Clinical-Regulatory value of Real-World Evidence

Industry perspective. Lessons learned.

Mariusz Mogielnicki

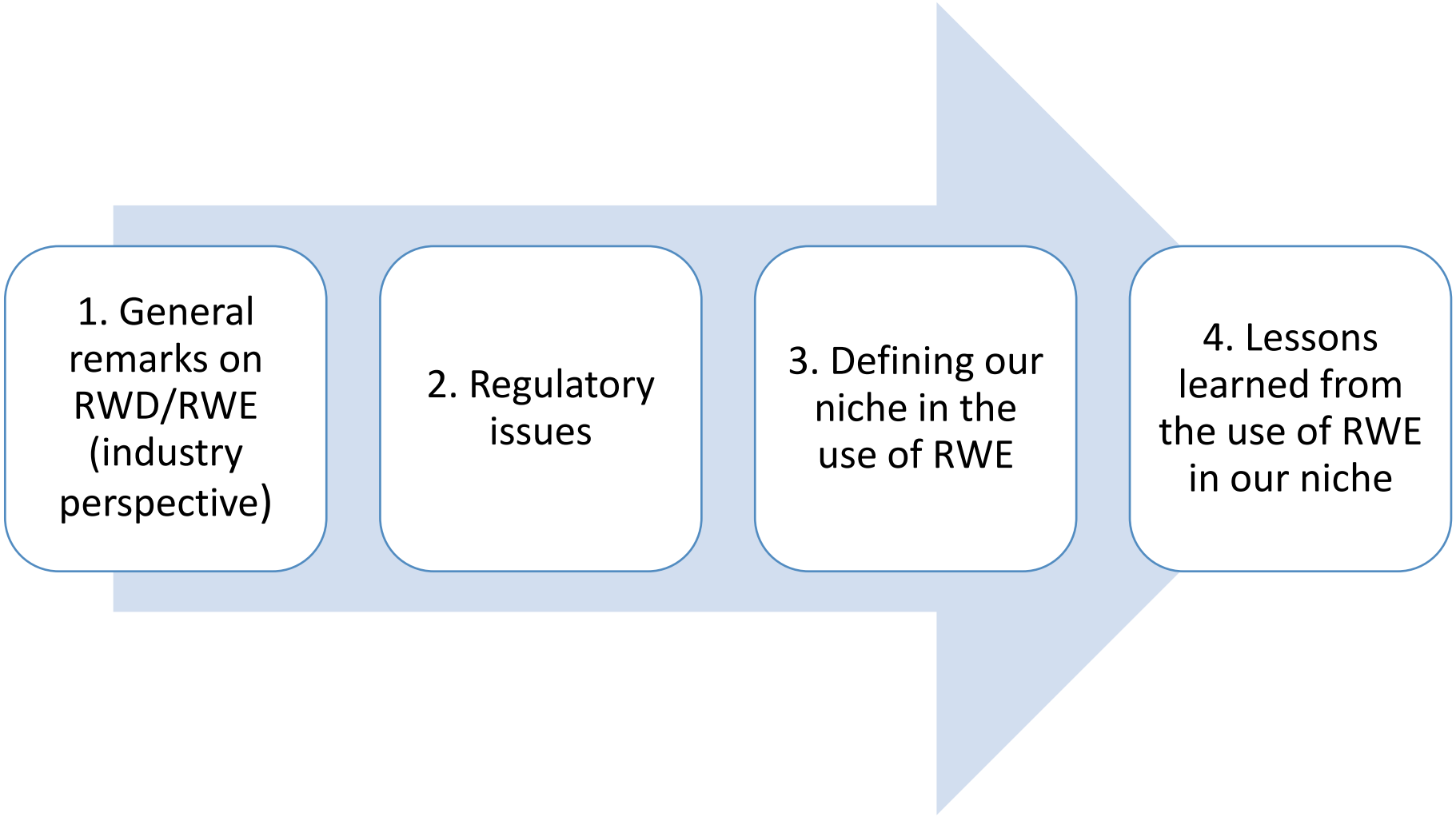
Clinical Excellence Team, Medical Department, Polpharma SA

September 22nd 2023

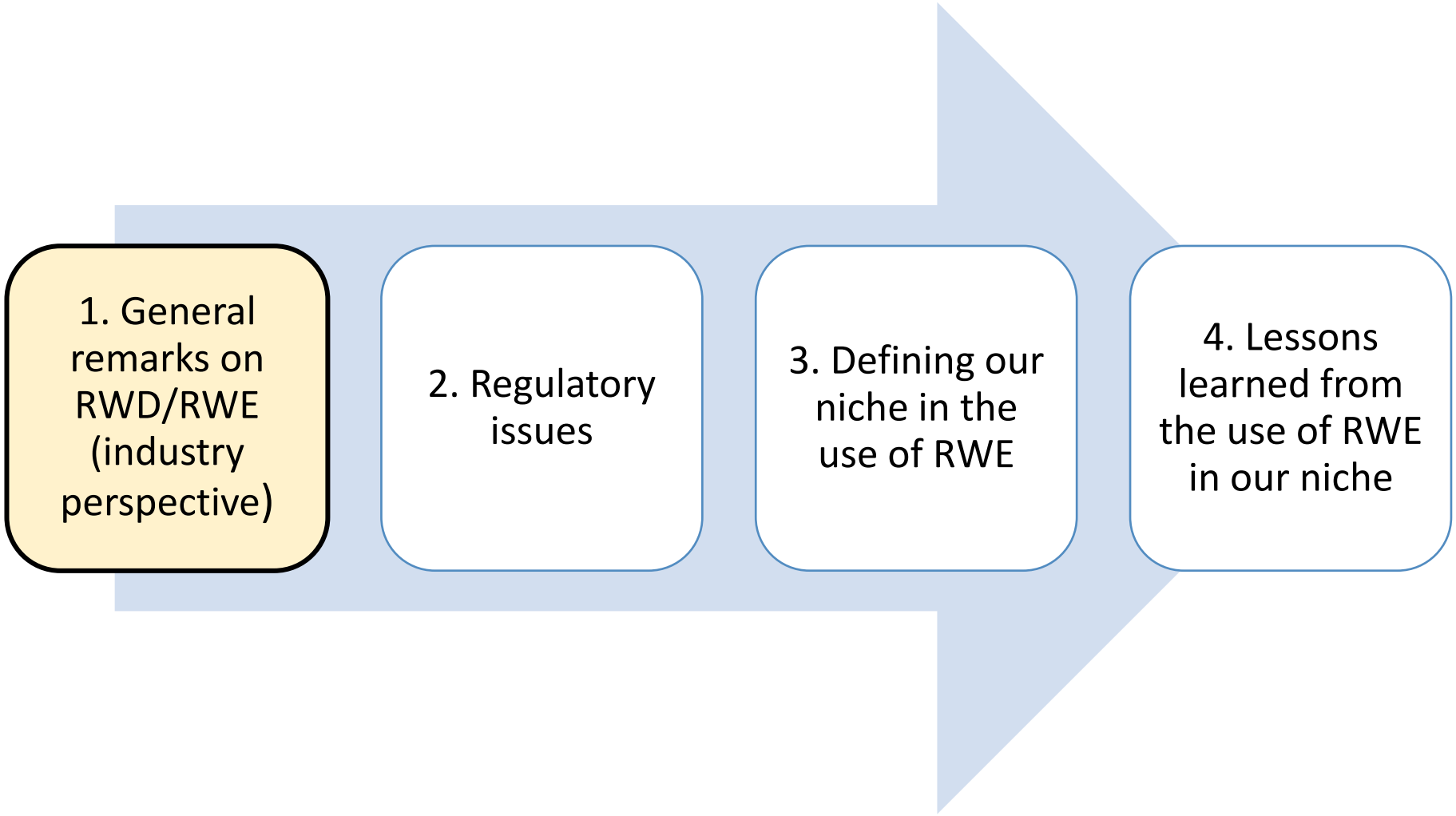
Disclaimer

This presentation represents the author’s personal opinion and does not necessarily represent the policy or recommendations of Zakłady Farmaceutyczne Polpharma S.A.

Presentation plan



Presentation plan



Potential uses of RWE

Apart from „traditional" exploratory use, RWE began to be used as clinical evidence for regulatory purposes

RWE may be used for:

Exploratory purposes („traditional" way)

- patients' demographics
- comorbidities
- comedications
- natural course of disease

https://pl.freepik.com/darmowe-wektory/prywatne-sledztwo-streszczenie-ilustracja_20891867.htm#query=%C5%9Bledztwo&position=32&from_view=search&track=sph

Regulatory purposes (new increasing trend)

- comparator arm in clinical trials (e.g. natural history of disease as untreated control)
- Rx→OTC switch
- extension of indications
- new FDCs comprised of well-known APIs

Potential uses of RWE

Apart from „traditional” exploratory use, RWE began to be used as clinical evidence for regulatory purposes

RWE may be used for:

Exploratory purposes („traditional” way)

- patients' demographics
- comorbidities
- comedications
- natural course of disease

https://pl.freepik.com/darmowe-wektory/prywatne-sledztwo-streszczenie-ilustracja_20891867.htm#query=%C5%9Bledztwo&position=32&from_view=search&track=sph

Regulatory purposes (new increasing trend)

- comparator arm in clinical trials (e.g. natural history of disease as untreated control)
- Rx→OTC switch
- extension of indications
- new FDCs comprised of well-known APIs

Retrospective or prospective RWE?

Retrospective RWE is an optimal choice for clinical-regulatory use from pragmatic point of view (timing, use of resources)

RWE may be performed:

Retrospectively

- secondary use of historical patients medical records
- faster (no patient recrutation phase)
- unlimited sample size (usually high like thousand(s) of patients)

Our 1st choice

Prospectively

- observational cohort study (e.g. Phase IV studies)
- takes longer (patient recruitment)
- limited sample size (higher sample size = ↑ study duration & ↑ use of resources)

Retrospective or prospective RWE?

Retrospective RWE is an optimal choice for clinical-regulatory use from pragmatic point of view (timing, use of resources)

RWE may be performed:

Retrospectively

- secondary use of historical patients medical records
- faster (no patient recrutation phase)
- unlimited sample size (usually high like thousand(s) of patients)

Our 1st choice

Prospectively

- observational cohort study (e.g. Phase IV studies)
- takes longer (patient recruitment)
- limited sample size (higher sample size = ↑ study duration & ↑ use of resources)

Retrospective or prospective RWE?

Retrospective RWE is an optimal choice for clinical-regulatory use from pragmatic point of view (timing, use of resources)

RWE may be performed:

Retrospectively

- secondary use of historical patients medical records
- faster (no patient recrutation phase)
- unlimited sample size (usually high like thousand(s) of patients)

Our 1st choice

Prospectively

- observational cohort study (e.g. Phase IV studies)
- takes longer (patient recruitment)
- limited sample size (higher sample size = ↑ study duration & ↑ use of resources)

Not feasible?

our 2nd choice
(similar time & resources compared to interventional clinical trials)

polpharma

Sources of RWD for retrospective studies

Plenty of RWD sources – choice is a challenge!
Electronic Medical Records from Healthcare systems usually gives the highest sample size (millions of patients per each country)

https://pl.freepik.com/darmowe-wektory/ilustracja-wektorowa-koncepcja-streszczenie-badania-cisnienia-krwi-placowka-farmaceutyczna-samokontrola-cisnienia-krwi-badanie-kliniczne-opieka-zdrowotna-abstrakcyjna-metafora-programu-badan_12468779.htm#query=dane%20medyczn&position=0&from_view=search&track=ais

Types of RWD sources

Healthcare system medical records

- Millions of patients
- Real-life population
- E.g. UK, France, Germany, Italy, Spain…
- Available for „commercial” purposes

Patient/disease-specific registries

- Less patients but the data collected in a tailor-made way for specific disease
- Real-life population?
- E.g. EURObservational Registry Programme (EORP) by European Society of Cardiology
- „Commercially” available?

Prescription/Drug utilization databases

- Huge amount of data
- Limited usability for efficacy & safety

Sources of RWD for retrospective studies

Plenty of RWD sources – choice is a challenge!
Electronic Medical Records from Healthcare systems usually gives the highest sample size (millions of patients per each country)

https://pl.freepik.com/darmowe-wektory/ilustracja-wektorowa-koncepcja-streszczenie-badania-cisnienia-krwi-placowka-farmaceutyczna-samokontrola-cisnienia-krwi-badanie-kliniczne-opieka-zdrowotna-abstrakcyjna-metafora-programu-badan_12468779.htm#query=dane%20medyczn&position=0&from_view=search&track=ais

Types of RWD sources

Healthcare system medical records

- Millions of patients
- Real-life population
- E.g. UK, France, Germany, Italy, Spain…
- Available for „commercial” purposes

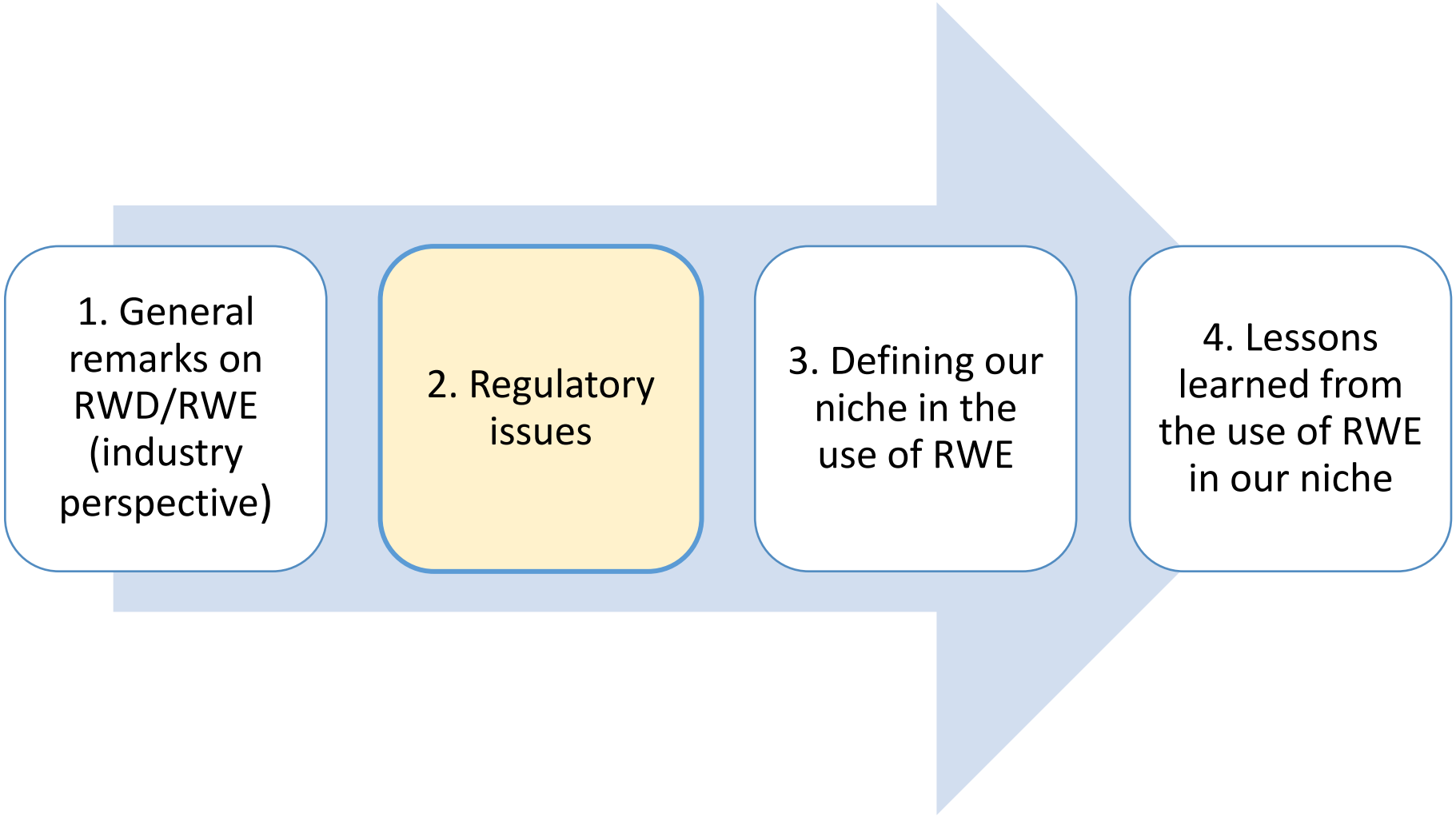
Patient/disease-specific registries

- Less patients but the data collected in a tailor-made way for specific disease
- Real-life population?
- E.g. EURObservational Registry Programme (EORP) by European Society of Cardiology
- „Commercially” available?

Prescription/Drug utilization databases

- Huge amount of data
- Limited usability for efficacy & safety

Presentation plan



First EMA Guideline - a cornerstone for RWE studies

EMA Guideline opens disscusion on definitions, general methodology and usability of RWD/RWE
From EMA Guideline perspective, RWE is still rather supportive than pivotal evidence (RCT is still the gold standard), but this will be considered case by case
Further guidelines are expected…

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 October 2021
EMA/426390/2021
Committee for Human Medicinal Products (CHMP)

Guideline on registry-based studies

https://www.ema.europa.eu/en/guideline-registry-based-studies-0

Guideline introduces general recommendations on:

- Methodology of RWE studies
- Creation & management of registries/RWD databases

polpharma

First EMA Guideline - a cornerstone for RWE studies

EMA Guideline opens disscusion on definitions, general methodology and usability of RWD/RWE
From EMA Guideline perspective, RWE is still rather supportive than pivotal evidence (RCT is still the gold standard), but this will be considered case by case
Further guidelines are expected…

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 October 2021
EMA/426390/2021
Committee for Human Medicinal Products (CHMP)

Guideline on registry-based studies

https://www.ema.europa.eu/en/guideline-registry-based-studies-0

Guideline introduces general recommendations on:

- Methodology of RWE studies
- Creation & management of registries/RWD databases

Consequences for RWE:

- Standardization of design
- Increased awareness & expectations regarding the quality
- RWE methodology will be a subject of deficiency letters during MA (the old Wild West is over!)

Regulatory use of RWE – EMA level experience

EMA tends to accept RWE as clinical evidence, but aproaches very carefully to each case:

- **5 of 16 attempts** resulted in central MA (3 cases as key evidence),
- **5 of 10 attempts** resulted in extension of indications (2 cases as key evidence)
- **EMA challenged the usability of submitted RWE** (in terms of quality and common limitations of RWE)

RWE plays an increasing role in central regulatory decisions, but for well justified cases so far (e.g. products for which RCTs are unethical or unfeasible, such as rare diseases)

Clinical Pharmacology & Therapeutics

Article | Open Access

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

Elisabeth Bakker, Kelly Plueschke, Carla J. Jonker, Xavier Kurz, Viktoriia Starokozhko, Peter G. M. Mol

First published: 17 October 2022 | https://doi.org/10.1002/cpt.2766

Opportunities to leverage the potential of RWD/RWE in medicines regulation

This study has shown that scientific advice procedures may be used as a platform to discuss the expected added value of RWD and difficulties already in an early planning stage, as the expected limitations of the RWD mentioned there by SAWP were usually in line with the remaining limitations mentioned in the final CHMP assessment, although noting the effort of applicants to address the SAWP advice as best as they could. Early interactions between applicants and regulators, as well as workshops and feasibility analyses focusing on how RWD can contribute to answering specific study questions and how abovementioned limitations could be minimized, are key to moving the appropriate use of RWE forward.[49,50]

CONCLUSIONS

In principle, RWE can be an endorsed type of evidence as part of the MA exercise as considered by CHMP as long as efforts are made to minimize its limitations. Additional efforts, such as spe-

Applications submitted between 2018-2019

Initial marketing authorization applications

158 reviewed	63 included RWE (40%)	32 for efficacy (20%)	16 preauthorisation (10%)	5 preauthorisation RWE contributed to decision making (3%)

Extension of indication applications

153 reviewed	28 included RWE (18%)	14 for efficacy (9%)	10 preauthorisation (6%)	5 preauthorisation RWE contributed to decision making (3%)

Figure 2 Reviewed initial MAAs and EoIs and its contribution to regulatory decision making. EoIs, extension of indication applications; MAAs, initial marketing authorization applications; RWE, real-world evidence.

polpharma

International level of disscusion on RWD/RWE

Different regulators around the world are working on the regulatory framework for RWD/RWE.
The discussion reached the international level (ICH), so harmonization is expected.
→ the role of RWE and requirements for its design & quality is evolving!

FDA U.S. FOOD & DRUG ADMINISTRATION

Guidance

- Framework for FDA's Real-World Evidence Program (2018)
- Use of Electronic Health Records in Clinical Investigations (2018)
- Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products (2021)
- Data Standards for Drug and Biological Product Submissions Containing Real-World Data (2021)
- Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products (2021)
- Digital Health Technologies for Remote Data Acquisition in Clinical Investigations (2022)
- Submitting Documents Utilizing Real-World Data and Real-World Evidence to FDA for Drugs and Biologics (2022)
- Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products (2023)
- Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products (2023)

https://www.fda.gov/science-research/real-world-evidence/center-biologics-evaluation-and-research-center-drug-evaluation-and-research-real-world-evidence

ICH harmonisation for better health

ICH Reflection Paper
Endorsed by the ICH Assembly on 13 June 2023

ICH harmonisation for better health

ICH Reflection Paper

International Harmonisation of Real-World Evidence Terminology and Convergence of General Principles Regarding Planning and Reporting of Studies Using Real-World Data, with a Focus on Effectiveness of Medicines

Under public consultation until 30 September 2023

Final Concept Paper

Establishment of a new ICH guideline on "General principles on plan, design, and analysis of pharmacoepidemiological studies that utilize real-world data for safety assessment of medicines"
23 March 2022
Endorsed by the Management Committee on 5 April 2022

Government of Canada / Gouvernement du Canada

Strengthening the use of real world evidence for drugs

From Health Canada

This project aims to improve our ability to assess and monitor the safety, efficacy and effectiveness of drugs across the drug life cycle. It will do this by optimizing the use of real world evidence (RWE) through stakeholder engagement.

- RWE is evidence about the use and potential benefits or risks of a medical product. This evidence comes from analysis of real world data relating to patient status and/or the delivery of health care routinely collected from a variety of sources.

We expect the outcomes of this project to include:

- increased use of RWE to enhance regulatory decision-making and risk communications throughout the drug life cycle
- improved use and sharing of RWE with our health care system partners
- increased clarity for stakeholders on where and how RWE can be used to support regulatory decision making
- improved access to drugs through the use of new sources of evidence to support approval of drug applications

https://www.canada.ca/en/health-canada/corporate/transparency/regulatory-transparency-and-openness/improving-review-drugs-devices/strengthening-use-real-world-evidence-drugs.html

polpharma

International level of disscusion on RWD/RWE

Different regulators around the world are working on the regulatory framework for RWD/RWE.
The discussion reached the international level (ICH), so harmonization is expected.
→ the role of RWE and requirements for its design & quality is evolving!

FDA U.S. FOOD & DRUG ADMINISTRATION

Guidance

- Framework for FDA's Real-World Evidence Program (2018)
- Use of Electronic Health Records in Clinical Investigations (2018)
- Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products (2021)
- Data Standards for Drug and Biological Product Submissions Containing Real-World Data (2021)
- Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products (2021)
- Digital Health Technologies for Remote Data Acquisition in Clinical Investigations (2022)
- Submitting Documents Utilizing Real-World Data and Real-World Evidence to FDA for Drugs and Biologics (2022)
- Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products (2023)
- Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products (2023)

https://www.fda.gov/science-research/real-world-evidence/center-biologics-evaluation-and-research-center-drug-evaluation-and-research-real-world-evidence

ICH harmonisation for better health

ICH Reflection Paper
Endorsed by the ICH Assembly on 13 June 2023

ICH Reflection Paper

International Harmonisation of Real-World Evidence Terminology and Convergence of General Principles Regarding Planning and Reporting of Studies Using Real-World Data, with a Focus on Effectiveness of Medicines

Under public consultation until 30 September 2023

ICH harmonisation for better health

Final Concept Paper

Establishment of a new ICH guideline on "General principles on plan, design, and analysis of pharmacoepidemiological studies that utilize real-world data for safety assessment of medicines"
23 March 2022
Endorsed by the Management Committee on 5 April 2022

Government of Canada / Gouvernement du Canada

Strengthening the use of real world evidence for drugs

From Health Canada

This project aims to improve our ability to assess and monitor the safety, efficacy and effectiveness of drugs across the drug life cycle. It will do this by optimizing the use of real world evidence (RWE) through stakeholder engagement.

- RWE is evidence about the use and potential benefits or risks of a medical product. This evidence comes from analysis of real world data relating to patient status and/or the delivery of health care routinely collected from a variety of sources.

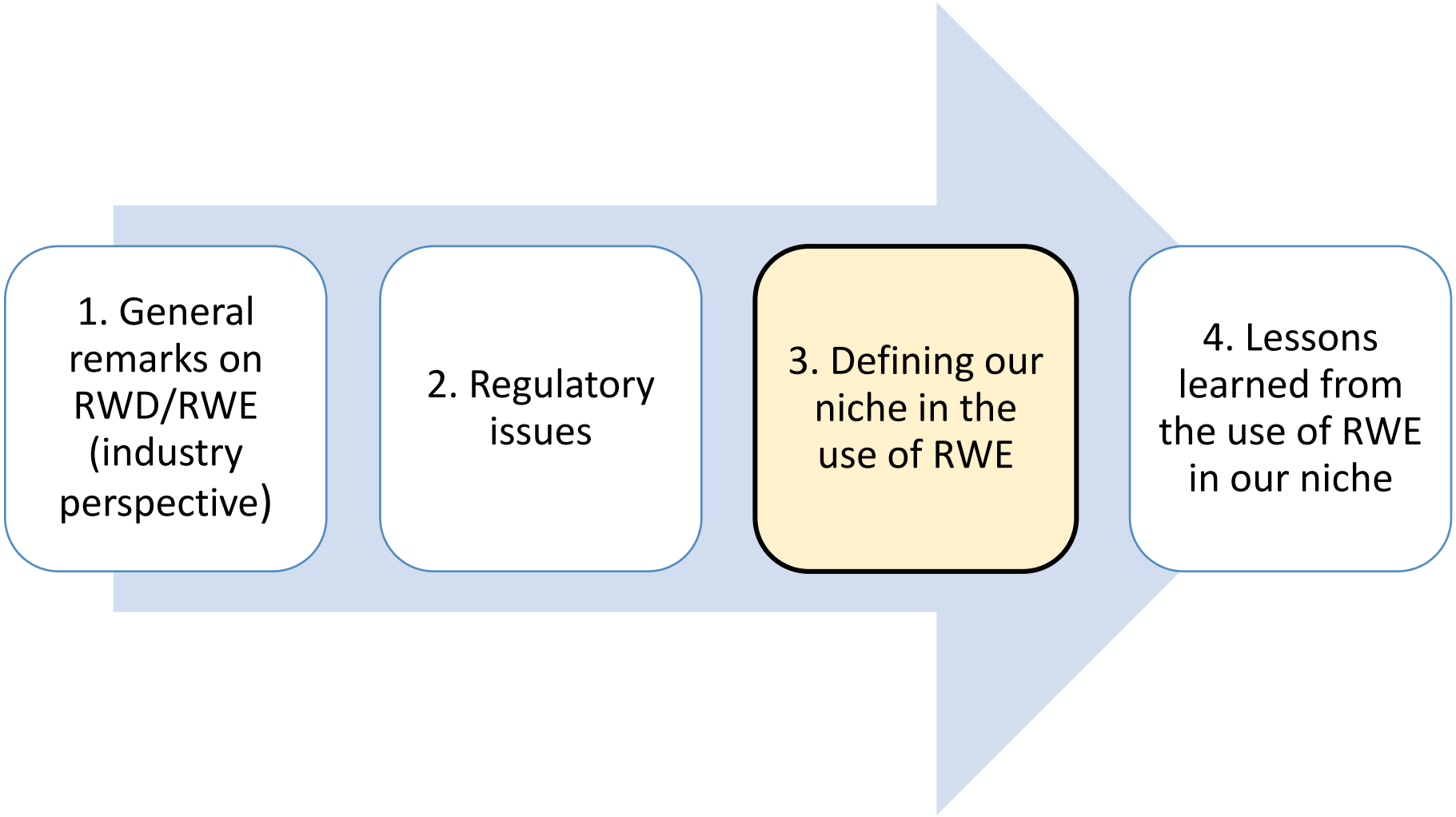
We expect the outcomes of this project to include:

- increased use of RWE to enhance regulatory decision-making and risk communications throughout the drug life cycle
- improved use and sharing of RWE with our health care system partners
- increased clarity for stakeholders on where and how RWE can be used to support regulatory decision making
- improved access to drugs through the use of new sources of evidence to support approval of drug applications

https://www.canada.ca/en/health-canada/corporate/transparency/regulatory-transparency-and-openness/improving-review-drugs-devices/strengthening-use-real-world-evidence-drugs.html

polpharma

Presentation plan



Retrospective RWE feasibility checklist

Best candidate for retrospective RWE study: ?

Question	Sensitive RWD/RWE area				Side comment	Answer
	RWD Availability	RWD Completeness	RWD/RWE Reliability	RWE Usability		
1. Well-known treatment of interest?	+					
2. Indication for investigated treatment in line with the therapeutic guidelines/clinical practice?	+			+	If not, difficult to use as key evidence	
3. Indication difficult to confuse with anything else?			+	+	a concern for retrospective analysis	
4. Chronic condition?	+	+			difficult to find retrospective data on acute condition	
5. A common disease?	+				difficult to find data on rare diseases	
6. Is recovery/remission possible without any treatment?			+	+		
7. Rx treatment only? OTC alternatives available?	+	+	+	+	difficult to find and follow patients self-treated with OTC drugs	
8. Are the patients likely to return to the clinic during the disease course or following the resolution of the disease?		+			risk of bias? (e.g. missing data)	
9. Are there well-established clinical endpoints measured in a routine clinical practice?	+			+		
10. Are the clinical endpoints measured and recorded in a standardized and objective way?	+		+	+		

Retrospective RWE feasibility checklist

Best candidate for retrospective RWE study:
frequent chronic disease, Rx drug, well-established indication with standardized endpoint(s)

Question	Sensitive RWD/RWE area				Side comment	Answer
	RWD Availability	RWD Completeness	RWD/RWE Reliability	RWE Usability		
1. Well-known treatment of interest?	+					
2. Indication for investigated treatment in line with the therapeutic guidelines/clinical practice?	+			+	If not, difficult to use as key evidence	
3. Indication difficult to confuse with anything else?			+	+	a concern for retrospective analysis	
4. Chronic condition?	+	+			difficult to find retrospective data on acute condition	
5. A common disease?	+				difficult to find data on rare diseases	
6. Is recovery/remission possible without any treatment?			+	+		
7. Rx treatment only? OTC alternatives available?	+	+	+	+	difficult to find and follow patients self-treated with OTC drugs	
8. Are the patients likely to return to the clinic during the disease course or following the resolution of the disease?		+			risk of bias? (e.g. missing data)	
9. Are there well-established clinical endpoints measured in a routine clinical practice?	+			+		
10. Are the clinical endpoints measured and recorded in a standardized and objective way?	+		+	+		

polpharma

Retrospective RWE feasibility checklist

Best candidate for retrospective RWE study:
frequent chronic disease, Rx drug, well-established indication with standardized endpoint(s)

Question	Sensitive RWD/RWE area				Side comment	Answer
	RWD Availability	RWD Completeness	RWD/RWE Reliability	RWE Usability		
1. Well-known treatment of interest?	+					☑
2. Indication for investigated treatment in line with the therapeutic guidelines/clinical practice?	+			+	If not, difficult to use as key evidence	☑
3. Indication difficult to confuse with anything else?			+	+	a concern for retrospective analysis	☑
4. Chronic condition?	+	+			difficult to find retrospective data on acute condition	☑
5. A common disease?	+				difficult to find data on rare diseases	☑
6. Is recovery/remission possible without any treatment?			+	+		☑
7. Rx treatment only? OTC alternatives available?	+	+	+	+	difficult to find and follow patients self-treated with OTC drugs	☑
8. Are the patients likely to return to the clinic during the disease course or following the resolution of the disease?		+			risk of bias? (e.g. missing data)	☑
9. Are there well-established clinical endpoints measured in a routine clinical practice?	+			+		☑
10. Are the clinical endpoints measured and recorded in a standardized and objective way?	+		+	+		☑

Treatment of hypertension! (our case study)

polpharma

The value of retrospective RWE in hypertension reseach: message from VIP

Key messages from G. Mancia:

1. RWE is not RCT, RCT is not a real-life evidence
2. Both RCTs and RWE have their strengths and limitations
3. RWE offers real-life heterogenous population, while RCTs are „hermetic”
4. RCTs are still gold standard for evaluation of new drugs
5. **Significant value of RWE for well-known substances for hypertension (=FDCs ?)**

ESC European Society of Cardiology
European Heart Journal (2022) **00**, 1–13
https://doi.org/10.1093/eurheartj/ehab899

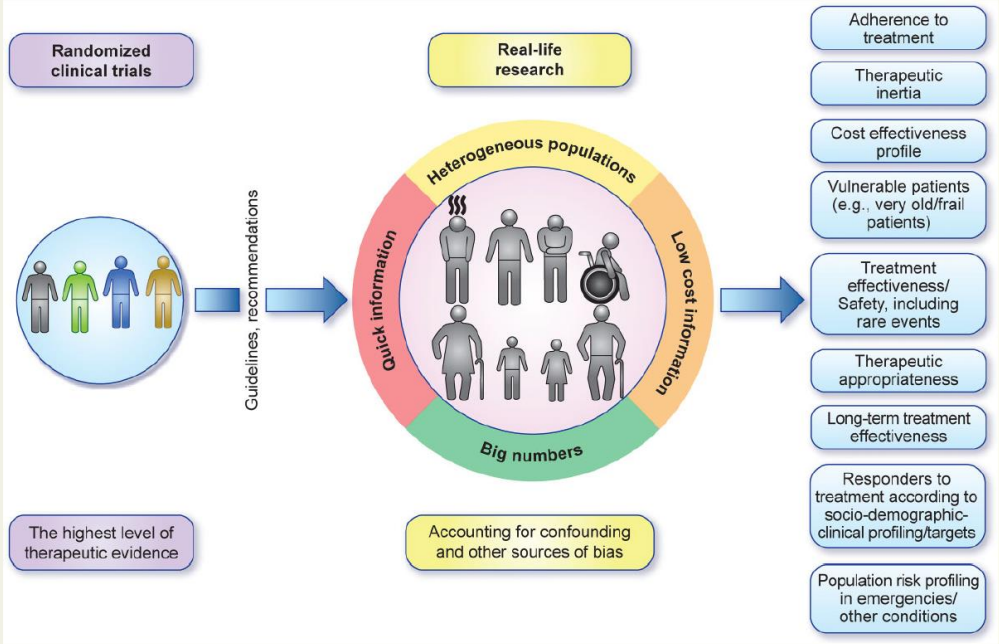
STATE OF THE ART REVIEW
Hypertension

Research strategies in treatment of hypertension: value of retrospective real-life data

Giovanni Corrao [1,2] and Giuseppe Mancia [3]*

[1]National Centre for Healthcare Research & Pharmacoepidemiology, Department of Statistics and Quantitative Methods, University of Milano-Bicocca, Milan, Italy; [2]Department

G. Mancia: a **pioneer** of clinical research in hypertension and main **author** of therapeutic **guideline** for hypertension!



Graphical Abstract Randomized clinical trials (RCTs) represent the highest level of therapeutic evidence, but they also have important limitations that affect the application of the results to clinical practice.

Table 1 Relative advantages (+) and disadvantages (–) of major data sources in healthcare research

Desired traits for healthcare research	Prospective data collection		Analysis of existing databases
	Controlled randomized trials	Longitudinal observational studies	Healthcare utilization databases
Less expensive	—	–	+++
Promptness of data availability	—	–	+++
Patient awareness/level of intrusion	—	—	+++
Data applicability to multiple conditions/diseases	—	–	+++
Size of collected data	—	–	+++
Patient heterogeneity representativeness	—	++	+++
Real-life clinical practice representativeness	—	+++	+++
Quality/extent of clinical information	+++	++	–
Absence of confounding by indication/group comparability	+++	–	—
Accessibility by health services investigators	—	–	+
Accuracy of disease coding	+++	+	–
Upcoding of diseases or services[a]	+++	+++	—
Control of collected information by investigators	+++	+++	—

Modified from Corrao and Mancia.[25]
[a]Done to maximize reimbursement.

Table 2 Major advantages of using healthcare utilization databases

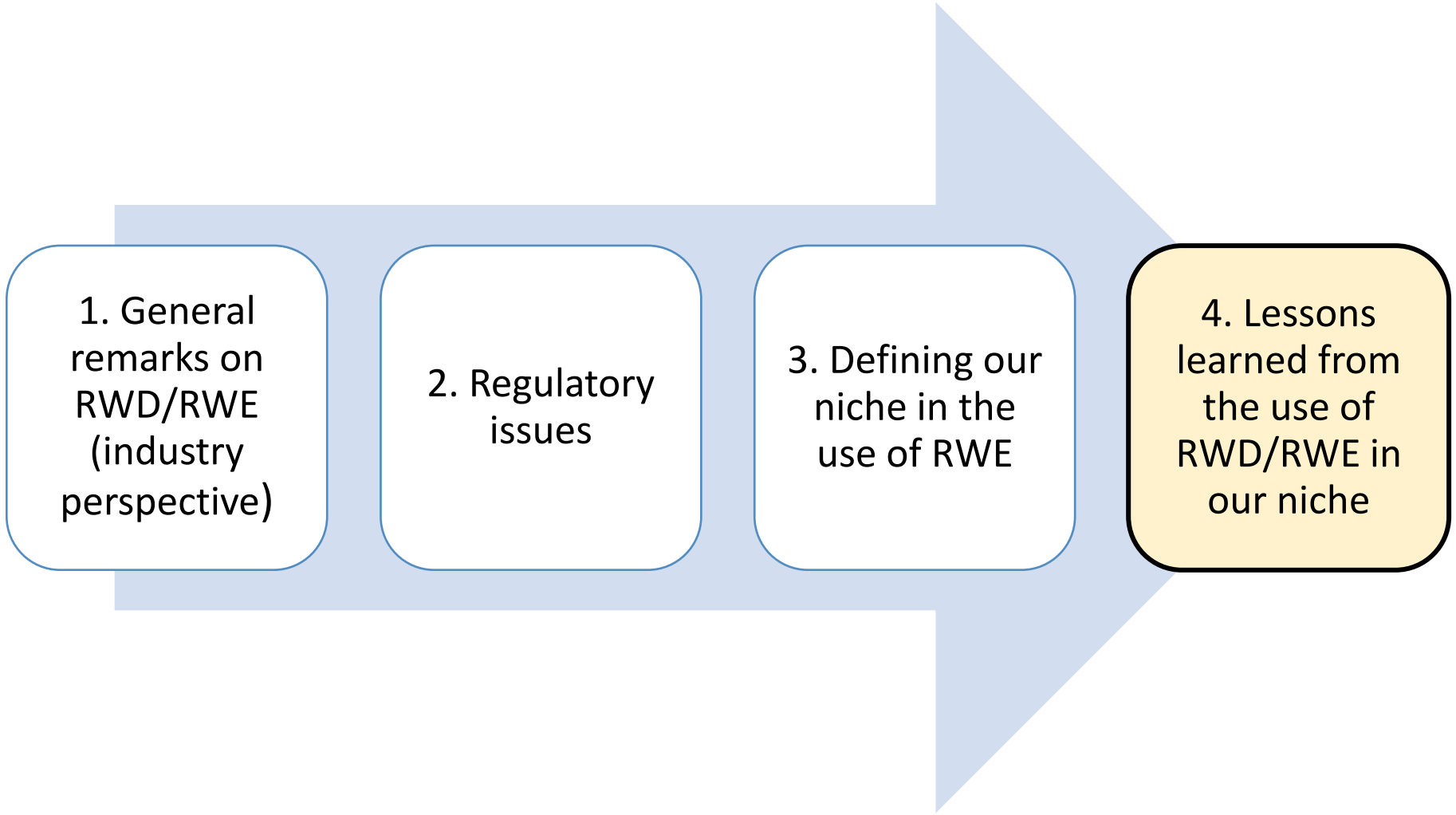
Data characteristics	Advantage
Data are available in electronic format	Low cost of investigation
Data include all healthcare services supplied to delivery system beneficiaries	A comprehensive healthcare history of each beneficiary of healthcare system may be available
Patients and doctors are not involved in data collection	Findings are free from bias generated by awareness of being under observation
Data cover very large populations	Outcomes that rarely occur may be investigated
Data collected from unselected populations	Information reflects the state of clinical practice in the general population (particularly where healthcare is assured to the whole citizenship)

Modified from Corrao and Mancia.[25]

Also tips on quality by design in retrospective RWE
→**Must-read!**

polpharma

Presentation plan



Industry experience in the EU so far

RWE has been used in MAA for new antihypertensive FDCs in the EU for at least 10 years
Different RMSs, virtually all Member States involved as CMS
There are cases were RWE was used as significant or even key evidence for clinical efficacy and safety

Examples of RWE used as clinical rationale/evidence for new antihypertensive FDCs (art. 10b of Dir. 2001/83/EC):

Year	Combination (Procedure number)	MAH	RMS	CMS	RWE type	RWE as key evidence?
2014	Perindopril + indapamide + amlodipine (NL/H/2636/001-005/DC)	Les Laboratoires Servier, FR	NL	AT, BE, BG, CY, CZ, EE, ES, FI, FR, GR, HU, IE, IT, LT, LV, LU, MT, PL, PT, RO, SK, SI	Observational studi**es** **Retrospective** study	?
2015	Bisoprolol + amlodipine (HU/H/0341/001-004/DC)	EGIS Pharmaceuticals Plc., HU	HU	BG, CZ, LT, LV, PL, RO, SK	Co-prescription data	**?** (limited literature)
2017	Candesartan + amlodipine (DE/H/5108/01-02/DC)	TAD Pharma GmbH, DE	DE	AT, BE, BG, CZ, EE, ES, FI, LV, PL, PT, RO, SI, SK	**Retrospective** study	**Yes?** (literature only for analogic combos)
2018	Telmisartan + amlodipine (CZ/H/0736/001-004/DC)	Krka, d.d, SI	CZ	PL	**Retrospective** study + co-prescription data	No
2019	Bisoprolol + amlodipine (DE/H/5057/01-04/DC)	TAD Pharma GmbH, DE	DE	CZ, SI	**Retrospective** study + co-prescription data	**Yes?** (limited literature)
2019	Lisinopril + torasemide (PL/H/0418/001-004/DC)	Accupharma Sp. z o.o., PL	PL	CZ, LT, SK	Co-prescription data	No
2021	Telmisartan + indapamide (CZ/H/0819/002)	PRO.MED.CS, CZ	CZ	PL, RO, SK	Co-prescription data	No
2022 /2023	Ramipril + bisoprolol **(refferal EMEA/H/A-29(4)/1519)**	Adamed Pharma S.A., PL (and others)	PL	BG, CY, CZ, DE, ES, GR, HR, IT, PT SK	Observational studi**es** **Retrospective** study Co-prescription data	**Yes!** (limited literature)

Acknowledgent: Zuzanna Miś, Polpharma

polpharma

Industry experience in the EU so far

RWE has been used in MAA for new antihypertensive FDCs in the EU for at least 10 years
Different RMSs, virtually all Member States involved as CMS
There are cases were RWE was used as significant or even key evidence for clinical efficacy and safety

Examples of RWE used as clinical rationale/evidence for new antihypertensive FDCs (art. 10b of Dir. 2001/83/EC):

Year	Combination (Procedure number)	MAH	RMS	CMS	RWE type	RWE as key evidence?
2014	Perindopril + indapamide + amlodipine (NL/H/2636/001-005/DC)	Les Laboratoires Servier, FR	NL	AT, BE, BG, CY, CZ, EE, ES, FI, FR, GR, HU, IE, IT, LT, LV, LU, MT, PL, PT, RO, SK, SI	Observational studi**es** **Retrospective** study	?
2015	Bisoprolol + amlodipine (HU/H/0341/001-004/DC)	EGIS Pharmaceuticals Plc., HU	HU	BG, CZ, LT, LV, PL, RO, SK	Co-prescription data	**?** (limited literature)
2017	Candesartan + amlodipine (DE/H/5108/01-02/DC)	TAD Pharma GmbH, DE	DE	AT, BE, BG, CZ, EE, ES, FI, LV, PL, PT, RO, SI, SK	**Retrospective** study	**Yes?** (literature only for analogic combos)
2018	Telmisartan + amlodipine (CZ/H/0736/001-004/DC)	Krka, d.d, SI	CZ	PL	**Retrospective** study + co-prescription data	No
2019	Bisoprolol + amlodipine (DE/H/5057/01-04/DC)	TAD Pharma GmbH, DE	DE	CZ, SI	**Retrospective** study + co-prescription data	**Yes?** (limited literature)
2019	Lisinopril + torasemide (PL/H/0418/001-004/DC)	Accupharma Sp. z o.o., PL	PL	CZ, LT, SK	Co-prescription data	No
2021	Telmisartan + indapamide (CZ/H/0819/002)	PRO.MED.CS, CZ	CZ	PL, RO, SK	Co-prescription data	No
2022 /2023	Ramipril + bisoprolol **(refferal EMEA/H/A-29(4)/1519)**	Adamed Pharma S.A., PL (and others)	PL	BG, CY, CZ, DE, ES, GR, HR, IT, PT SK	Observational studi**es** **Retrospective** study Co-prescription data	**Yes!** (limited literature)

Acknowledgent: Zuzanna Miś, Polpharma

polpharma

Ramipril+Bisoprolol breakthrough case (refferal EMEA/H/A-29(4)/1519)

Probably the 1st case of EMA-level disscusion on the acceptance of RWE for a new antihypertensive FDC (art. 10b)
Majority of EMA Member States took a pragmatic approach and voted in favor of this „obvious" FDC despite lack of RCTs supporting relevant contribution and limitations of the presented data and inconsistent results
Divergent positions of some Member States were not strictly related to the type of the evidence (RWE)!!!

Proposed indications (substitution scenario):

- Hypertension, hypertension with coexisting CCS and/or HFrEF
- Chronic coronary syndrome(CCS) and/or chronić heart failure with reduced EF (HFrEF)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 December 2022
EMA/15850/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Referral under Article 29(4) of Directive 2001/83/EC

Rambis and associated names

INN: ramipril/bisoprolol

Procedure number: EMEA/H/A-29(4)/1519

Clinical rationale/evidence:

- Prospective RWE, N=~230
- Meta-analysis of 6 RWEs (retrospective and prospective?) N= ~77.000 patients
- Retrospective RWE, N=~56.000 (FR + DE healthcare medical records)
- Coprescription data
- Public domain studies on monocomponents, analogic combinations (ACEI + BB) and interchangeability of different ACEIs or BBs.

Limitations identified by the CHMP:

- doses not specified, or not separated by treatment arms
- possible confounding effect by other treatments
- low sample size **(?!)**
- results insufficiently detailed
- results were inconsistent (**no clear superiority vs. monotherapy was seen!)**

Grounds for the CHMP POSITIVE desision:

- well-established additive effect of ACEI+BB combinations (literature and real-life practice)
- „ totality of the data submitted"

Divergent positions (CZ, DE, FR, IT, NO, SK):

- Lack of literature data (RCTs?) showing superiority of R+B over monocomponents
- Disagreed on extrapolation of data on analogic ACEI+BB combos to R+B
- Inconclusive results of presented RWE studies **(but not type of evidence RWE per se!)**

Lessons learned in RWE design and usability
→Must-read!

polpharma

Our experience in RWE so far – performed studies

Studies performed for new antihypertensive combinations:

- 3 retrospective studies on UK patients' medical records
- Patients with hypertension using free combinations of well-known drugs
- Patients switched to free combination therapy from baseline monotherapy period
- Searching for a relevant contribution of each substance to the desired therapeutic effect and safety
- Enrolled population:
  - Large, i.e. ~thousands of patients (compared to few hundreds of patients usually seen in RCTs!)
  - Heterogenous, incl patients >90 y.o. (!), with different comorbidities and comedications, etc.
- Main results:
  - combination therapy gives significant blood pressure reduction in patients previously treated with monotherapy
  - no safety concerns identified
  - consistent results and logical dependences across different subgroups analyses

Challenges:

- Deep dive into raw healthcare records (identification & sorting & classification of codes on coexisting diseases, concomitant treatment, AEs etc.) requires a lot of time → use of AI to search relevant codes?
- Regression to the mean? → adressed by sensitivity analyses.

Also important:

- Smart and open-minded clinical consultants and data analysts ☺

Further studies planned or on feasibility stage…

What was the regulatory perception of RWD/RWE in our cases?

https://pl.freepik.com/darmowe-wektory/ilustracja-wykresu-analizy-danych_2807756.htm#query=data%20science&position=4&from_view=keyword&track=ais

polpharma

Our experience in RWE so far – regulatory feedback

Of course each case (product) should be considered separately
but the approach to the RWD/RWE seems to be country-specific.
Is it worth to perform SA in case we plan to have RWE as pivotal clinical evidence?

https://pl.freepik.com/darmowe-zdjecie/krecace-sie-kolo-ruletki-niesie-ze-soba-szanse-na-bogactwo-i-ryzyko-uzaleznienia-generowane-przez-sztuczna-inteligencje_49573028.htm#query=ruletka&position=5&from_view=keyword&track=sph

DL from UK (FDC):

Provide data on relevant contribution, it might be supported by (…) or retrospective RWE.

Endorsed by BE!

2x SA in DE (FDC; new indication for well-known API):

Clinical studies required.

SA in CZ (new indication for well-known API):

Clinical studies required. RWE can be **only supportive**.

2023

Pre-submission meeting in PL (FDC):

No objections regarding the use of RWE as **supportive** evidence.

polpharma

Take home messages

1. **The use and importance of RWE** in clinical development is **increasing** (we cannot stop the advance of data science!)
2. **RWE** is a valuable source of **clinical evidence** especially for products comprised of **well known substances** (e.g. cardiologic FDCs)
3. **Retrospective** RWE is an **optimal choice for clinical-regulatory use** (faster, higher sample size)
4. **Ongoing works on regulatory framework** may significantly impact the design & usability of RWE (ICH harmonization is coming…)
5. **Regulators approach carefully** to each case, tend to accept RWE as supportive evidence in **well-justified cases** (but divergent opinions between different EMA Member States!)
6. **Quality by design** of retrospective RWE plays a significant role for its acceptance as clinical evidence by Regulators
7. Currently it's better to **take a chance on MAA with „pivotal" RWE**, SA may result in a conservative answer which may put you in an awkward position!

Thank you!