

More-EUROPA

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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

Patients in randomized trials

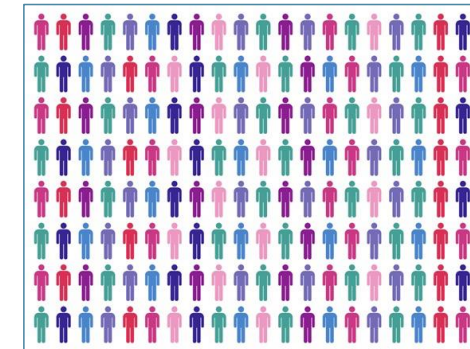
In- and exclusion criteria!



Exclusion for melanoma trials:

- Brain metastases
- ECOG score ≥ 2
- Auto-immune disease
- Immunosuppression
- Other malignancies
- Not Recist evaluable
- Etc.

Patients in daily practice



The majority of patients with metastatic melanoma are not represented in pivotal phase III immunotherapy trials

Marco Donia^{a,b,*}, Marie Louise Kimper-Karl^c, Katrine Lundby Høyer^d, Lars Bastholt^c, Henrik Schmidt^d, Inge Marie Svane^{a,b}



The role of WE 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).

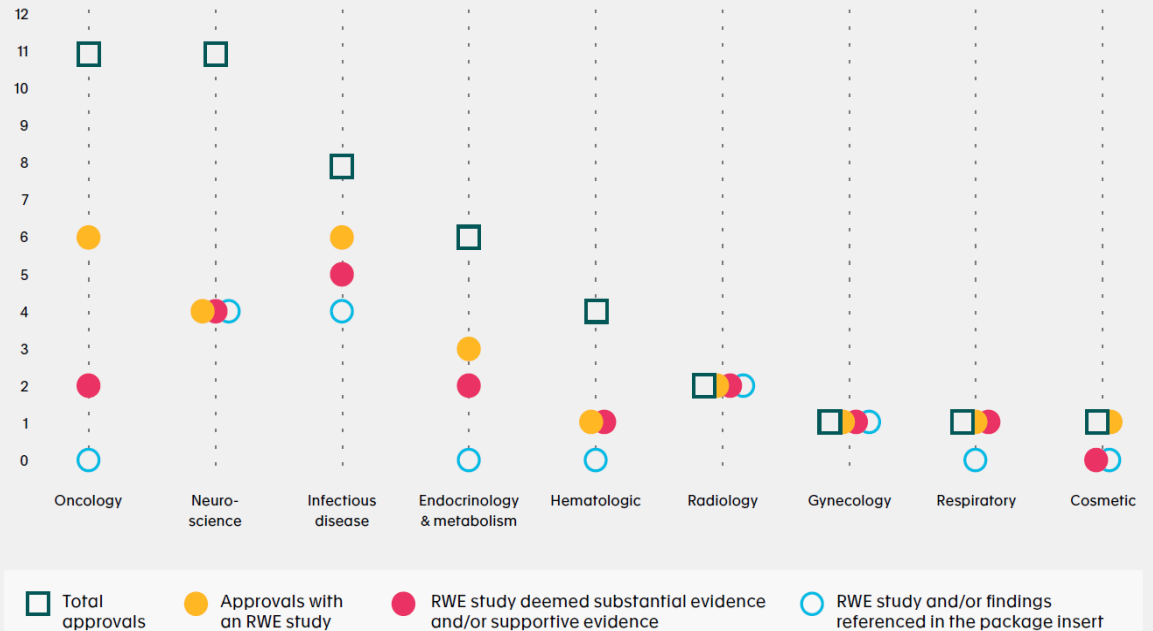
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2

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



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

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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

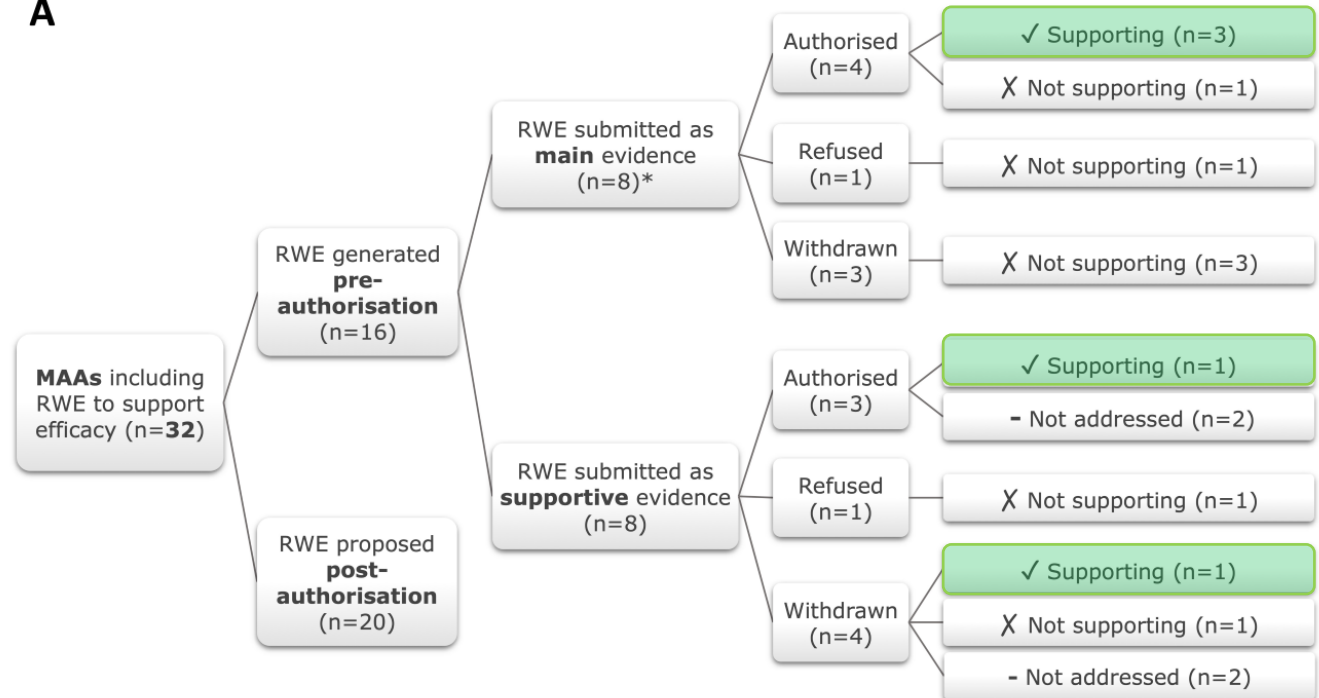
Table 1: Summary of FDA-identified limitations of RWD-based external control group included in submission package for Selinexor

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.

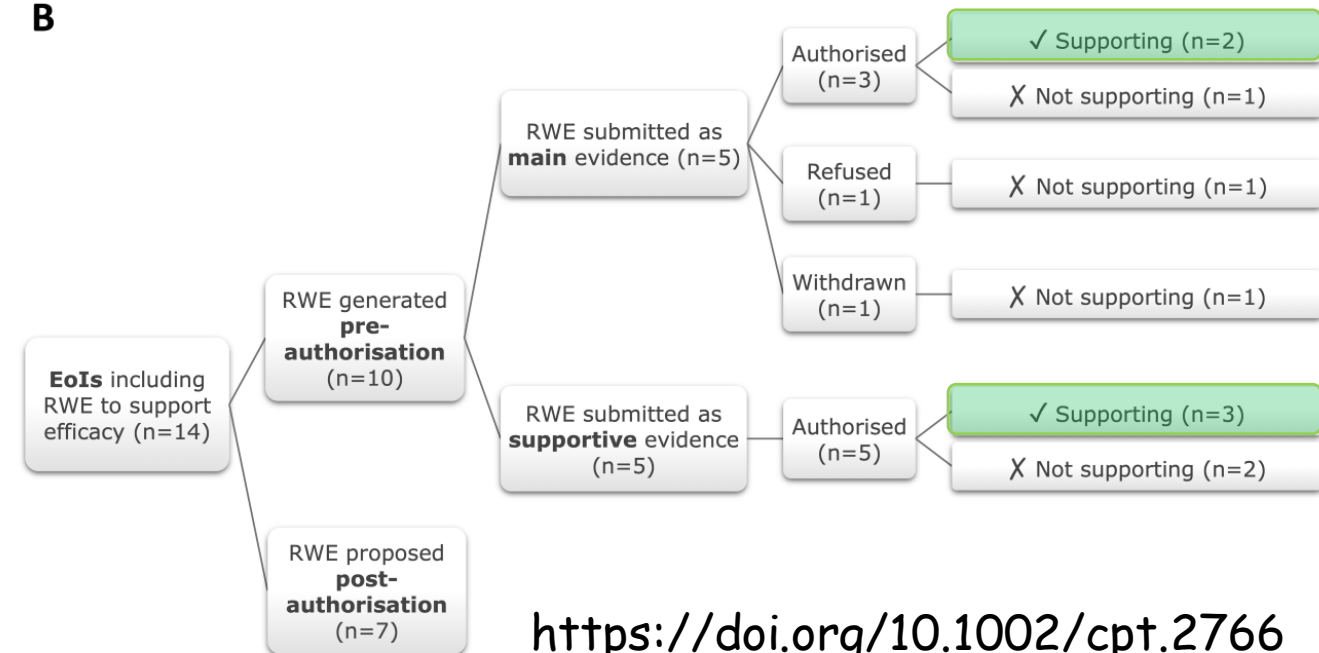
Real-world evidence in recent EMA centralised initial marketing authorisation applications (MAAs) and extension of indication applications (EoIs)

- 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

A



B



More-EUROPA



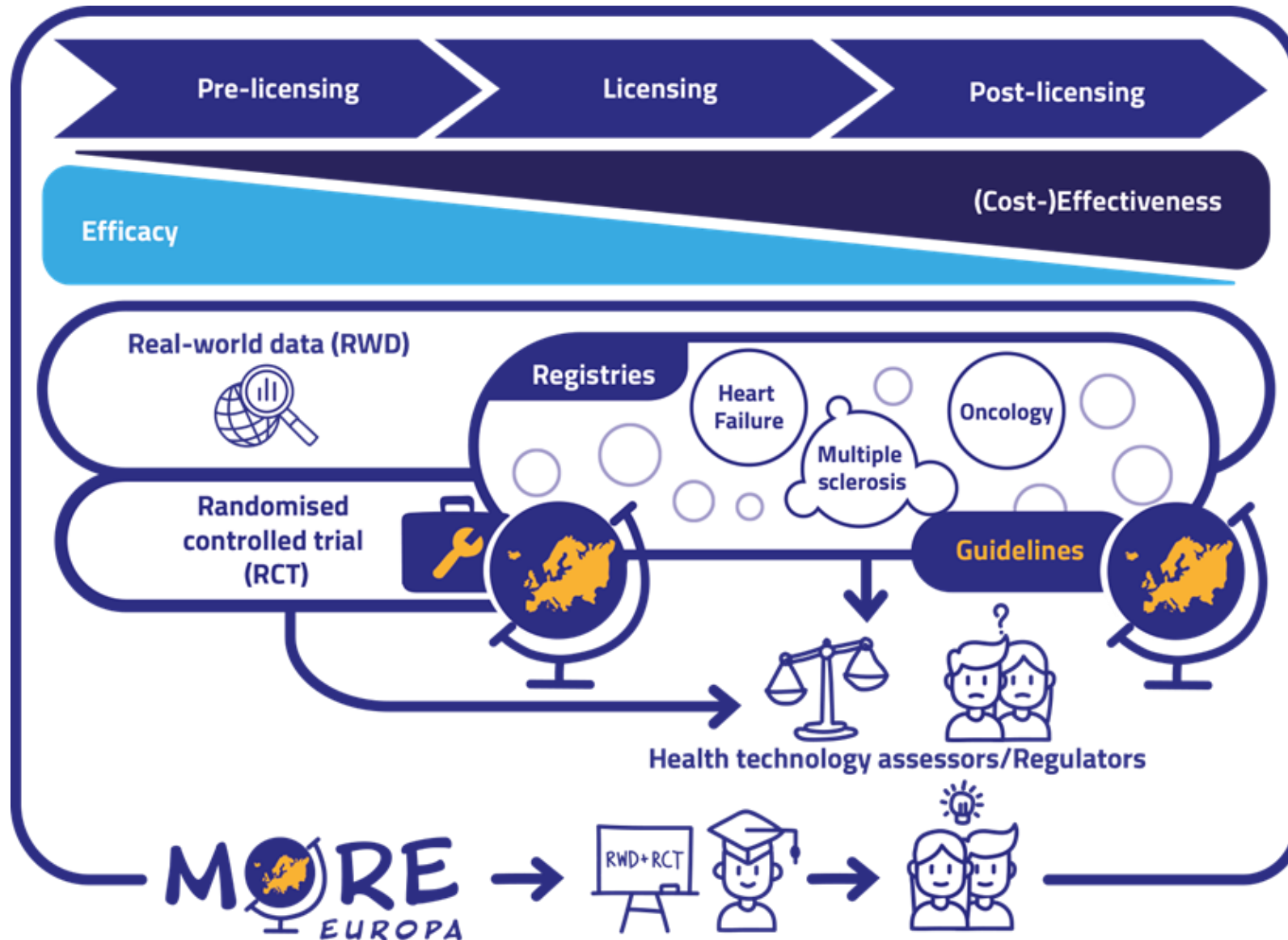
Aims:

- 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>

Summary introduction



14 Organisations



1921 — 2021



UNIVERSITÀ
CATTOLICA
del Sacro Cuore

quint**ten**
health

Radboudumc

U

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UNIVERSIDADE DE LISBOA



FACULDADE DE
FARMÁCIA
Universidade de Lisboa



Karolinska
Institutet



UPPSALA
UNIVERSITÄT

DICA



emsp

EUROPEAN
MULTIPLE SCLEROSIS
PLATFORM

IQVIA



Université
Paris Cité

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

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



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



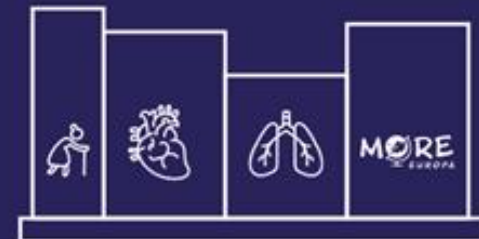
Dissemination WP5



Training



**Adoption
& Use**



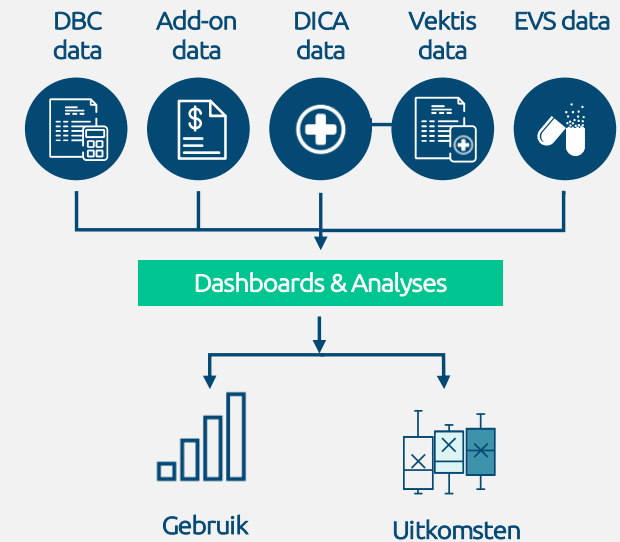
**Guideline and Framework
Development**



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)

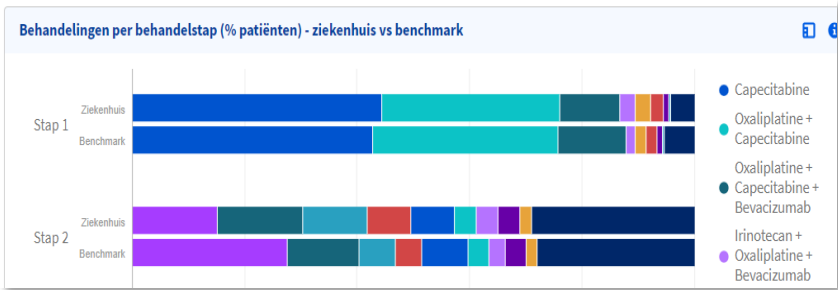
DICA -DMA (Dutch Medication Audit) 56 hospitals



DICA Life saving data

DICA dashboard allows hospitals to compare own data to the benchmark

Behandelingen per behandelstap



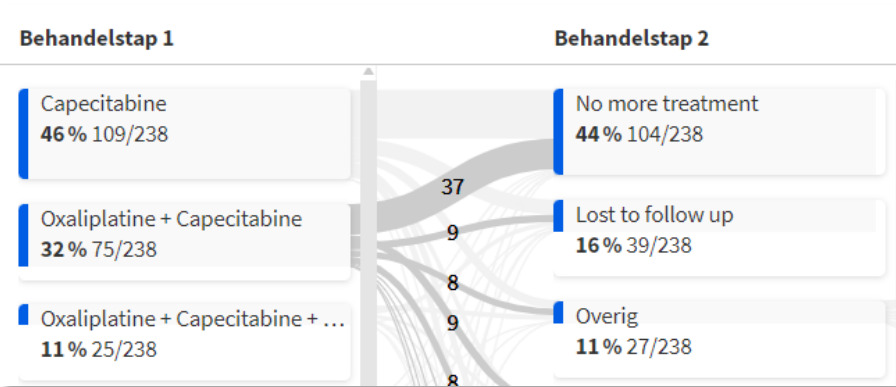
Filteren op patient karakteristieken

WHO status

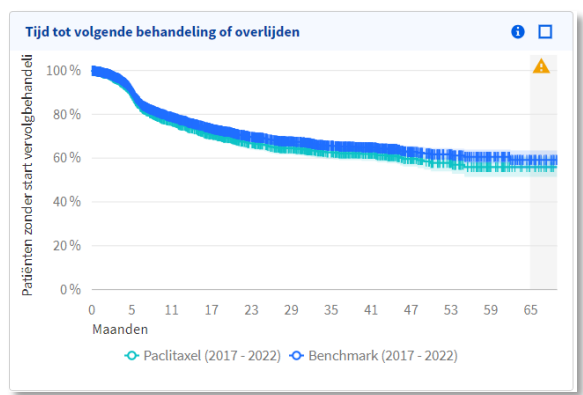
PD-L1 expressie

Mutaties - ALK

Therapie flow



Uitskomsten



Real-world overall survival following a hybrid dosing strategy of pembrolizumab in NSCLC

Some Dutch hospitals apply a hybrid dosing strategy for pembrolizumab

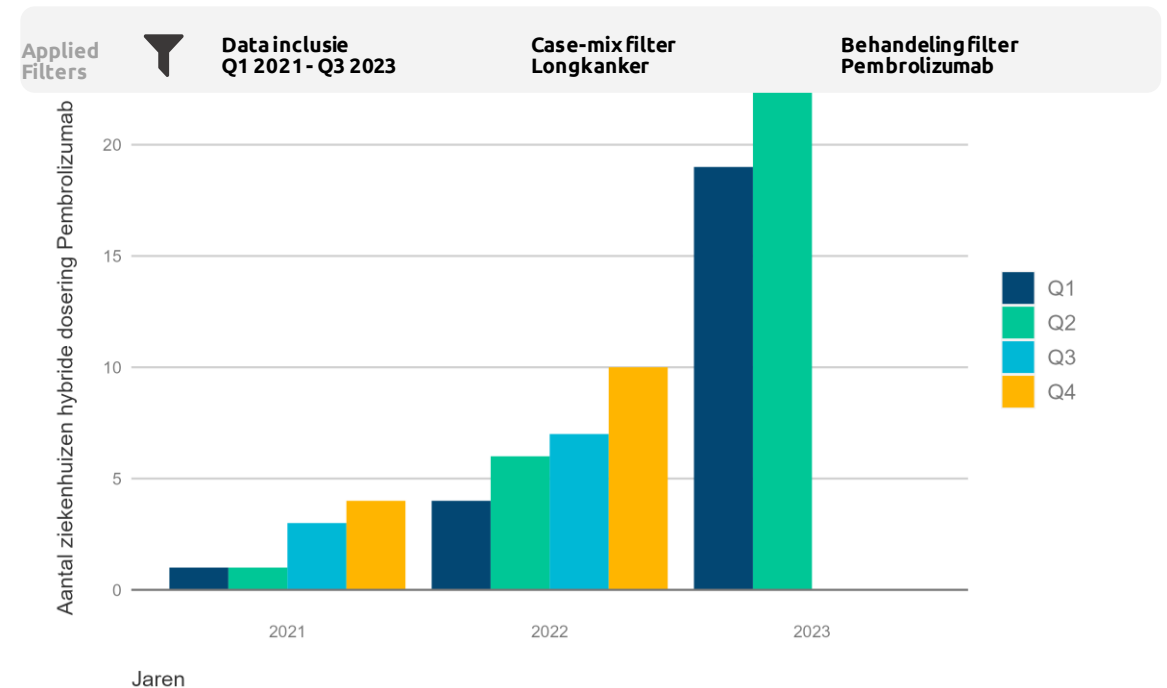
Standard: 200mg Q3W or 400mg Q6W

Hybrid: 100 or 150 mg (weight dependent) Q3W; 200 or 300 mg (weight dependent) Q6W;

Patients . 90 kg get standard dose

Between Q1 2021 and Q2 2023 the number of DMA hospitals that implemented* hybrid dosing increased from 1 to 23 of 44 hospitals

*implemented if >30% of all pembro doses are hybrid dose schemes



• Case mix of standard vs hybrid dosed patients



• Analysis

- **Applied Filters**
- **Data inclusie**
 - Q1 2021 - Q1 2023
- **Case-mix filter**
 - NSCLC
- **Behandeling filter**
 - Pembrolizumab, 1e behandelstap

	Standaard (N=2066)	Hybride (N=574)	P-Value
Leeftijd (Jaar)			
Mean (SD)	66.9 (9.19)	66.6 (9.28)	0.554
Median [Min, Max]	68.0 [22.0, 89.0]	67.0 [32.0, 89.0]	
Geslacht			
Man	1121 (54.3%)	316 (55.1%)	0.772
Vrouw	945 (45.7%)	258 (44.9%)	
Behandeling			
Cis/Carboplatine + Pemetrexed + Pembrolizumab	1191 (57.6%)	323 (56.3%)	0.825
Paclitaxel + Pembrolizumab	337 (16.3%)	95 (16.6%)	
Pembrolizumab	538 (26.0%)	156 (27.2%)	
Comorbiditeitscore			
<5	658 (31.8%)	209 (36.4%)	0.0464
>=5	1402 (67.9%)	364 (63.4%)	
Missing	6 (0.3%)	1 (0.2%)	



• Observaties

- Hybride dosering wordt met name toegepast in UMC's. We zien geen verschillen in leeftijd, geslacht en behandeling.
- Bij de standaard dosering populatie is het percentage patiënten met een comorbiditeitscore ≥ 5 67.9% tegenover 63.4% in de groep met hybride dosering



• Methodes

- Een ziekenhuis wordt gedefiniëerd als 'heeft hybrid dosing geïmplementeerd' vanaf het kwartaal dat in een ziekenhuis >30% van de giften hybride is.
- Hybrid patient: start Pembrolizumab $\geq$ kwartaal hybrid dosing implementatie.
Non-hybrid patient: geen hybride dosing geïmplementeerd in ziekenhuis.
Exclusie: start Pembrolizumab < kwartaal hybrid dosing implementatie.

Hybrid dosing of Pembrolizumab does not (seem to) affect overall survival

Applied
Filters



Data inclusie
Q1 2021 - Q1 2023

Case-mix filter
NSCLC

Behandeling filter
1e behandelstap, Pembrolizumab,
alle combinaties



Observaties

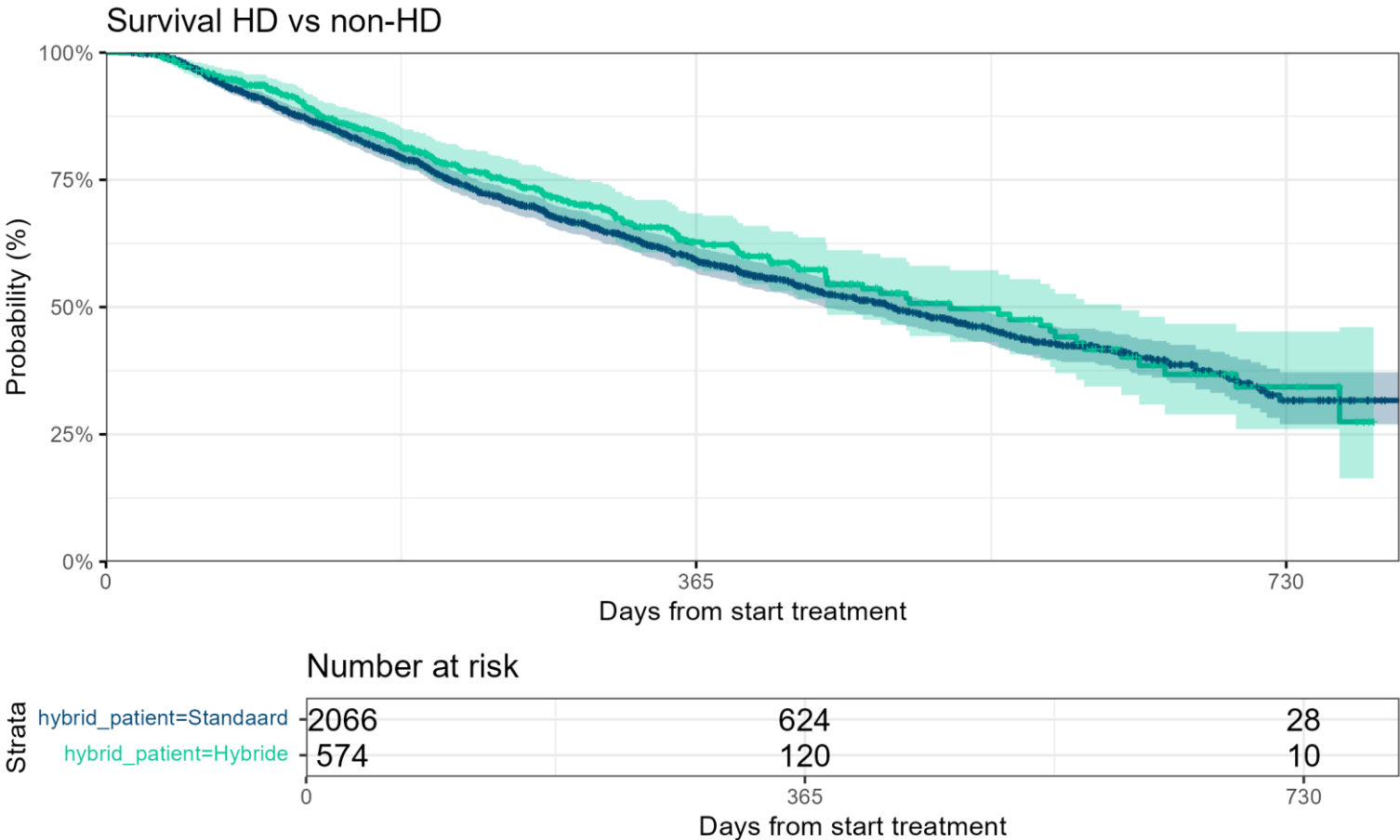
Op basis van het Cox PH model is er geen significant verschil in de OS voor hybride en standaard dosering.



Methodes

Hybrid patient: start Pembrolizumab $\geq$ kwartaal hybrid dosing implementatie.
Non-hybrid patient: geen hybride dosing geïmplementeerd in ziekenhuis.
Exclusie: start Pembrolizumab $<$ kwartaal hybrid dosing implementatie.

Cox proportional hazards model met covariaten: behandelcombinatie, leeftijd, geslacht, comorbiditeitscore, ziekenhuistype



Next steps

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



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

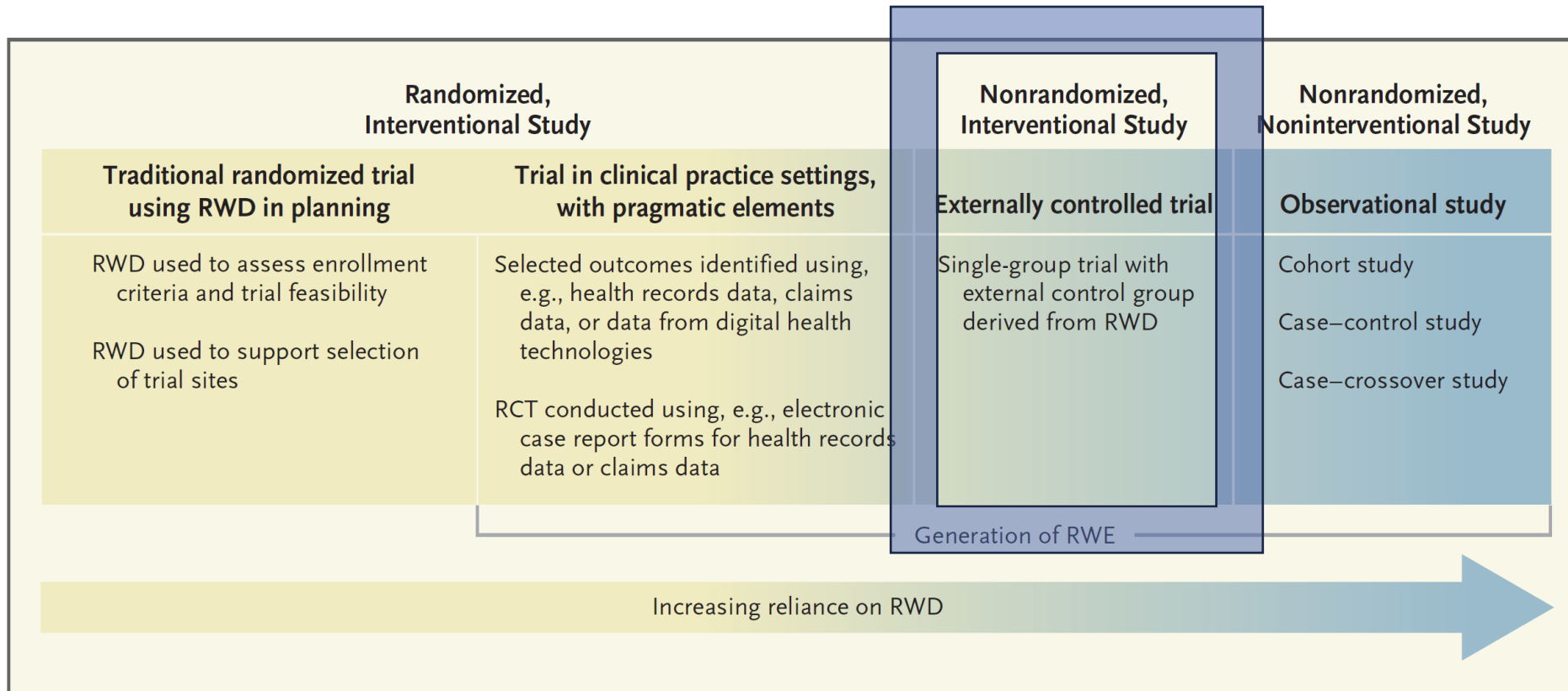


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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-arm trials submitted as pivotal evidence in a marketing authorisation
- 5
- 6
- 7 Considerations on evidence from single-arm trials

RWD evidence generation continuum



Reliance on RWD in Representative Types of Study Design.

RCT denotes randomized, controlled trial; RWD real-world data; and RWE real-world evidence.

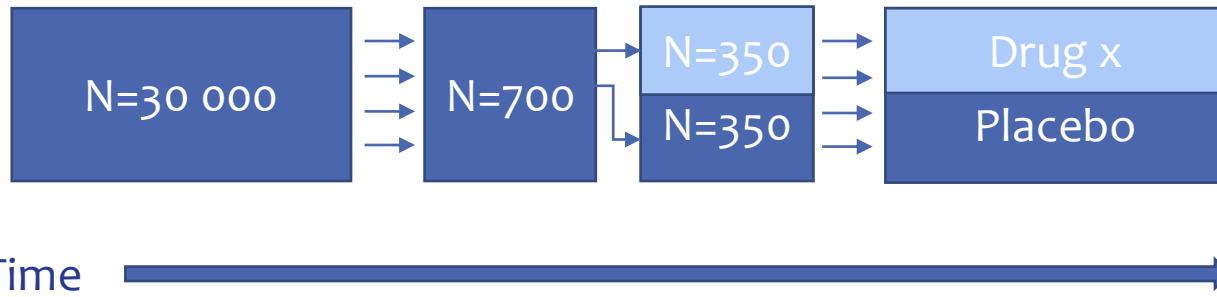
Registries will increasingly be used for

Registry-based RCTs

Clinical registry with measures of patient baseline characteristics

Patient subgroup selection & randomization

Follow-up of patient outcomes using patient registry



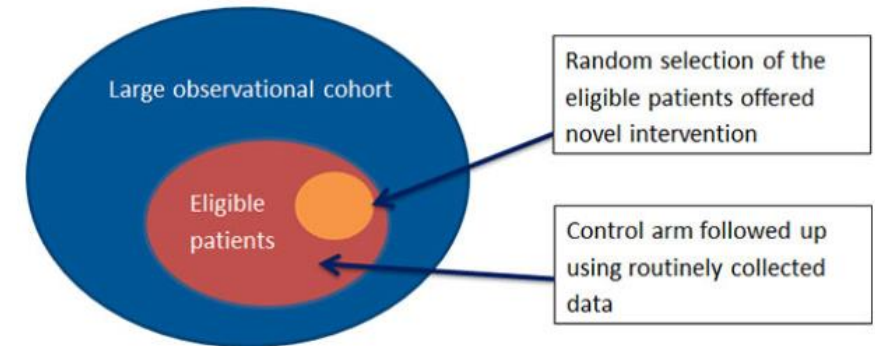
Clinical Trials Transformative Initiative

<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>

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***
- 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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