Registry data to support regulatory decisions in oncology: More-EUROPA's first experiences with DICA data, minimal data set and outcome of different dosing strategies in clinical practice

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Conflicts of interest

- I am participating in IMI-EPND, and receive unrestricted research grants from CBG-MEB, HORIZON EUROPE (PRIME-CKD, More-EUROPA)
- All my views presented today are my own, and may not necessarily reflect the opinion of the CBG-MEB, the EMA or one of its committees or working parties

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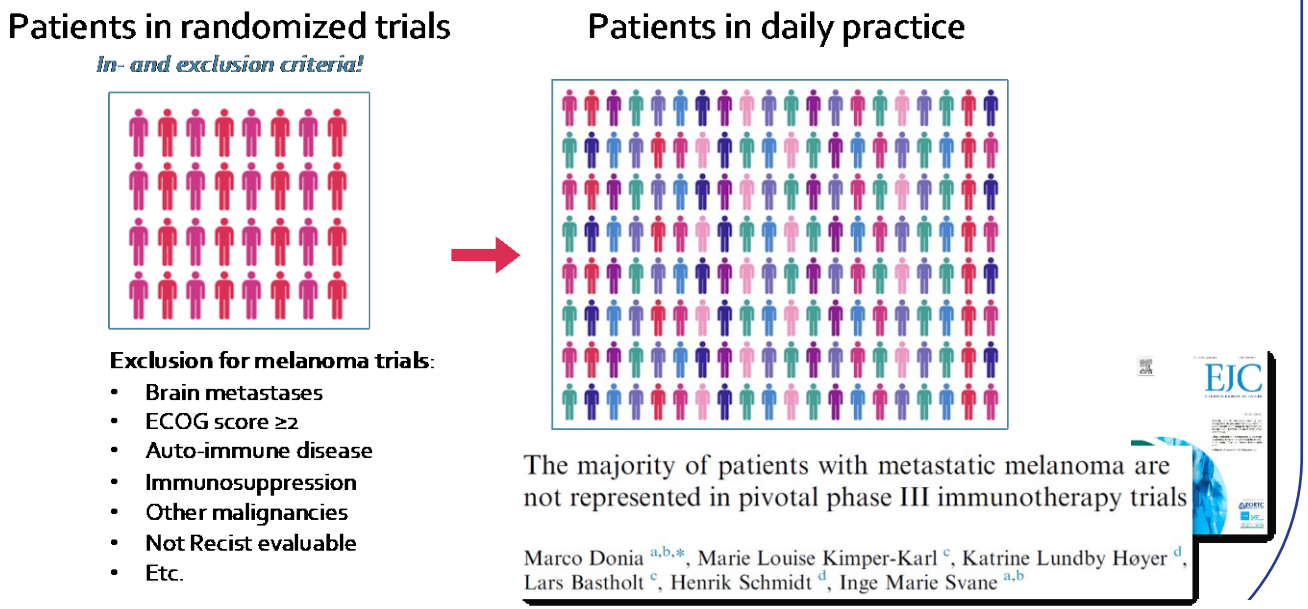
RCTs and RWD

- RCTs mainstay of drug efficacy and safety information for regulators/HTAs
- Value of RWD increasingly acknowledged
  - transform, accelerate and de-risk decision making
  - improve efficiency in design and conduct of trials
  - increase public health
- Around licensing: contextualize study results, ensure generalisability of results to target population
  - E.g., Yescarta SmPC (Crump et al. 2017 https://doi.org/10.1182/blood-2017-03-769620)
- Post-licensing: appreciate real-world value, long-term B/R



Donia et al. EJC, 2017

The role of RWE in FDA approvals

DID YOU KNOW?

1 in 2

of 2019 approved FDA submissions for new drugs and biologics included a real-world evidence study.

Aetion generates decision-grade real-world evidence (RWE) for biopharma, payers, and regulatory agencies.

As industry prepares for the FDA's draft RWE guidance in 2021, we conducted a systematic review of FDA approval documents from 2019 to understand how RWE informs today's regulatory decisions.

This eBook will guide you through when, where, and how RWE studies have supported the approvals of New Drug Applications (NDAs) and Biologics License Applications (BLAs).

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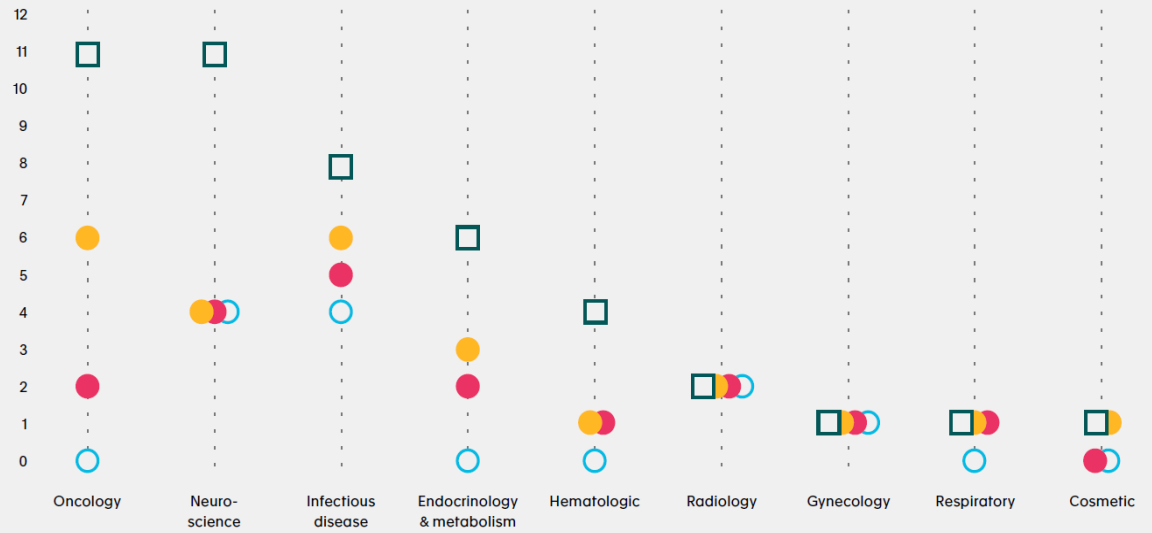
2019 FDA approvals that included RWE studies span nine therapeutic areas.



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The following therapeutic areas (representing six approvals) did not have any RWE submissions: Dermatology, Gastrointestinal, Inflammation & Immunology, Ophthalmology.

Ebook AETION.com The role of real-world evidence in FDA approvals

Let's talk Re@l: Let's talk external controls!

"A quick dive into the latest FDA guidance, SIG discussions and the industry's experience so far by Elizabeth Merrall, Rima Izem and Josie Wolfram on behalf of the PSI RWD SIG"

Selixenor for treatment of refractory multiple myeloma (FDA application in 2018), based on a single arm trial and electronic health records data from Flatiron Health Analytic Database

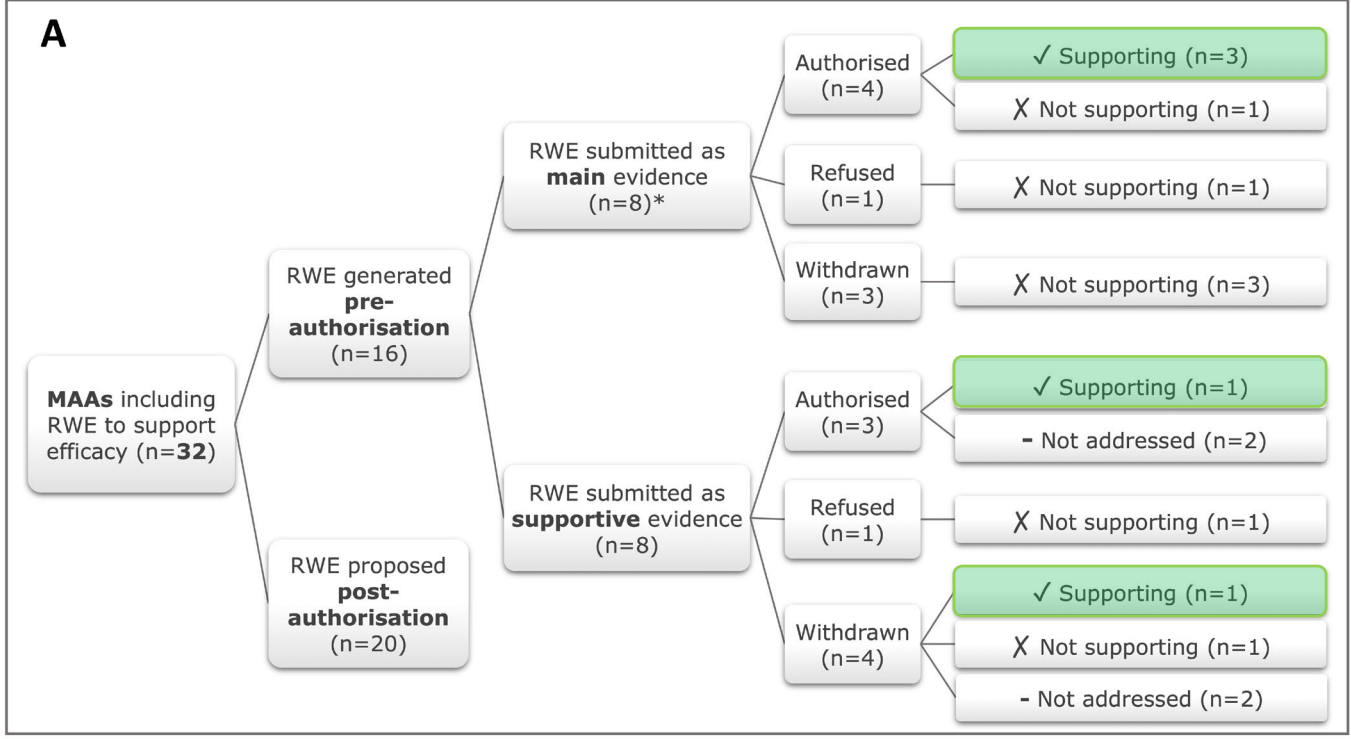
https://www.psiweb.org/docs/default-source/resources/psi-subgroups/rwd-sig/let's-t@lk-real-blog/rwd_sig_lets_talk_re@l_edition2_18may2023.pdf

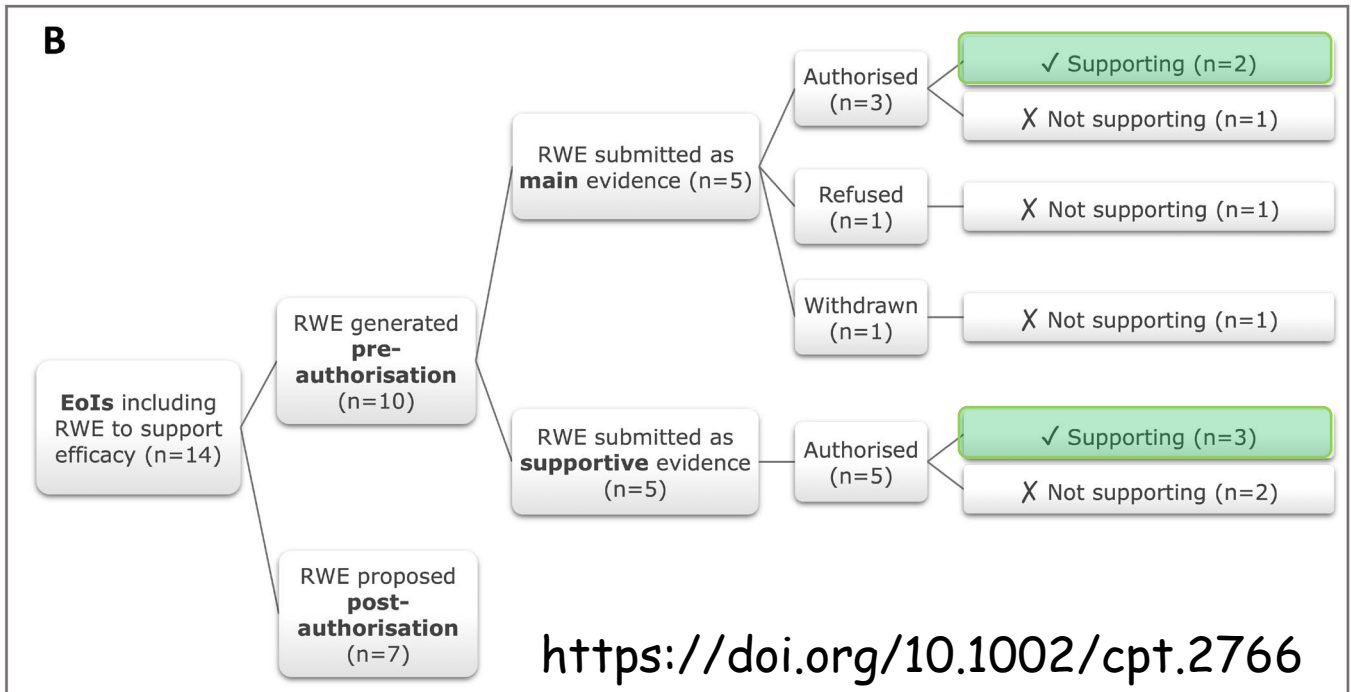
Table 1: Summary of FDA-identified limitations of RWD-based external control group included in submission package for Selinexor

Limitations identified	FDA comments on RWD part of results
Small sample size	After key inclusion/exclusion criteria were aligned, the number of eligible patients in the FHAD set reduced to 13 - likely too small to be representative and corresponding analyses underpowered to show a difference between the groups
Confounding	Imbalances between treatment groups were not adequately accounted for in the design or analysis phases, which likely resulted in confounding bias, primarily favoring survival for the STORM cohort.
Selection bias	More stringent exclusion criteria for trial patients such that these were more likely to be healthier than controls. For example, the Applicant cited real-world OS of patients with penta-exposed, triple-class refractory MM as 3.5–3.7 months; however, patients with less than 4 months life expectancy were excluded from STORM.
Immortal time bias	Time zero defined as date upon which a patient failed his or her last treatment – by design, STORM patients are required to have lived long enough to enroll in the study, i.e., immortal person-time between failure of prior therapy and randomization. No such requirement applied to the FHAD patients.
Performance/misclassification bias	Potential differential treatment misclassification as a result of the differing inclusion/exclusion criteria for the STORM and FHAD cohorts (e.g. 27/64 FHAD patients had no subsequent treatment after time zero so should have been excluded).
Missing data	Substantial missingness of key confounding factors, among others, ECOG was missing in 31% of control patients and baseline tumor stage status mostly unknown (65-78% II/Unknown).
Lack of pre-specification	Without having reviewed and consented to a protocol and SAP, FDA cannot be certain that the protocol and SAP were pre-specified and unchanged during the data selection and analyses. This uncertainty and the knowledge that subsequent unmasked analyses have been performed could lead to overly optimistic conclusions.

Real-world evidence in recent EMA centralised initial marketing authorisation applications (MAAs) and extension of indication applications (EoIs)

- Due to the heterogeneity in types and contexts of use of RWD/RWE submitted in medicines' applications, the appraisal of its impact requires a case-by-case analysis
- RWD/RWE limitations often restrict its use in CHMP decision making
- It is important to be aware of each data source's limitations and opportunities when planning a RWD-based study, and to interact with regulators at an early stage:
  - e.g., in a scientific advice procedure, as they were often able to identify potential limitations to be addressed
- As RWD is usually considered in the overall evidence package of the applications, it is difficult to isolate its exact impact on CHMP decision making
- A structured approach of presenting RWD/RWE in applications and assessment reports could facilitate monitoring its use in future procedures to enable further establishing its impact on regulatory decision making





https://doi.org/10.1002/cpt.2766

More-EUROPA

European Commission

Aims:

- Establish value of registry-based RWD in augmenting RCTs
- Enable more effective and ethical use of registry data to support patient-centered regulatory and health technology assessment decision-making

Real-World Evidence in EU Medicines Regulation: Enabling Use and Establishing Value. Arlett p. et al. CPT 2021 https://doi.org/10.1002/cpt.2479

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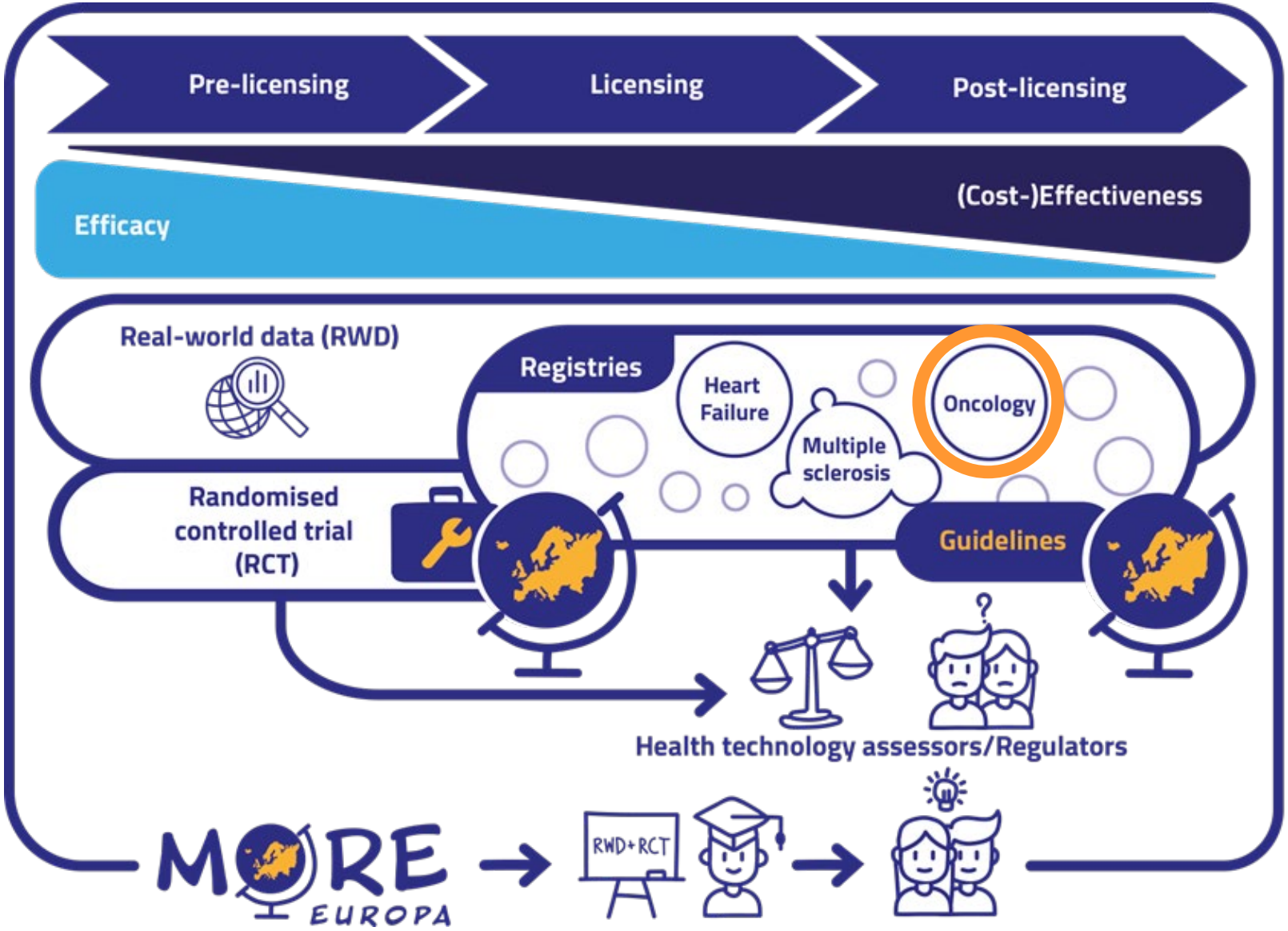
Summary introduction



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Ultimate goal

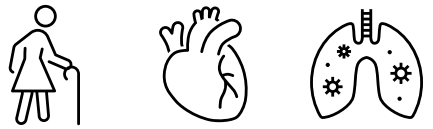
- Decrease costs of drug development/licensing
- Speed up accessibility and reimbursement of drugs in European people/patients in need

Priorization of registries as RWD source

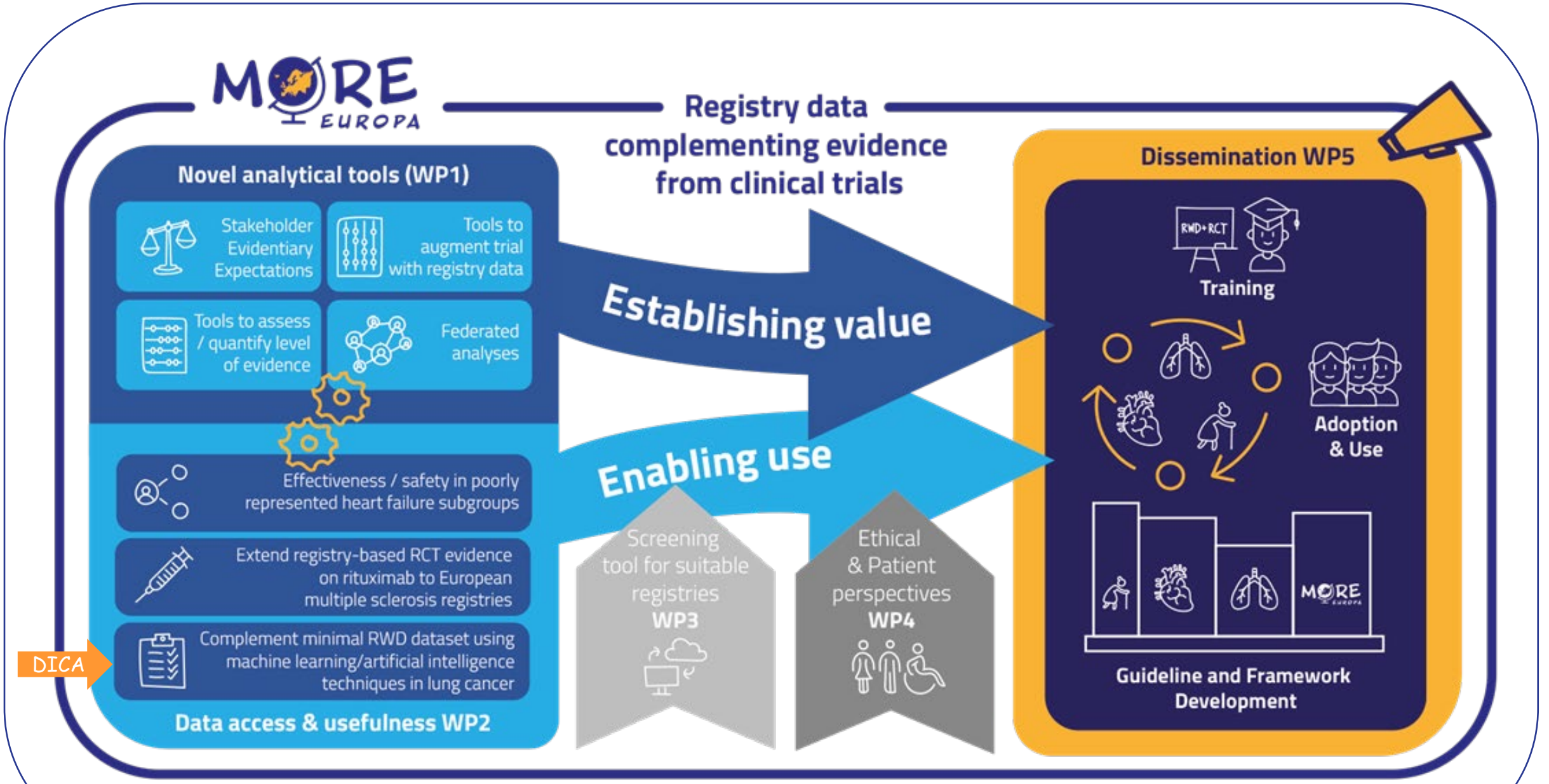
- Quality standards already available
- Data immediately available for analyses case studies

-> Outcomes practical, implementable and adopted

Focus on 3 registries



	Swedish Multiple Sclerosis registry (SMSreg)	Swedish Heart Failure Registry (SwedeHF)	Dutch Institute for Clinical Auditing (DICA)‡
Disease	Multiple sclerosis	Heart failure	Cancer (lung cancer)
Established since	1997	2000	2010
# patients captured in the registry	20,000	Till 2018, 156.000 registrations from 90.000 patients	In the pilot DICA-medicines: 10,000 patients (2018-2022)§
Data linkage	Cause of Death Registry National Patient Registry Statistics Sweden Prescribed Drug Registry		Hospital database (possible to scale up to nation-wide participation) PALGA (pathology) Vektis (claim database)
Age range	12-96 years	18-106 years	19-104 years
Sex	70% females	39% females	54% females
Registry-based RCT	**RIFUND-MS (EudraCT 2015-004116-38)**	**SPIRRIT-HFpEF (clinicaltrial.gov NCT02901184)**	N/A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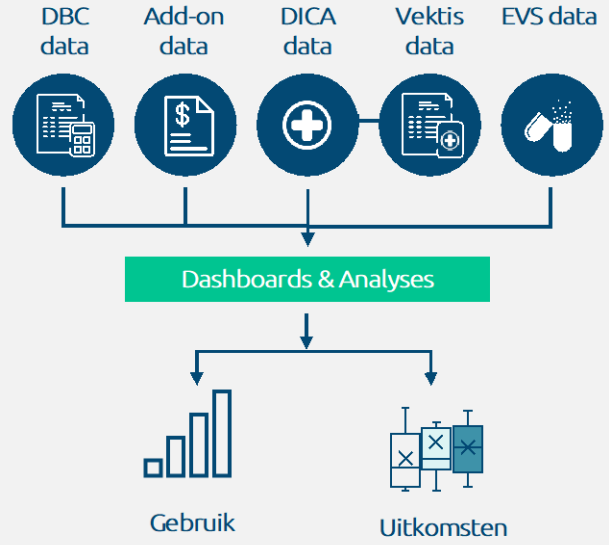
Registry data complementing evidence from clinical trials
Novel analytical tools (WP1)
Stakeholder Evidentiary Expectations
Tools to augment trial with registry data
Tools to assess / quantify level of evidence
Federated analyses
Effectiveness / safety in poorly represented heart failure subgroups
Extend registry-based RCT evidence on rituximab to European multiple sclerosis registries
DICA
Complement minimal RWD dataset using machine learning/artificial intelligence techniques in lung cancer
Data access & usefulness WP2
Establishing value
Enabling use
Screening tool for suitable registries WP3
Ethical & Patient perspectives WP4
Dissemination WP5
RWD+RCT
Training
Adoption & Use
MORE
Guideline and Framework Development

Case studies

- Studying generalisability of drug estimates across different heart failure sub-populations
- Evaluating (cost-)effectiveness/safety of 'off-label' rituximab in people with MS
- **Improving the evidence for therapies using registry data as external controls in lung cancer**
  - *(Lead: Dutch Institute for Clinical Auditing)*

DICA -DMA (Dutch Medication Audit)
56 hospitals



DICA Life saving data

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Next steps

- Define minimal data set for more detailed covariate control
  - External control
- Apply natural language processing to identify not routinely collected / structured data

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27 March 2020
EMA/661159/2019
Inspections, Human Medicines, Pharmacovigilance and Committees Division

Report of the workshop on the use of registries in the monitoring of cancer therapies based on tumours' genetic and molecular features - 29 November 2019

Patient registries initiative

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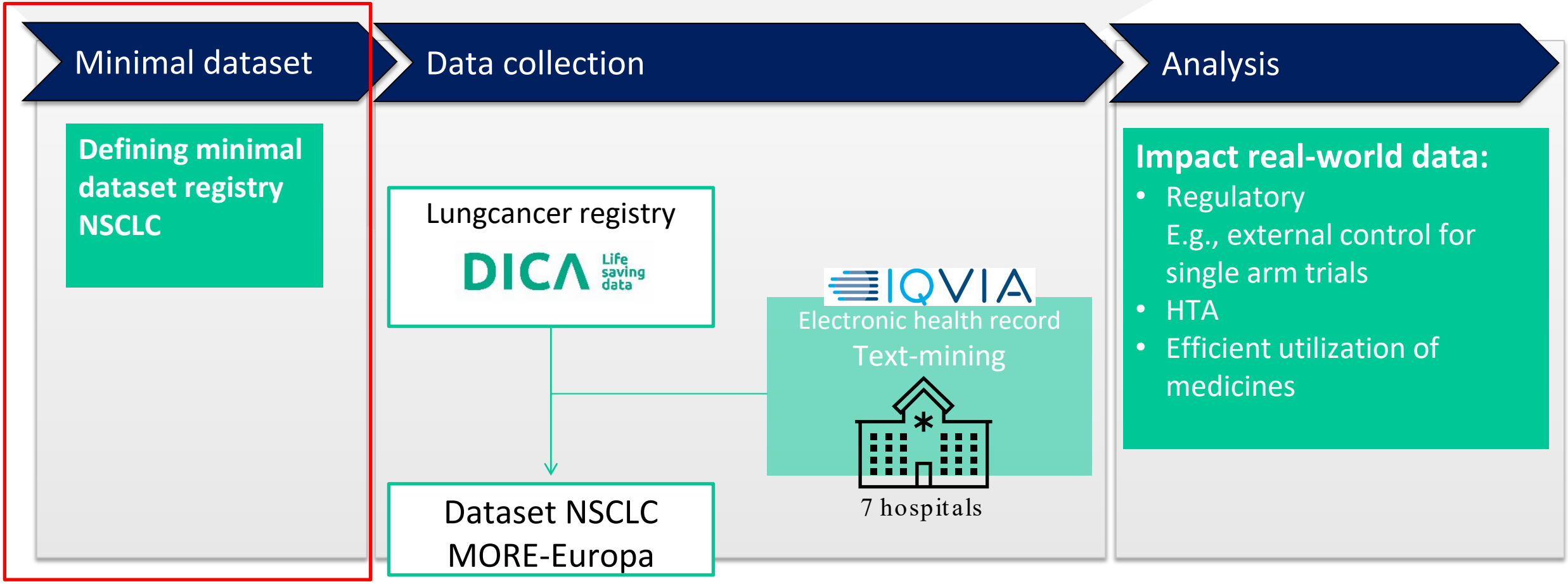
1 17 April 2023
2 EMA/CHMP/564424/2021
3 Committee for Medicinal Products for Human Use (CHMP)

4 Reflection paper on establishing efficacy based on single-
5 arm trials submitted as pivotal evidence in a marketing
6 authorisation
7 Considerations on evidence from single-arm trials

Case study – lung cancer registry

> The use of real-world data in the regulatory and HTA assessment of high-cost drugs



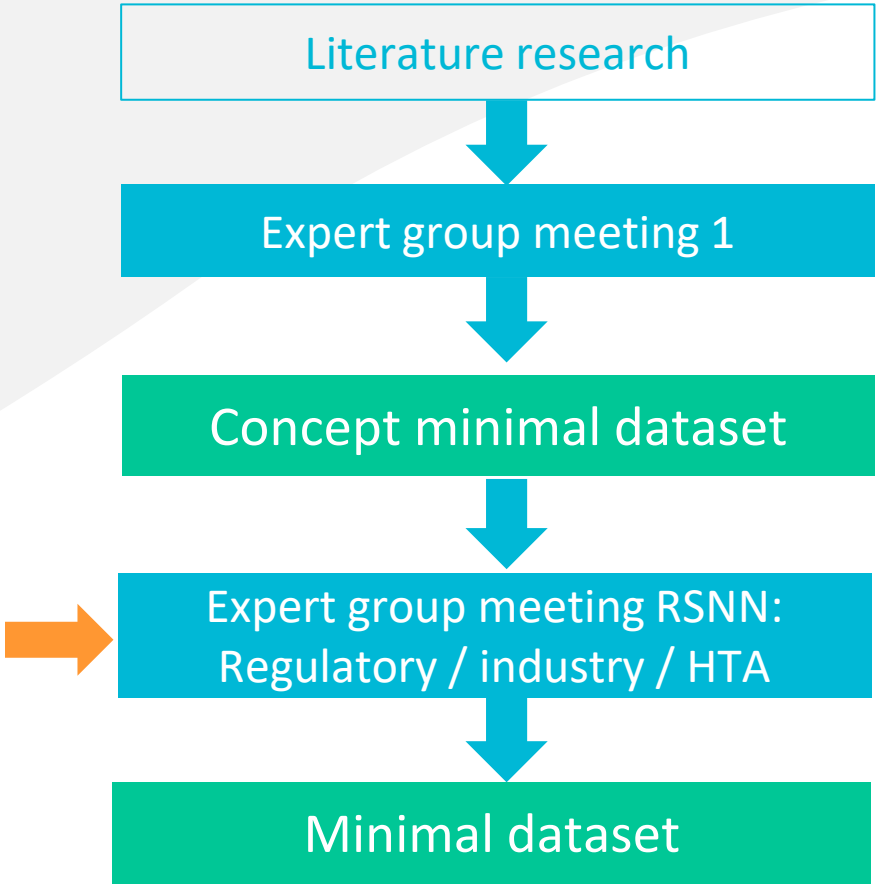
Minimal dataset non-small cell lung cancer (NSCLC)

Scope

- Purpose: Quality registry
- Population: Adults (≥18 jaar) diagnosed with NSCLC treated with oncolytics (chemotherapy, immunotherapy, targeted therapy)

Aim

- Effectiveness/adverse effects of oncolytics
- Suitable for various stakeholders (regulatory/HTA agencies, healthcare providers, and patients)



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Case study – lung cancer registry

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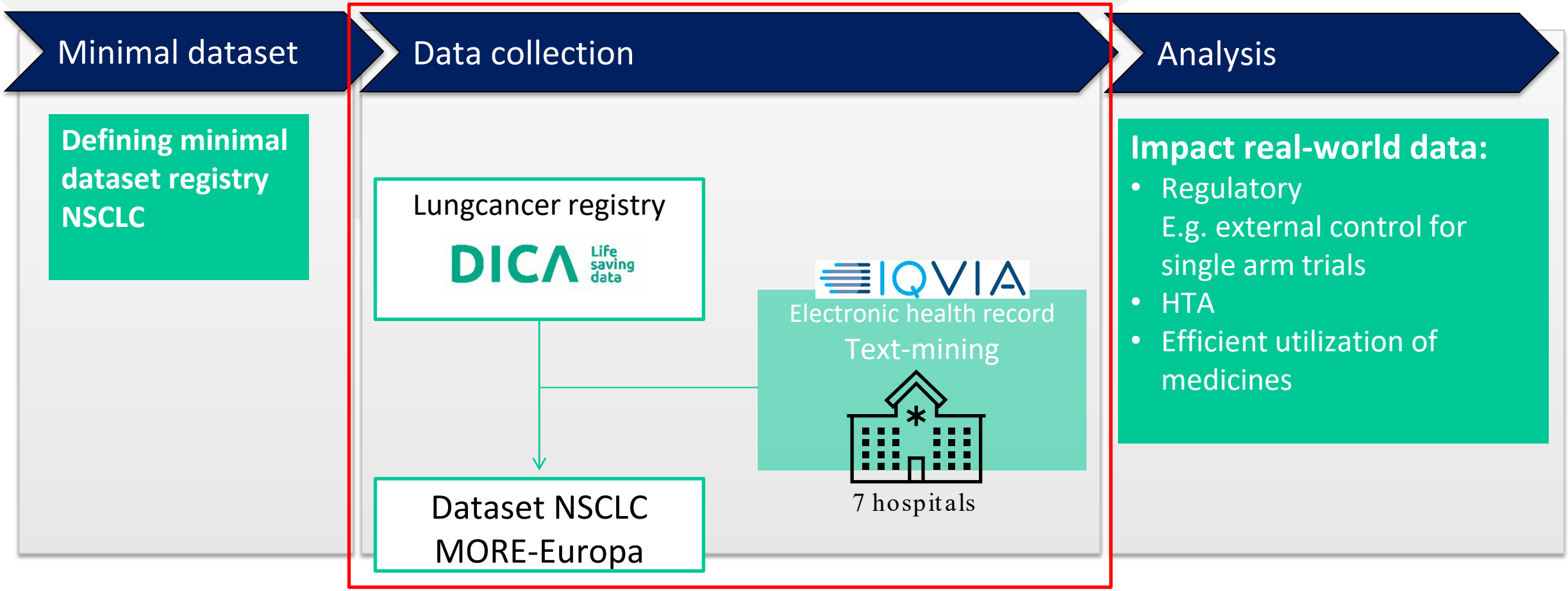


Text-mining Ctcue

> How to exract minimal dataset?
>> **Focus: unstructrured patient data**

Example: comorbidity myocardial infarction

Confidence	Description	Paragraph title
96% Has taken place	infarct inferoposterolateraal	overige voorgeschiedenis

2018 Stabiele angina pectoris
post infarct inferoposterolateraal

Confidence	Description	Paragraph title
0% Applies to family	hartinfarct	risicofactoren

Risicofactoren:
Moeder op 65 jarige leeftijd hartinfarct.

Case study – lung cancer registry

Minimal dataset

Defining minimal dataset registry NSCLC

Data collection

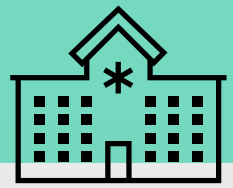
Lungcancer registry

DICA Life saving data

IQVIA

Electronic health record

Text-mining



7 hospitals

Dataset NSCLC MORE-Europa

Analysis

Impact real-world data:

- Regulatory
  E.g. external control for single arm trials
- HTA
- Efficient utilization of medicines

Conclusion

- More-EUROPA focuses on disease registries
  - Curated data sets – proven data collection
  - **Data linkage & NLP to generate more data rich data sets**
  - R-RCTs performed in Swedish registries
- Activities centered around complementing trial datasets
  - Effect estimates in subpopulations – effect modification / outcomes estimations
  - Early (to late) stage drug development, e.g., trial design
  - ***External controls, but cave SAT shortcomings***
    - ***Minimal data set, appropriate analysis, timing, transparency, …***
- Registries as platform for trials (in More-EUROPA)
  - Evaluate critical steps in designing, executing & evaluating R-RCTs
  - Design an R-RCT
  - *Platform non randomised trials not in scope*

Thank for your attention

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