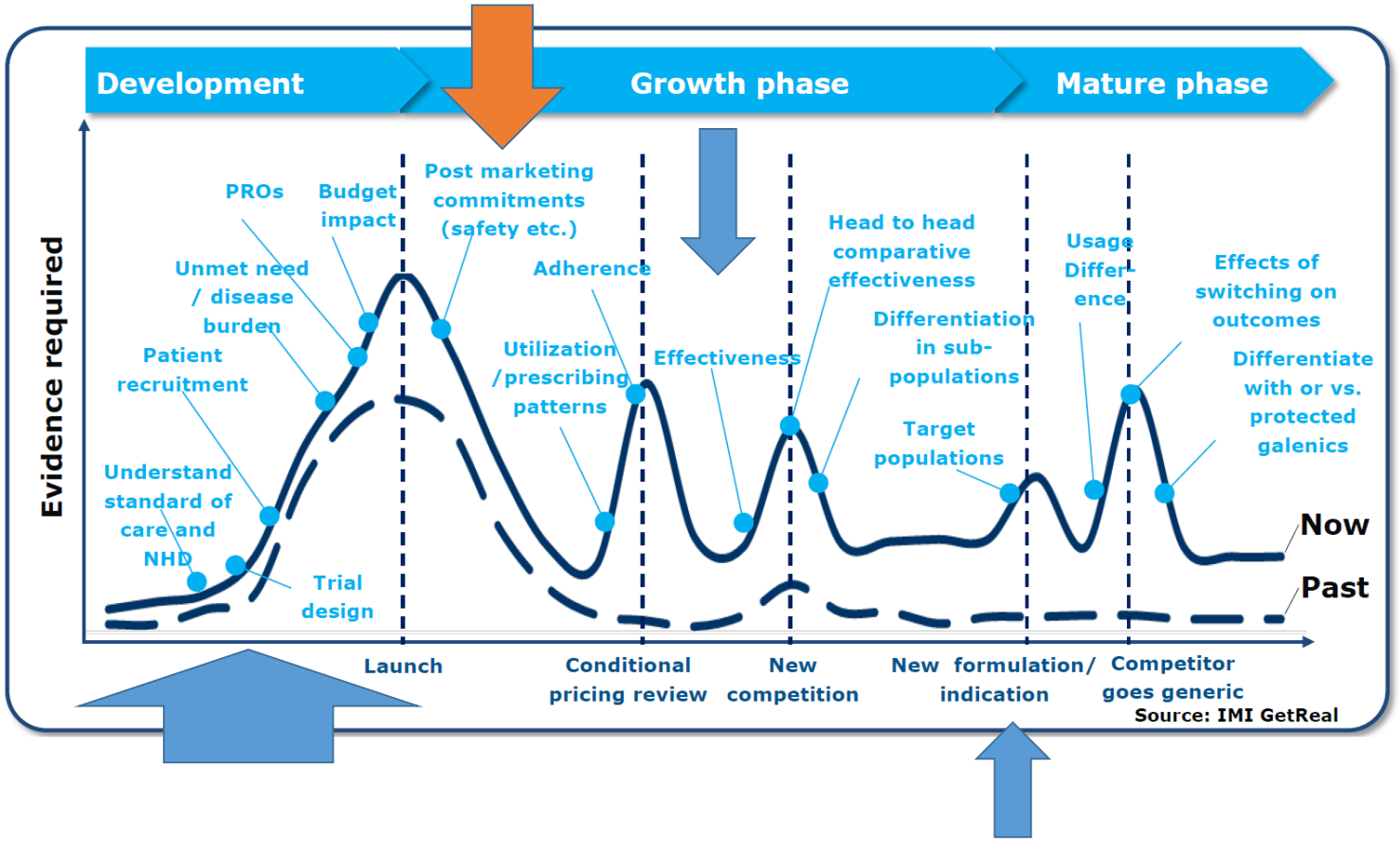
Network

- Building expertise & skills
- Expert advice
- Collaboration

Implementation forum



Opportunities for Real World Evidence

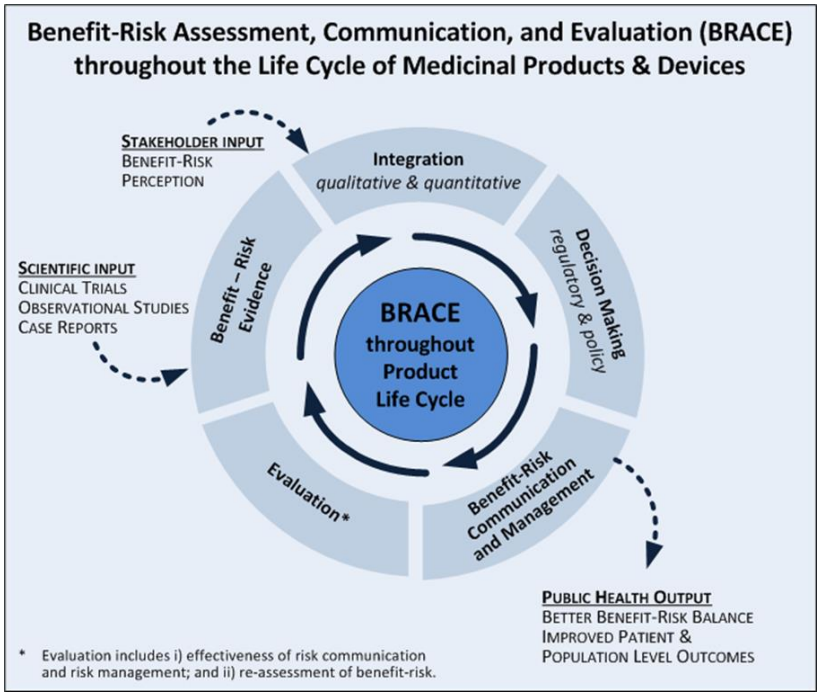


Post-Licensing Evidence Generation

- Benefit-risk assessment through out the product lifecycle
  - PLEG revolves around effectiveness / safety *within* approved indication
  - PASS/PAES guidance

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/12/WC500219040.pdf

https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/post-authorisation-safety-studies-pass



Radawski C., et al. 2015 Pharmacoepidemiology Drug Safety

Patient Registry Initiative

Registry

An organised system that uses observational methods to collect uniform data on specified outcomes in a population defined by a particular disease, condition or exposure.

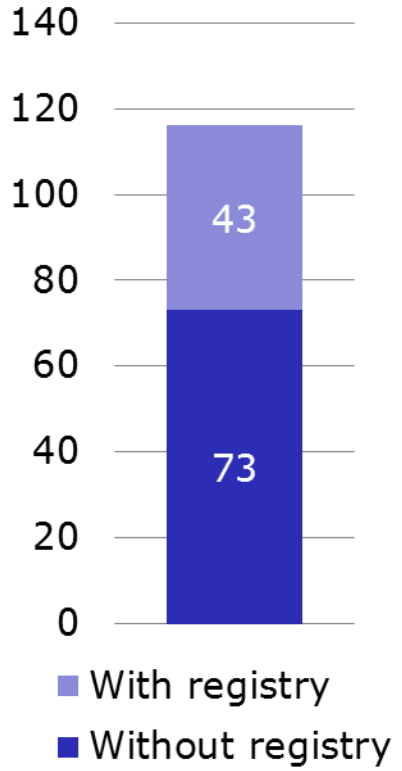
Regulators generally prefer *patient (disease) registries* over *product registries*

- They gather insights on clinical outcomes of conditions with different treatments, rather than on the outcomes of specific treatments
- They allow comparisons
- They are generally better integrated into health care systems.

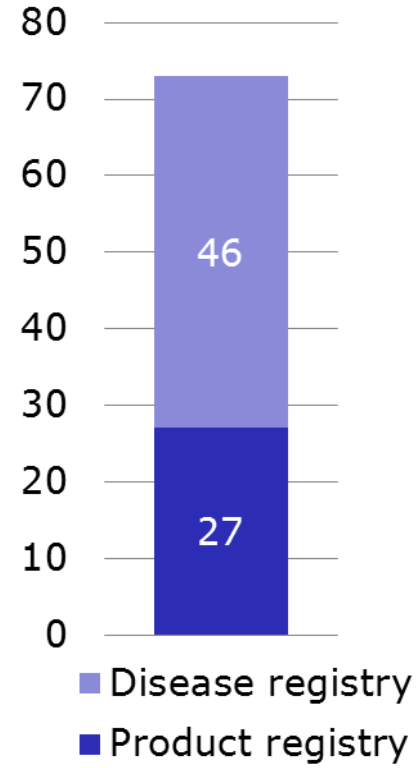
Registries supporting new drug applications

1 Jan 2007 to 31 Dec 2010

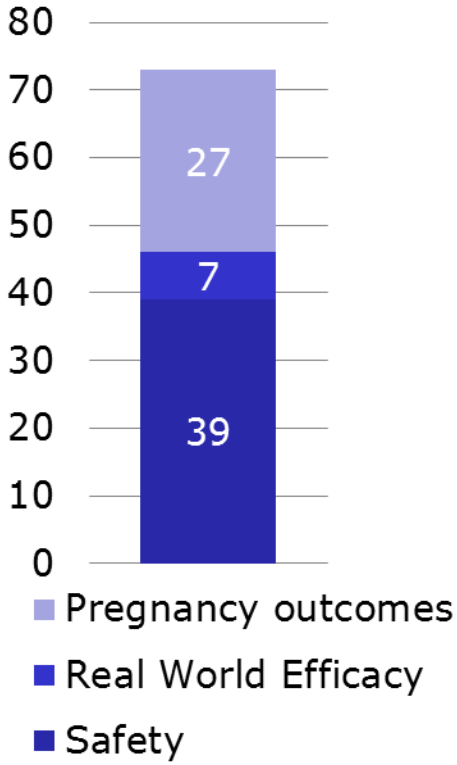
New Drugs



Type of Registry



Primary Aim



Key facts

43 new drugs with 1 to 6 registries

9 imposed registries

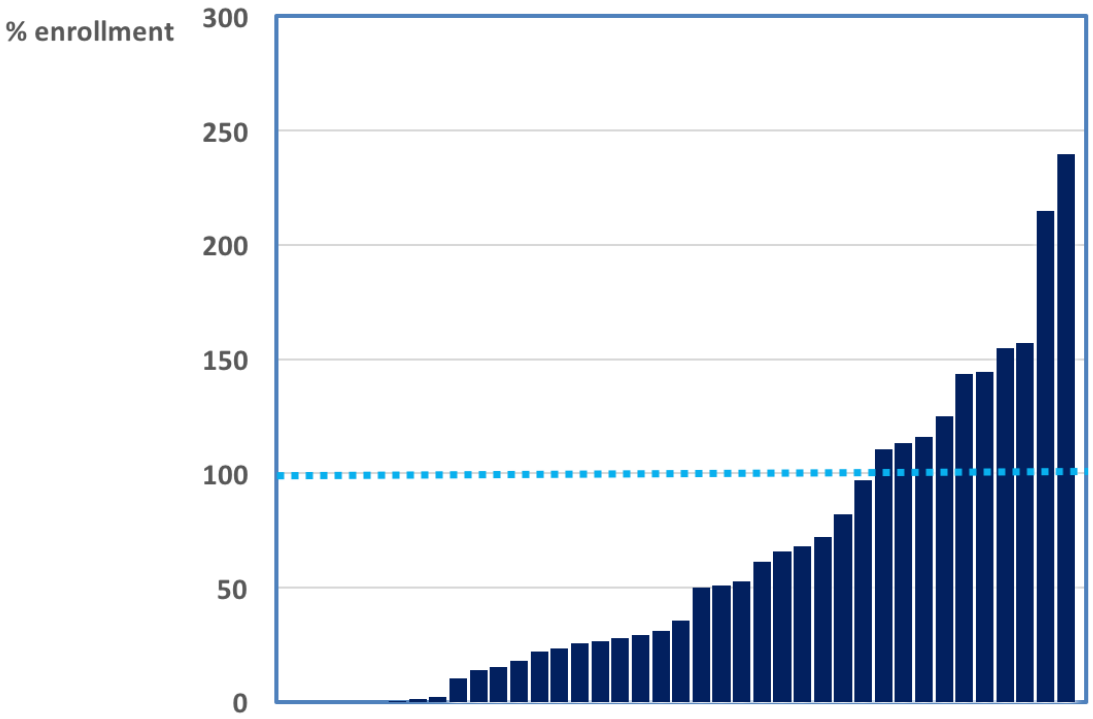
15 Orphan drugs

13 Conditional Approval / Exceptional Circumstances

-> level of innovation and orphan status predict approval with registries

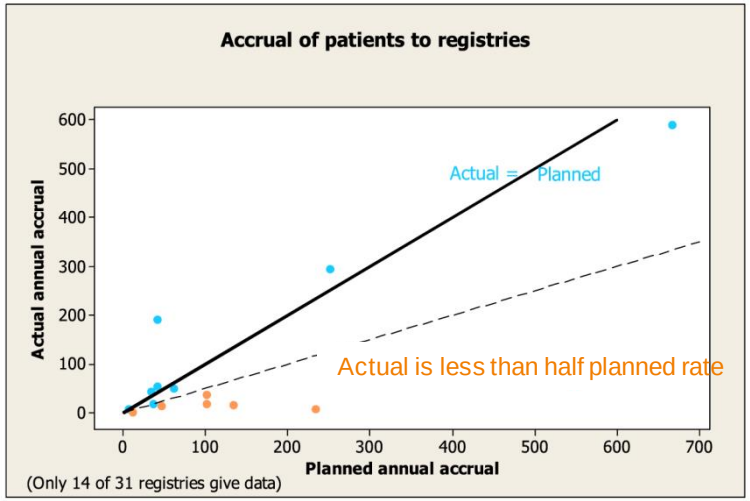
C. Jonker et al. Pharmacoepidemiol Drug Saf. 2017;1–7

Enrolment



Enrolment in 41 of 73 registries (registry studies) with predefined sample sizes (a median of) 5 years after approval

Jonker C et al. Clinical Therapeutics 2018 (in press)



Bouvy J et al. Pharmacoepidemiol Drug Saf. 201

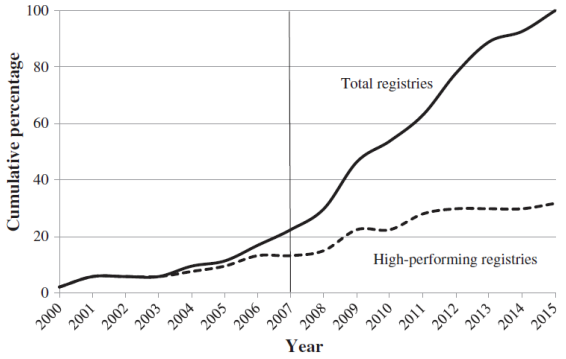
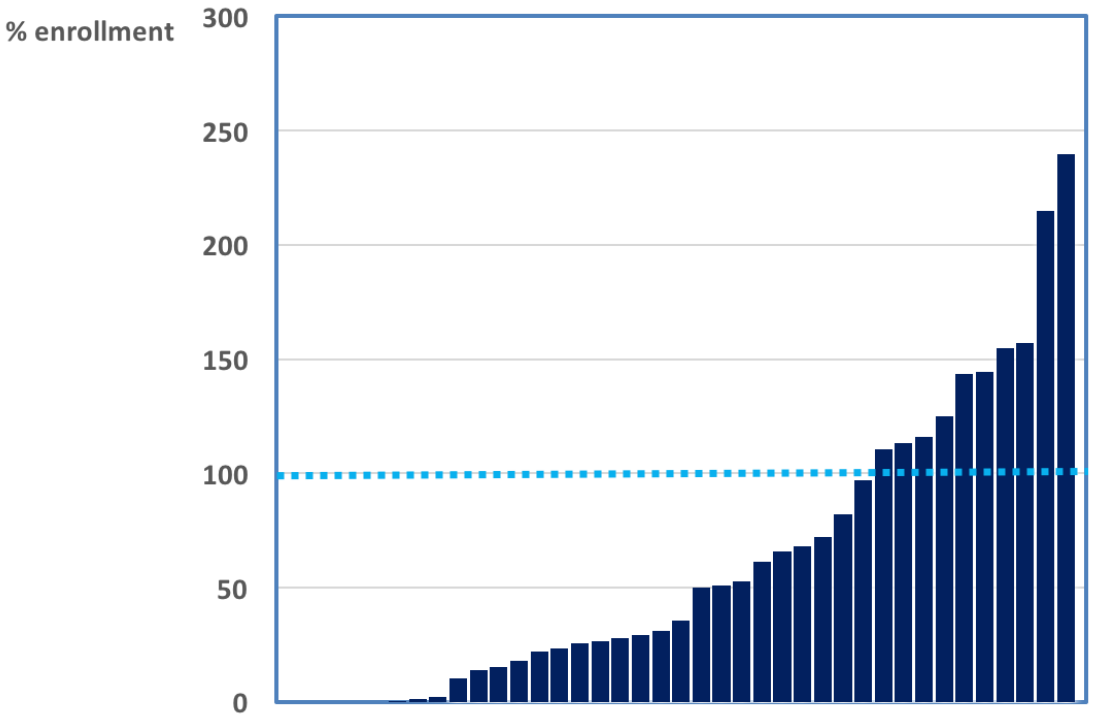


FIGURE 1 Cumulative distribution of postmarket product registries. Total registries represent the 54 registries identified that have initiated (nonpending status)

Zhao Y et al. Pharmacoepidemiol Drug Saf. 2018

Enrolment



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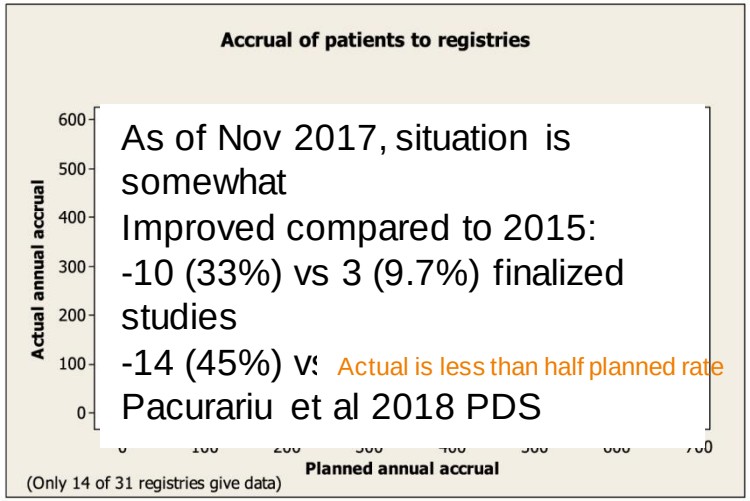


Bouvy J et al. Pharmacoepidemiol Drug Saf. 201

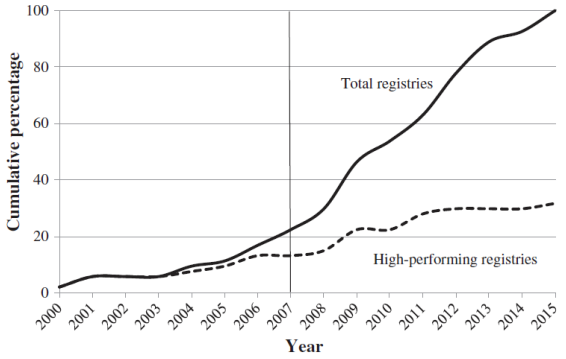


FIGURE 1 Cumulative distribution of postmarket product registries. Total registries represent the 54 registries identified that have initiated (nonpending status)

Zhao Y et al. Pharmacoepidemiol Drug Saf. 2018

Reasons for problems encountered

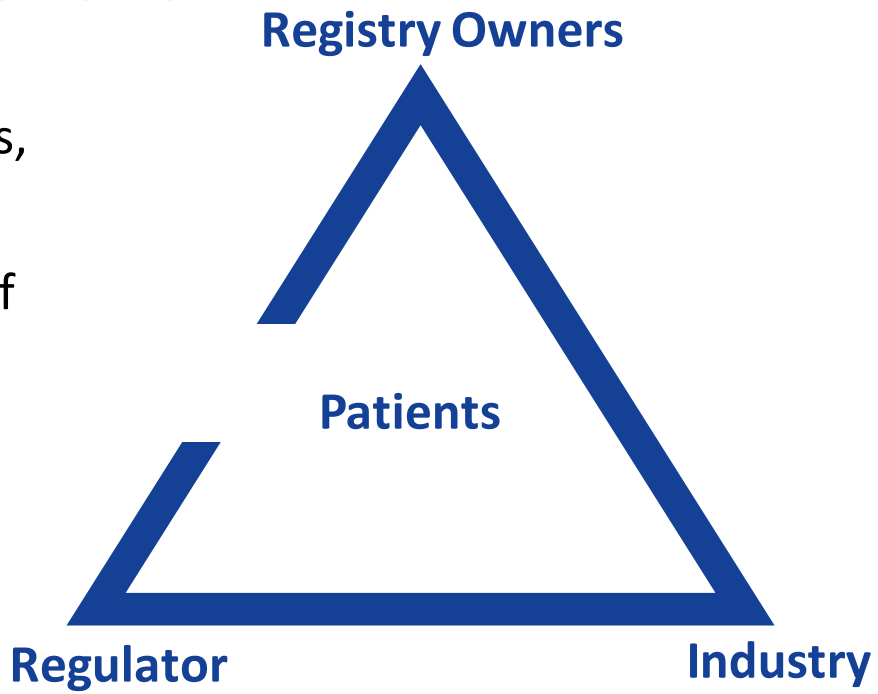
Approach to registries often suboptimal in scientific and resource terms

- Existing registries not fully exploited →duplication of efforts and inefficiencies
- Discrepancy between data collected by registries and data requested by regulators

- *Existing patient (disease) registries were not set up for regulatory purposes*
- *Challenges in using registries for regulatory studies:*
  - **Recruitment:** lack of physician engagement due to administrative burdens, patient consent, low product usage and competing registries
  - **Data quality**: representativeness of registry population, missing data
  - Lack of consistent data **quality control**
  - **Sustainability** (funding)
- So companies may prefer to establish individual product registries

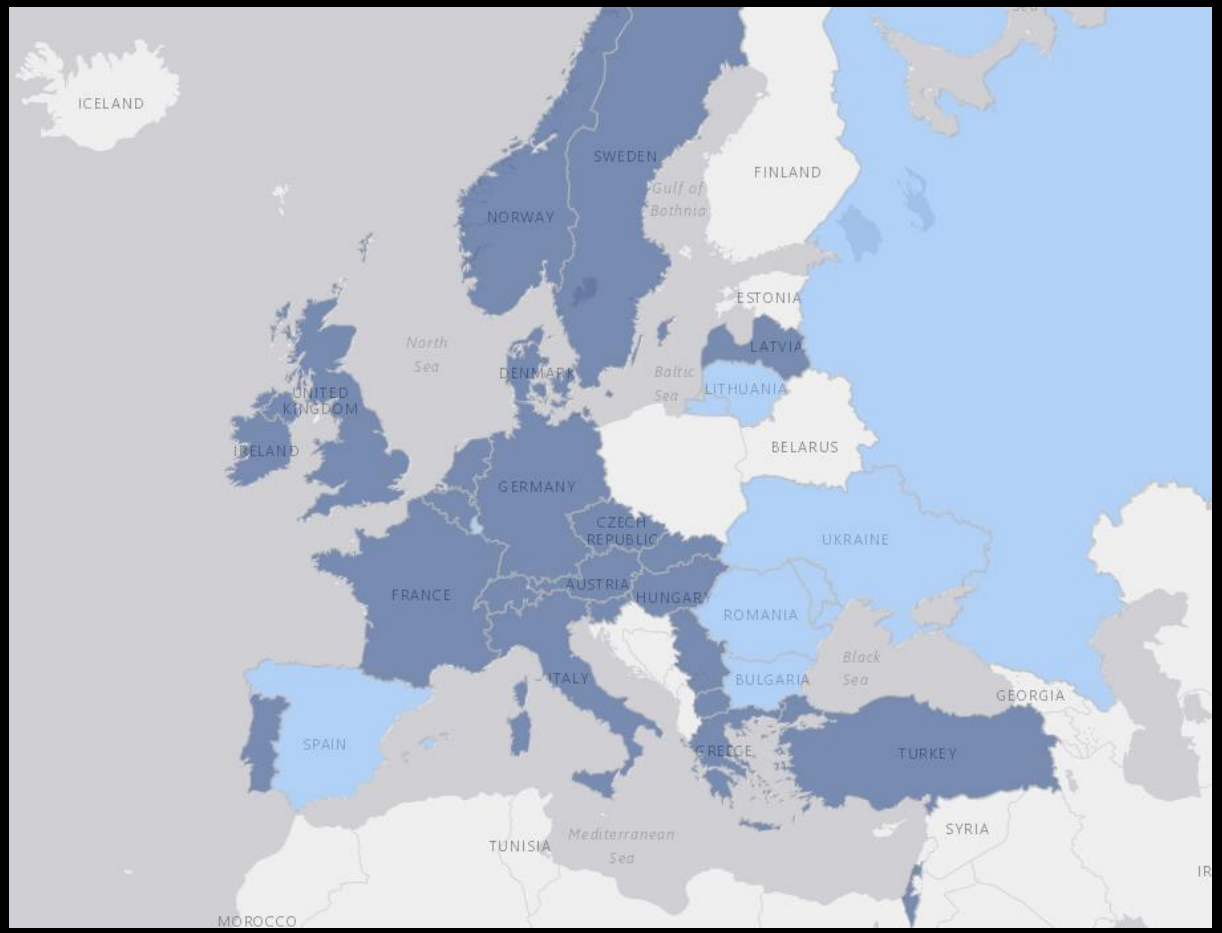
The EMA's Patient Registry Initiative

- ***Aims to facilitate use of patient (disease) registries by introducing and supporting a systematic approach to their contribution to the benefit-risk evaluation of medicines***
- To promote dialogue between regulators, companies and registry holders to understand barriers and opportunities of using disease registries.
- To clarify concepts: **registry vs. study** that may be registry-based
- Guideline on registry-based studies to be released this fall



General Queries: Coverage of ECFS Registries

- 31 Countries
- **>42,000 patients**
- 17 National Registries
  - 12 Upload
- 85 centres use ECFS Registry Software*
- GPP not currently required
- Broad coverage



* + 13 centres of the CF Registry Ireland

Presented ECFS 2017

Procedure No.: EMEA/H/SAB/080/1/QA/2017
EMA/CHMP/SAWP/802259/2017
Product Development and Scientific Support Department

Qualification Opinion

The European Cystic Fibrosis Society Patient Registry (ECFSPR)

CBG MEB

Context of Use

Drug utilisation studies

- For total recorded population and by subgroup such as CF complications, age, gender, FEV1 status, genotype, etc.

Drug efficacy/effectiveness studies

- For concurrent assessment of post authorisation efficacy/effectiveness using annual best FEV1, mortality, pulmonary exacerbations using the ECFSPR working definition or CF complications;
- As a source of historical control data ..for contextualization, e.g. for comparative purposes in the context of non-randomized clinical trials (i.e. when this would be the only reasonable option).

Drug safety evaluation

- As a tool to collect safety data with a particular focus on important identified and potential risks.

{and some fine print qualifications}

EMA SAWP

By law: Article 56(3) of European Parliament and Council Regulation (EC) 726/2004: *"The Executive director, in close consultation with the Committee for Medicinal Products for Human Use …Article 57 (1)(n) … shall establish* ***a standing working party with the sole remit of providing scientific advice to undertakings****."*

Currently 69 **experts** (NCA, academia) from 18 countries + EMA secretariat

Monthly 4 day meeting to discuss

- Approx. 70 drug development plans (1st reports, 2nd round meetings)
- Qualification of Novel Methodologies
- PRIME designation

Advice signed-off by CHMP

RWE – (How) is it being used?

Review of 12 months SA procedures – Jane Moseley / Ines Lucas *(July '16- June '17)*

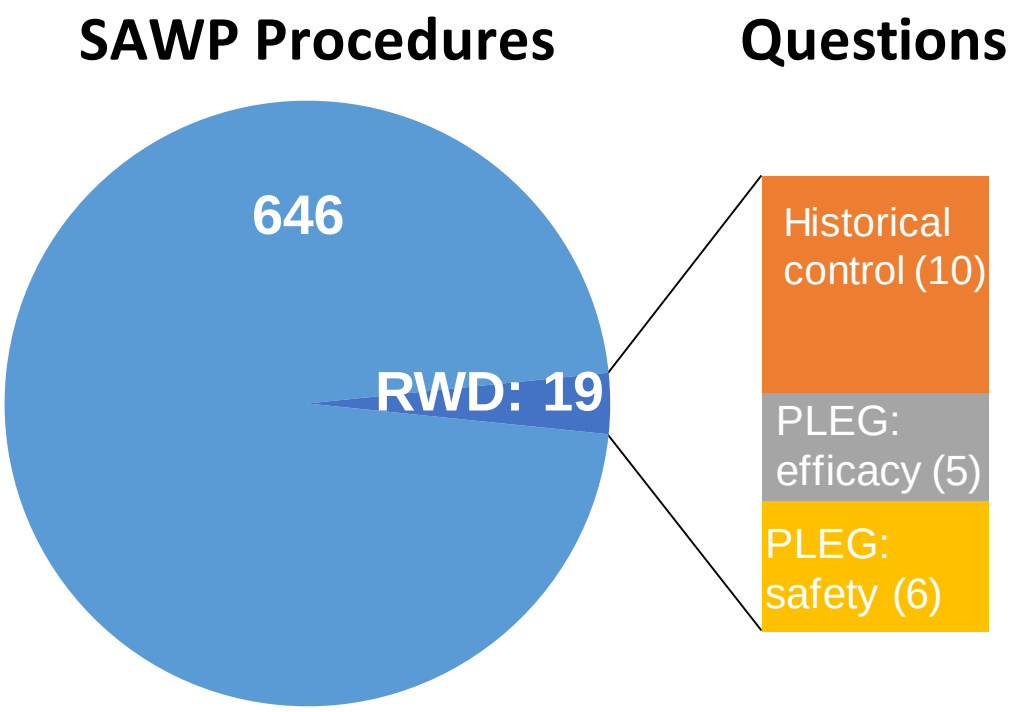
To identify the objective for which RWD data are proposed and the study designs employed

To identify which sources of RWE drug manufacturers are using.

To identify timing of request advice pre MAA or post MAA, to RWE, type of marketing authorisation they are planning to apply for (conditional, under exceptional circumstances, accelerated assessment, full marketing authorisation

To analyse the content of the answers provided by the CHMP (qualitative analysis) and if CHMP agreed with the manufacturer's proposal.

SAWP experience: RWD in scientific advice (July 2016 – June 2017)



Ines Lucas, Jane Moseley EMA 2018

Main conclusions
Experience still limited

Pre-licensing:

"Option of a small randomised controlled trial, even if unpowered, could be preferred. External controls could be supportive/for contextualisation"

Post-licensing

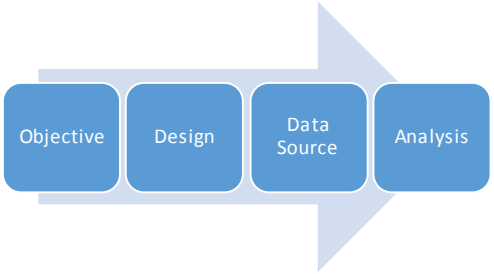
-efficacy: primary data collection, 2x registry, claims database, pragmatic trial

-safety: proposals *often lacking detail*:

3 registries & 2 EHR studies

Focus on demonstrating efficacy using data generated in clinical practice

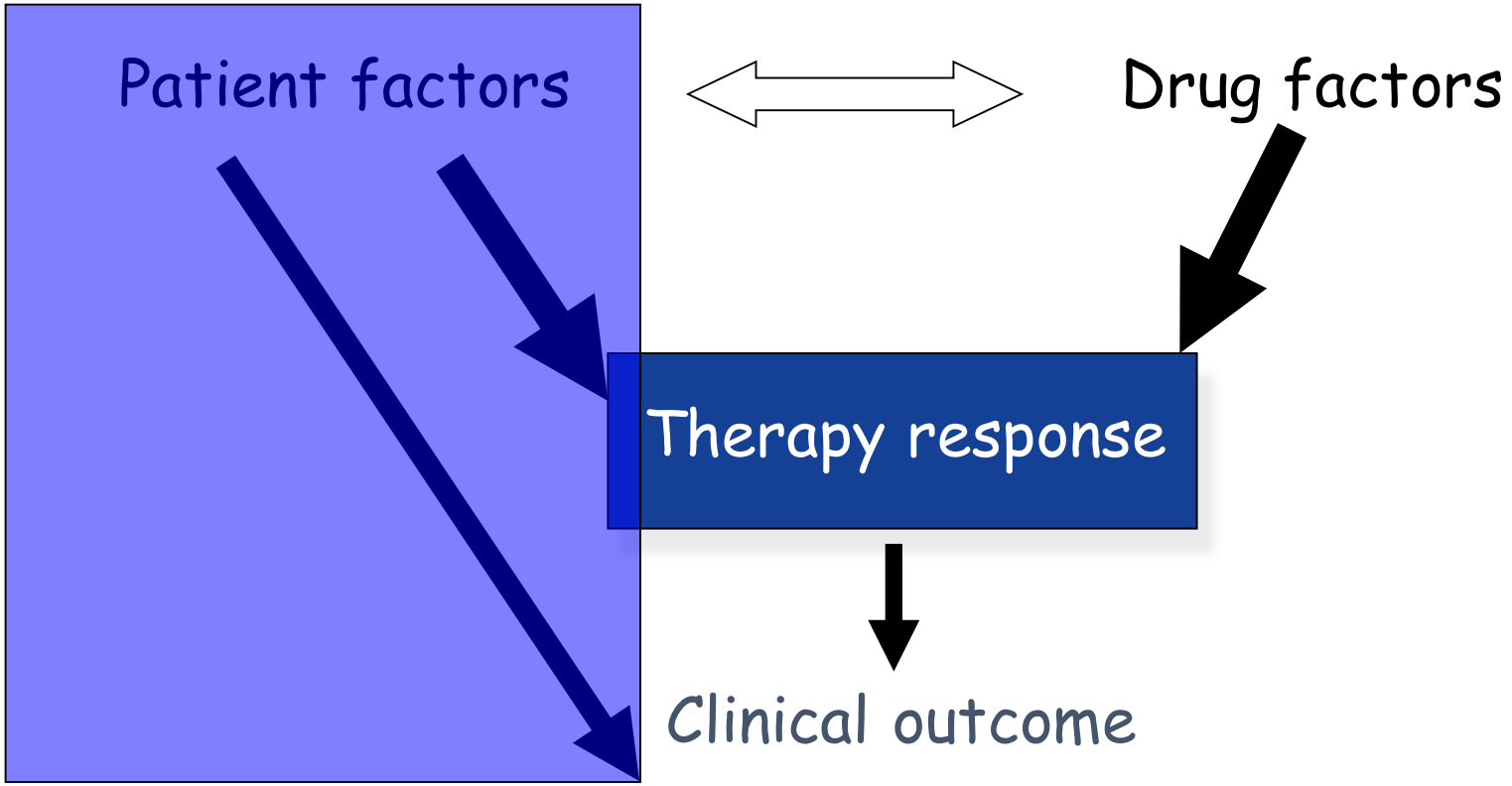
Design: The **objective(s)** will determine the design, including need for control arm, randomisation and data collection



Data source: The design will determine the data source to be used (clinical trial, healthcare records, registry etc.)

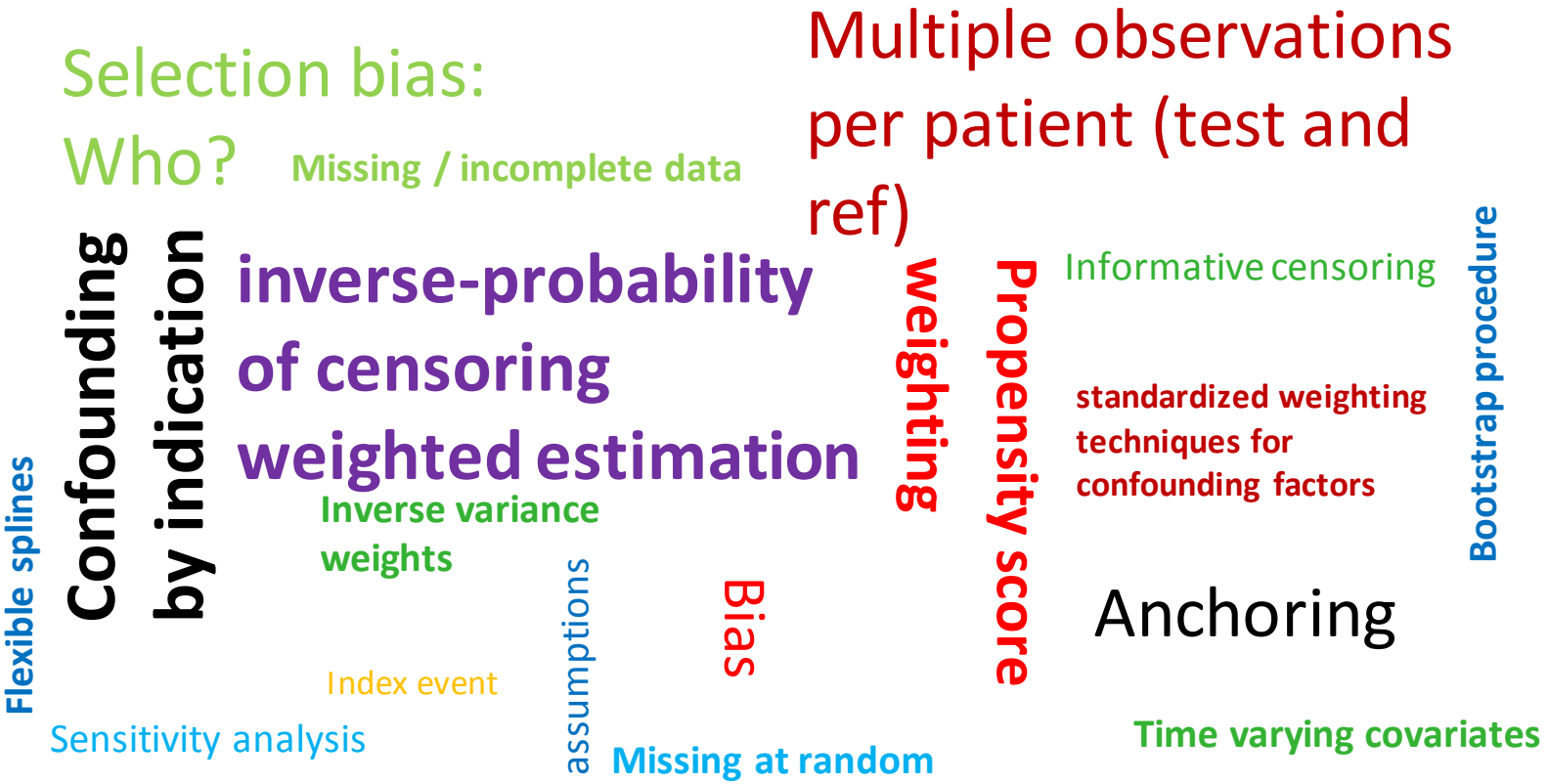
Analysis: Planned to generate reliable and interpretable estimates of treatment effect in relation to the objective

Determinants of drug response: a balanced view



Comparative clinical trial: Randomization to ELIMINATE patient factors

Advanced analyses techniques needed



Regulators' experience

Main Questions asked:

"Can we use a registry [*study*] to:

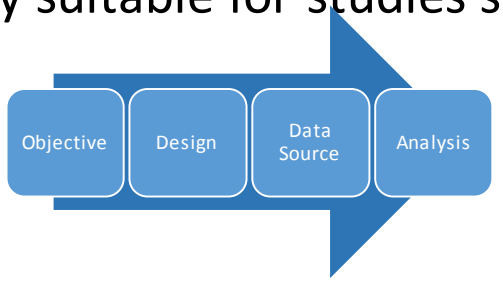
- contextualise Single Arm Trial results

PLEG

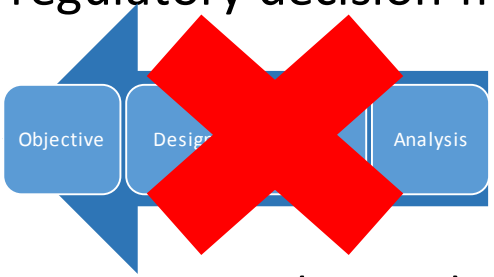
- provide long-term *maintenance* of efficacy
- provide long-term safety
- extrapolate to [e.g.] *paediatric** efficacy & safety"

"Is our registry suitable for studies supporting regulatory decision-making?"

Our answer:



Not



data availability, data quality, governance (access)

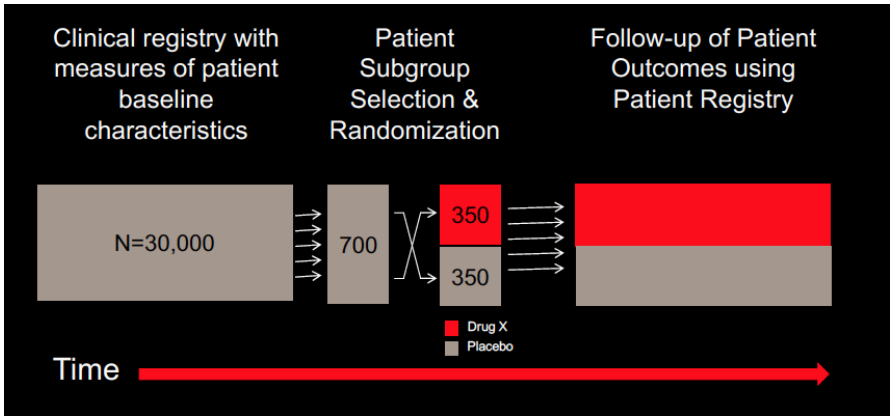
* *formulation*

Some Real World Evidence / Registry examples

Setting	RWE	SAWP advice
Rare disease – extend indication	– comparative effectiveness study vs. standard of care - Scattered single arm trial data - PK modeling	RWE considered supportive
Oncology – change of posology / formulation (BID to OD)	- RCT data not supportive - PK data (incl. modeling) - Comparative effectiveness study in EHR	New RCT
CV disease	Large pragmatic trial with randomization and patient follow-up in EHR	Perform traditional RCT; specific indication with many failed studies, improved safety monitoring needed
Gene therapy	Single Arm Trials in haematological malignancies	F-up for extended duration (15 years) Use existing disease registry
Chronic disease	- Comparative better rare adverse event outcome: SmPC claim based on EHR / registries	RCT preferred, but …
Immunological therapy	Extend indication to paediatric population - PK data (incl. modeling) - registry & EHR data on Off label use	Justify population & endpoints - USA vs Europa - Severity of disease supportive

So my positive view
Registries will increasingly be used for

Registry-based randomized trials

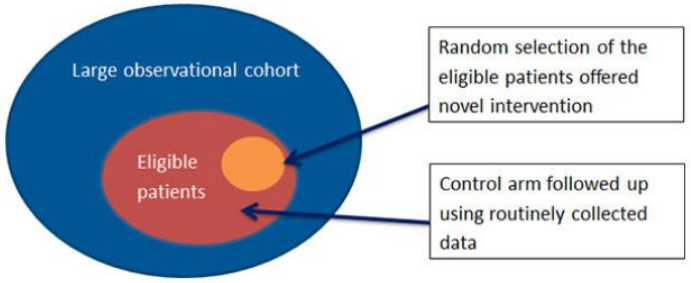


(Clinical Trials Transformative Initiative)
https://www.ctti-clinicaltrials.org/projects/registry-trials

Cohort multiple randomised controlled trial (cmRCT)

The cmRCT study design is a type of pragmatic trial. It is also known as a 'trial within cohort' study design (TwiCs).

Figure. Cohort multiple randomised controlled trial



Cluster cmRCTs are a variation on this design using groups (clusters) of patients rather than individuals randomised to different treatments (similar to cluster RCTs). For example, a cluster might be within a GP practice, hospital or community. This can increase the speed of recruitment to the trial and help reduce costs because interventions are administered in fewer places.

IMI GetReal http://www.imi-getreal.eu

My positive view

Drug Safety
https://doi.org/10.1007/s40264-020-01031-1

ORIGINAL RESEARCH ARTICLE

Incidence Rates of Autoimmune Diseases in European Healthcare Databases: A Contribution of the ADVANCE Project

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Accepted: 2 December 2020

Abstract

Introduction The public–private ADVANCE collaboration developed and tested a system to generate evidence on vaccine benefits and risks using European electronic healthcare databases. In the safety of vaccines, background incidence rates are key to allow proper monitoring and assessment. The goals of this study were to compute age-, sex-, and calendar-year stratified incidence rates of nine autoimmune diseases in seven European healthcare databases from four countries and to assess validity by comparing with published data.

Methods Event rates were calculated for the following outcomes: acute disseminated encephalomyelitis, Bell's palsy, Guillain–Barré syndrome, immune thrombocytopenia purpura, Kawasaki disease, optic neuritis, narcolepsy, systemic lupus erythematosus, and transverse myelitis. Cases were identified by diagnosis codes. Participating organizations/databases originated from Denmark, Italy, Spain, and the UK. The source population comprised all persons registered, with at least 1 year of data prior to the study start, or follow-up from birth. Stratified incidence rates were computed per database over the period 2003 to 2014.

Results Between 2003 and 2014, 148,947 incident cases of nine autoimmune diseases were identified. Crude incidence rates were highest for Bell's palsy [23.8/100,000 person-years (PYs), 95% confidence interval (CI) 23.6–24.1] and lowest for Kawasaki disease (0.7/100,000 PYs, 95% CI 0.6–0.7). Specific patterns were observed by sex, age, calendar time, and data sources. Rates were comparable with published estimates.

Conclusion A range of autoimmune events could be identified in the ADVANCE system. Estimation of rates indicated consistency across selected European healthcare databases, as well as consistency with US published data.

Key Points

In the safety of vaccines, background incidence rates are key to allow proper monitoring and assessment.

Between 2003 and 2014, 148,947 new cases of nine autoimmune diseases were identified in seven European healthcare databases from four countries.

Incidence rates were highest for Bell's palsy and lowest for Kawasaki disease. Specific patterns were observed by sex, age, calendar time, and data sources.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40264-020-01031-1.

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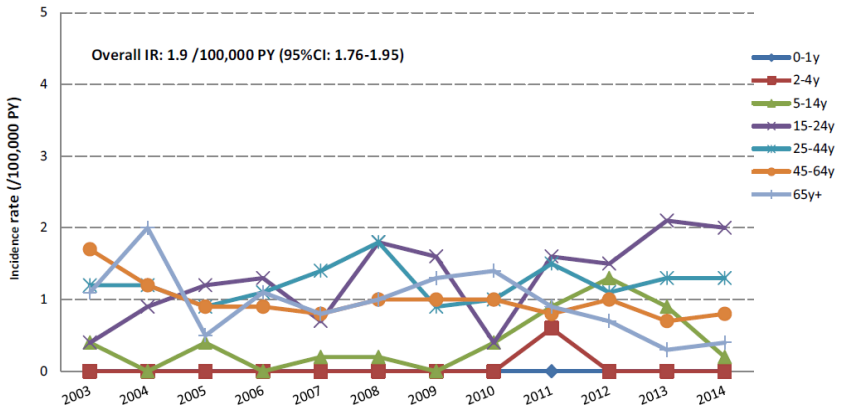
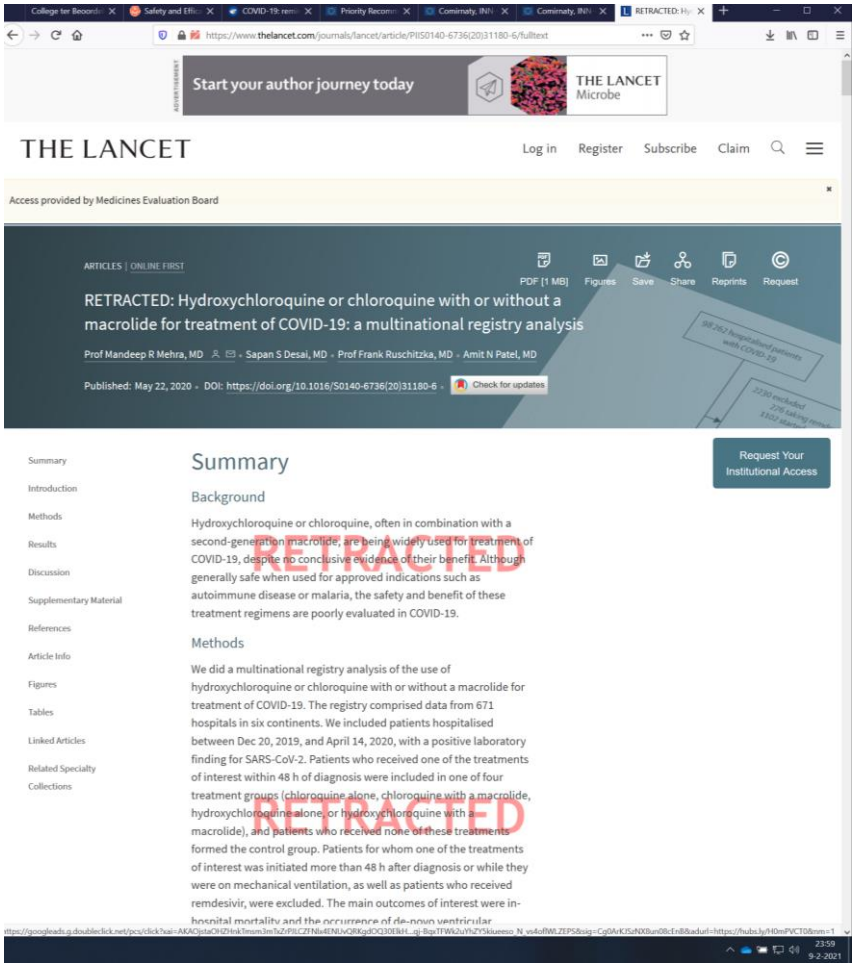
C. Willame et al.



Incidence rates for narcolepsy in the AUH/SSI database, per age group and calendar year. *IR* incidence rate, *PY* person-years, *CI* confidence interval, *AUH/SSI* Aarhus University Hospital/Staten Serum Institute

My more negative view



The members of the writing committee (Peter Horby, F.R.C.P., Marion Mafham, M.D., Louise Linsell, D.Phil., Jennifer L. Bell, M.Sc., Natalie Staplin, Ph.D., Jonathan R. Emberson, Ph.D., Martin Wiselka, Ph.D., Andrew Ustianowski, Ph.D., Einas Elmahi, M.Phil., Benjamin Prudon, F.R.C.P., Tony Whitehouse, F.R.C.A., Timothy Felton, Ph.D., John Williams, M.R.C.P., Jakki Faccenda, M.D., Jonathan Underwood, Ph.D., J. Kenneth Baillie, M.D., Ph.D., Lucy C. Chappell, Ph.D., Saul N. Faust, F.R.C.P.C.H., Thomas Jaki, Ph.D., Katie Jeffery, Ph.D., Wei Shen Lim, F.R.C.P., Alan Montgomery, Ph.D., Kathryn Rowan, Ph.D., Joel Tarning, Ph.D., James A. Watson, D.Phil., Nicholas J. White, F.R.S., Edmund Juszczak, M.Sc., Richard Haynes, D.M., and Martin J. Landray, Ph.D.) assume responsibility for the overall content and integrity of this article.

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*A complete list of collaborators in the RECOVERY trial is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Horby, Mafham, and Linsell and Prof. Juszczak, Dr. Haynes, and Dr. Landray contributed equally to this article.

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ORIGINAL ARTICLE

Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19

The RECOVERY Collaborative Group*

ABSTRACT

BACKGROUND

Hydroxychloroquine and chloroquine have been proposed as treatments for coronavirus disease 2019 (Covid-19) on the basis of in vitro activity and data from uncontrolled studies and small, randomized trials.

METHODS

In this randomized, controlled, open-label platform trial comparing a range of possible treatments with usual care in patients hospitalized with Covid-19, we randomly assigned 1561 patients to receive hydroxychloroquine and 3155 to receive usual care. The primary outcome was 28-day mortality.

RESULTS

The enrollment of patients in the hydroxychloroquine group was closed on June 5, 2020, after an interim analysis determined that there was a lack of efficacy. Death within 28 days occurred in 421 patients (27.0%) in the hydroxychloroquine group and in 790 (25.0%) in the usual-care group (rate ratio, 1.09; 95% confidence interval [CI], 0.97 to 1.23; P=0.15). Consistent results were seen in all prespecified subgroups of patients. The results suggest that patients in the hydroxychloroquine group were less likely to be discharged from the hospital alive within 28 days than those in the usual-care group (59.6% vs. 62.9%; rate ratio, 0.90; 95% CI, 0.83 to 0.98). Among the patients who were not undergoing mechanical ventilation at baseline, those in the hydroxychloroquine group had a higher frequency of invasive mechanical ventilation or death (30.7% vs. 26.9%; risk ratio, 1.14; 95% CI, 1.03 to 1.27). There was a small numerical excess of cardiac deaths (0.4 percentage points) but no difference in the incidence of new major cardiac arrhythmia among the patients who received hydroxychloroquine.

CONCLUSIONS

Among patients hospitalized with Covid-19, those who received hydroxychloroquine did not have a lower incidence of death at 28 days than those who received usual care. (Funded by UK Research and Innovation and National Institute for Health Research and others; RECOVERY ISRCTN number, ISRCTN50189673; ClinicalTrials.gov number, NCT04381936.)

Take home

- Novel methods and data
  - Increasingly used to support drug development
  - Context of use determines rigour of validation
  - Early interaction with regulator key for acceptance
- RWE useful for extrapolation, maintenance of effect, safety evaluation, contextualisation, large pragmatic trials
  - Question first
  - Data & data quality, feasibility, protocol registered, transparency
  - Complimentary to DBRCT

STARS
STRENGTHENING
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SCIENCE

University Medical Center Groningen

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Any questions?

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