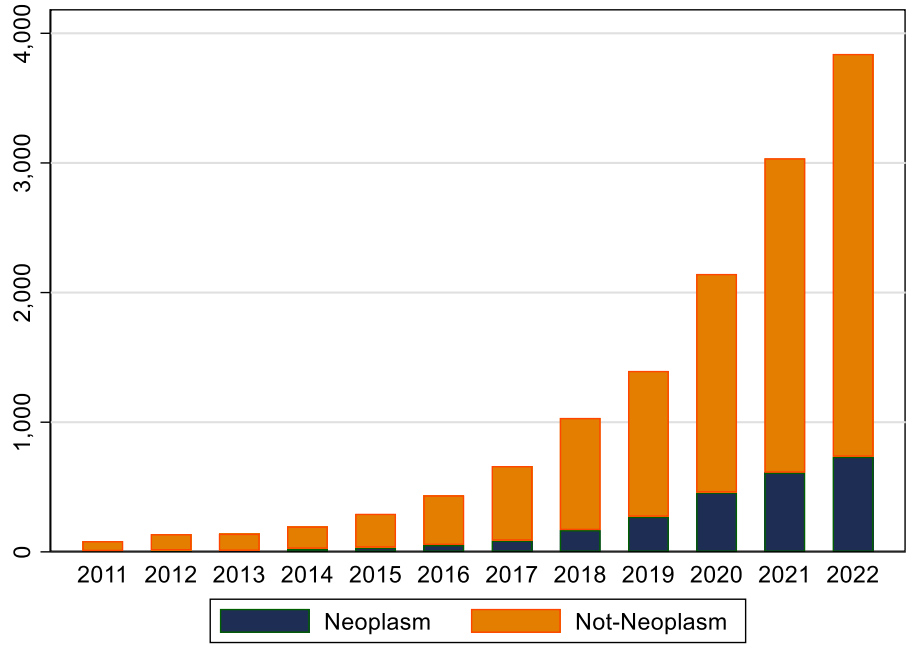
Real World Data in oncology uses and new perspectives

October 27th 2023

Real World Data – Real World Evidence

Pubmed Research 2011 to 2022



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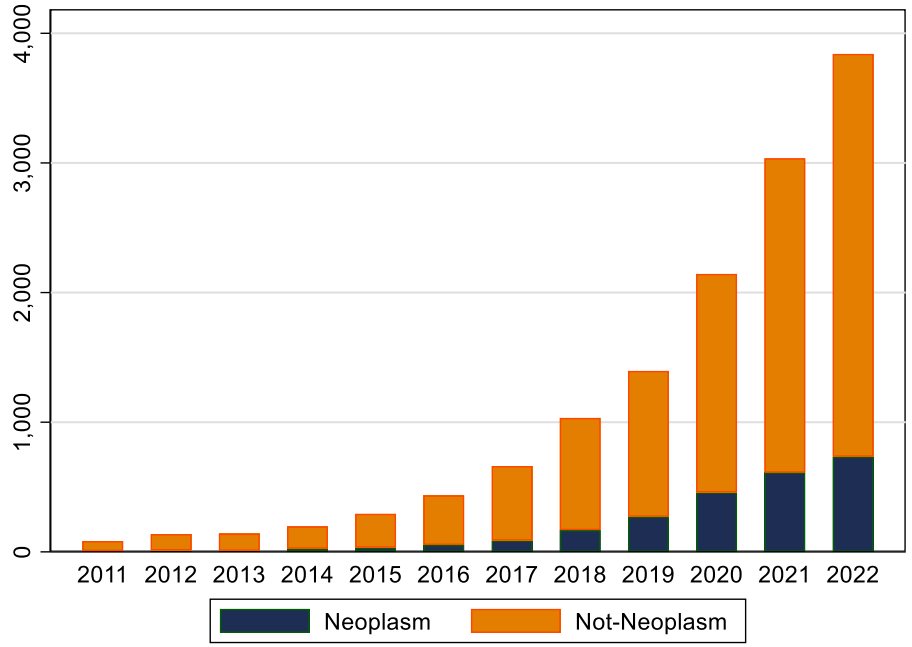
Real World Data – Real World Evidence – External Control

Pubmed Research 2011 to 2022



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External control arms in oncology: current use and future directions
(Mishra-Kalyani, Annals of Oncol 2022)

Addressing challenges with real-world synthetic control arms to demonstrate the comparative effectiveness of Pralsetinib in non-small cell lung cancer
(Popat, Nat Com 2022)

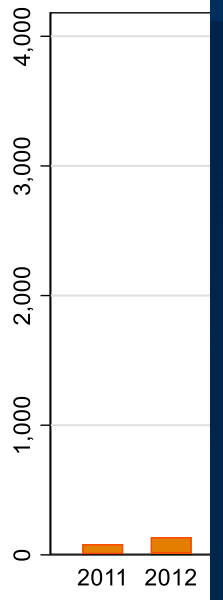
A Comparison of 7 Oncology External Control Arm Case Studies: Critiques From Regulatory and Health Technology Assessment Agencies
(Jaksa, Value in Health 2022)

Pertuzumab Plus Trastuzumab for Treatment-Refractory *HER2*-Amplified Metastatic Colorectal Cancer: Comparison of the MyPathway Trial With a Real-World External Control Arm
(Yin, JCO Clinical Cancer Informatics 2022)

Design and Evaluation of an External Control Arm Using Prior Clinical Trials and Real-World Data
(Ventz, Clin Can Res 2019)

Real World Data – Real World Evidence – External Control

Pubmed



ANNALS OF ONCOLOGY

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

SPECIAL ARTICLE | ARTICLES IN PRESS

ESMO Guidance for Reporting Oncology real-World evidence (GROW)

L. Castelo-Branco • A. Pellat † • D. Martins-Branco † • A. Valachis † • J.W.G. Derksen † • K.P.M. Suijkerbuijk • U. Dafni • T. Dellaporta • A. Vogel • A. Prelaj • R.H.H. Groenwold • H. Martins • R. Stahel • J. Bliss • J. Kather • N. Ribelles • F. Perrone • P.S. Hall • R. Dienstmann • C.M. Booth • G. Pentheroudakis ‡ • S. Delaloge ‡ • M. Koopman ‡ • Show less • Show footnotes

Published: October 15, 2023 • DOI: https://doi.org/10.1016/j.annonc.2023.10.001

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in Health 2022)

(Yin, JCO Clinical Cancer Informatics 2022)

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Design and Evaluation of an External Control Arm Using Prior Clinical Trials and Real-World Data

(Ventz, Clin Can Res 2019)

Setting the scene

Precision Medicine

- Historically, « One-size-fits-all »
  - Patients suffering from cancer are treated on the basis of their tumor site of origin and histological subtype.
  - Oncology practice relies on average-population-benefit decisions, often derived from randomized clinical trials of “unselected” patients.

Setting the scene

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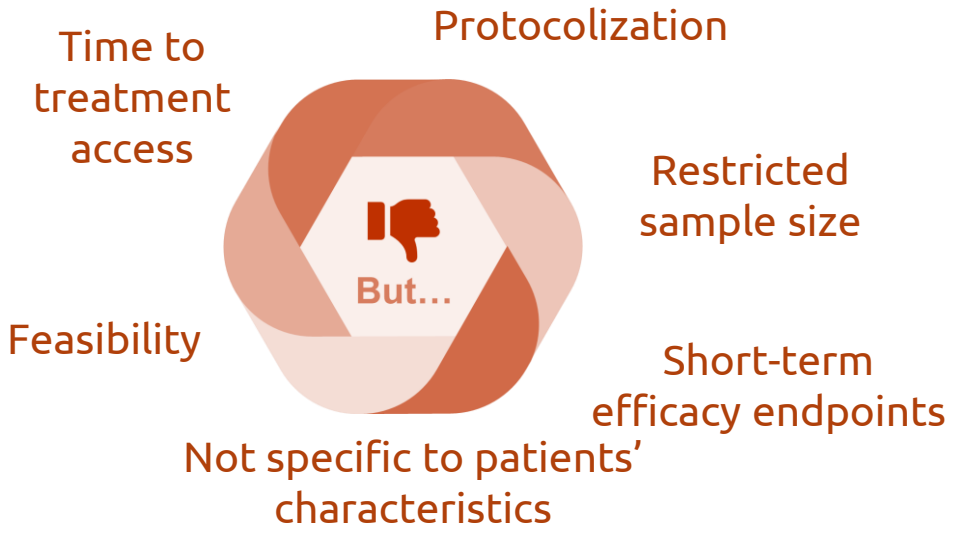
  - Patients suffering from cancer are treated on the basis of their tumor site of origin and histological subtype.
  - Oncology practice relies on average-population-benefit decisions, often derived from randomized clinical trials of “unselected” patients,

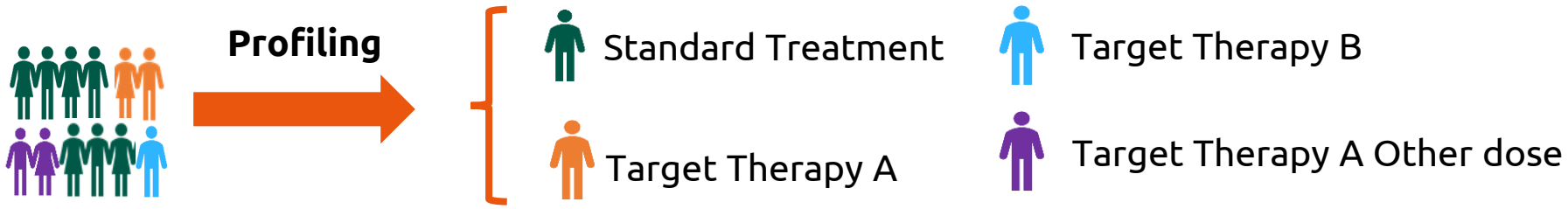
RCT= Gold standard
Causality +++



Setting the scene

Precision Medicine

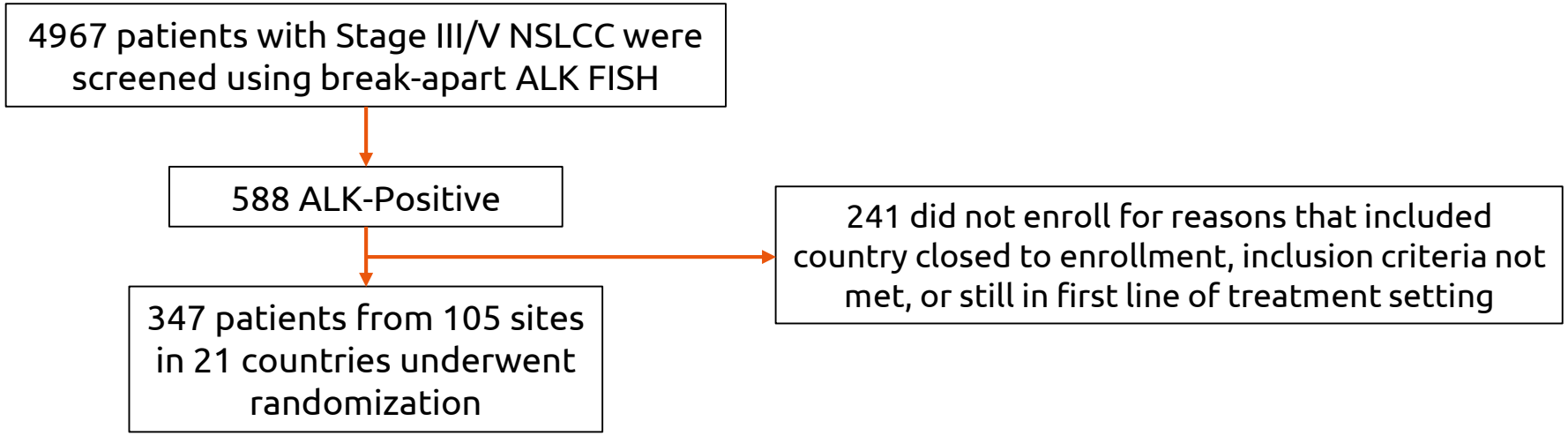
- Scientific breakthrough and technological advancements
  - Understanding of the cancer biology
  - Accessibility to tumour genomic sequencing technologies
  - Genome-driven cancer treatment emerges as a promising strategy
- Goal of precision medicine: To deliver the right cancer treatment to the right patient at the right dose and the right time



Setting the scene

MTA Development: The realities of the conventional screening approach

- **Crizotinib versus chemotherapy in advanced ALK-positive lung cancer** (Shaw, NEJM 2013)



Setting the scene

MTA Development: The realities of the conventional screening approach

- **Crizotinib versus chemotherapy in advanced ALK-positive lung cancer** (Shaw, NEJM 2013)
- **New targets in lung cancer**

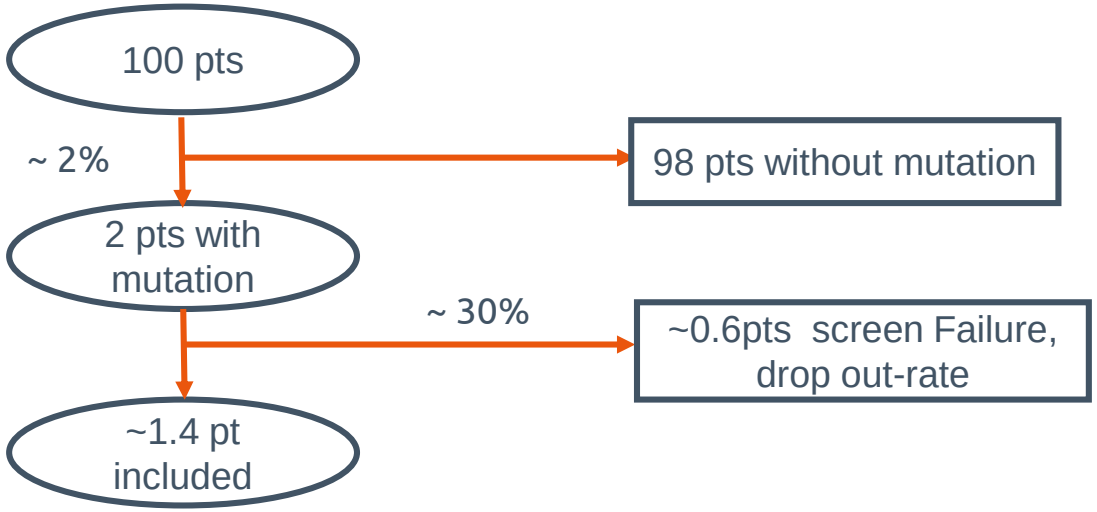
Target	Genetic alteration	%
EGFR ex, 18, 19, 21	Mutation Deletion	11%
EGFR ex 20	Insertion	1%
ALK	Translocation	4%
Braf	Mutation V600E	2%
ROS1	Translocation	1%
HER2	Mutation	1%
KRas	Mutation	25%
…		

< 5% of Lung cancer

Setting the scene

MTA Development: The realities of the conventional screening approach

- **Crizotinib versus chemotherapy in advanced ALK-positive lung cancer** (Shaw, NEJM 2013)
- **New targets in lung cancer**
- **Tissue Agnostic drug candidate trial**
  - Rare disease mutation: ~ 2% of all cancer patients



- To include 200 patients in a trial, it's necessary to screen 14 300 patients
- RCT may not be a « feasible » option
- Single-arm trials are conducted

EMA point of view

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

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

[1]European Medicines Agency (EMA), Amsterdam, The Netherlands; [2]Medical University of Vienna, Vienna, Austria; [3]EMA's Committee for Orphan Medical Products (COMP), Amsterdam, The Netherlands; [4]London School of Hygiene and Tropical Medicine, London, UK; [5]Danish Medicines Agency, Copenhagen, Denmark; [6]University Tor Vergata, Rome, Italy. *Correspondence: Hans-Georg Eichler (Hans-Georg.Eichler@ema.europa.eu)

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

doi: 10.1002/cpt.2083

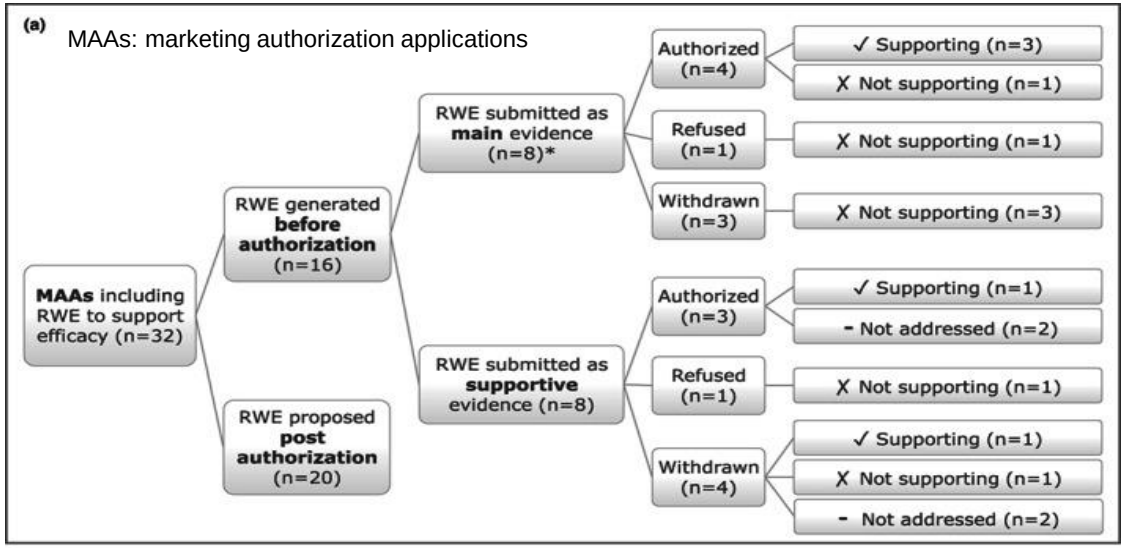
Contribution of Real-World Evidence in European Medicines Agency's Regulatory Decision Making

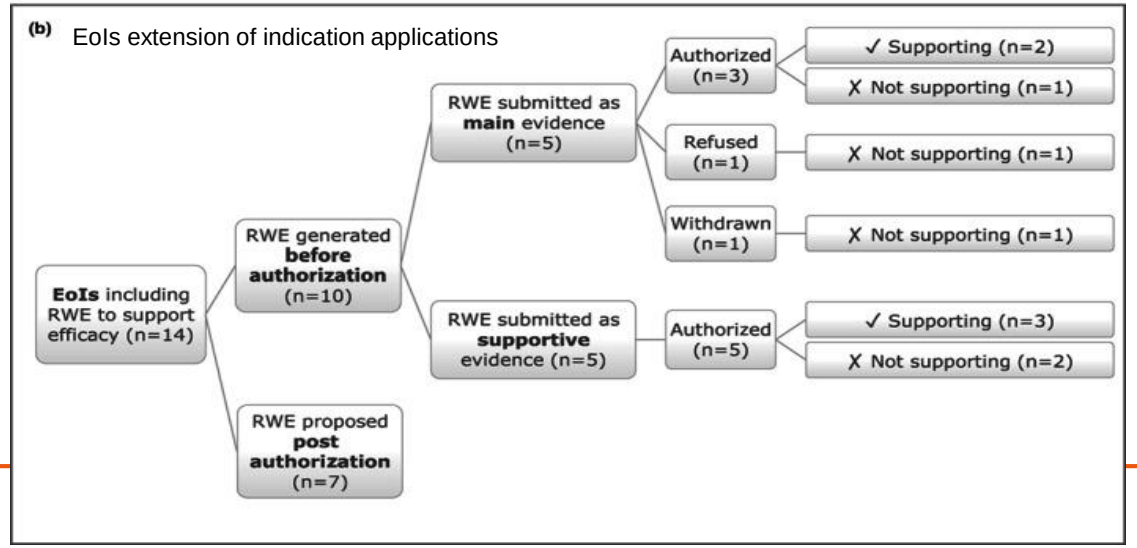
Elisabeth Bakker[1], Kelly Plueschke[2], Carla J. Jonker[2,3], Xavier Kurz[2], Viktoriia Starokozhko[1,3] and Peter G. M. Mol[1,3,4,*]

Received August 17, 2022; accepted October 10, 2022. doi:10.1002/cpt.2766

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 113 NUMBER 1 | January 2023

doi: 10.1002/cpt.2766





FDA point of view

FDA's RWE Activities

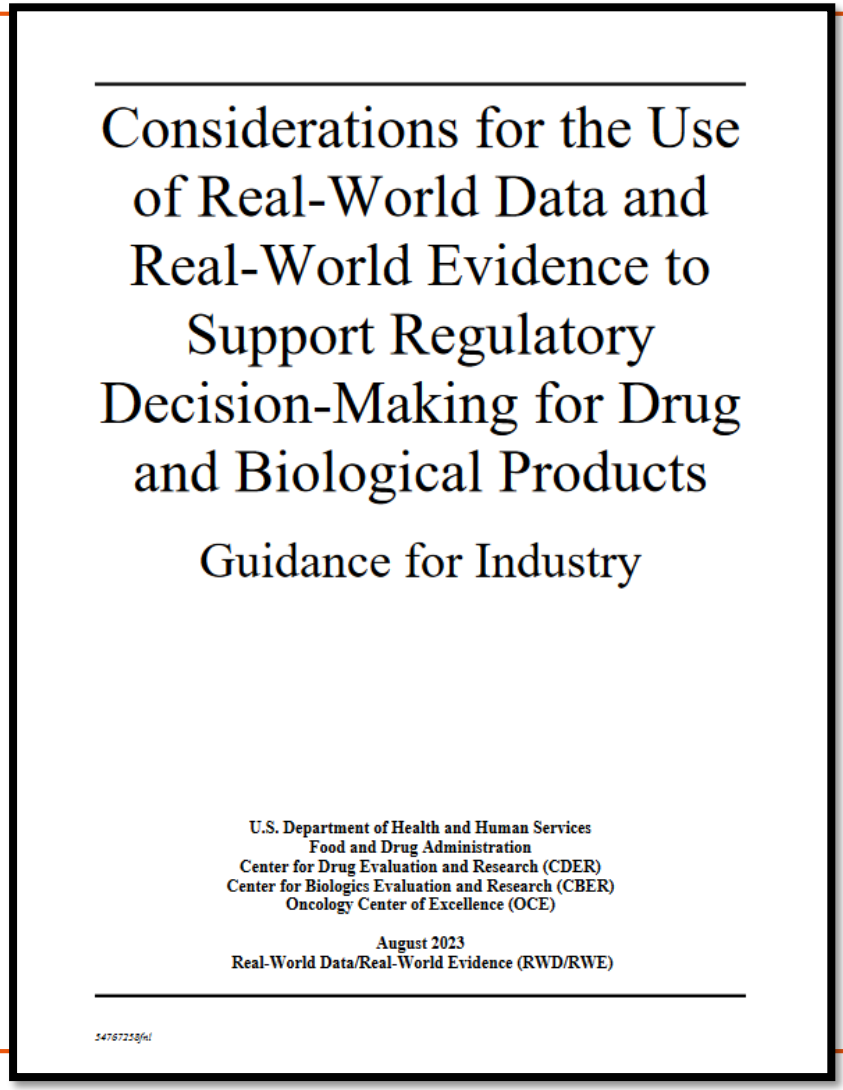
The 21st Century Cures Act of 2016 was designed to accelerate medical product development and bring new innovations and advances faster and more efficiently to the patients who need them. In response, FDA created a Framework in 2018 for evaluating the potential use of RWE to help support the approval of a new indication for a drug already approved under section 505(c) of the FD&C Act or to help support or satisfy drug post-approval study requirements. In addition to drug and biological products approved under section 505(c), this framework is also intended for application to biological products licensed under the Public Health Service Act.

Multiple FDA centers incorporate RWD and RWE into daily activities based on the nature of their work and the scope of their regulations:

See CBER/CDER page for more information.

See OCE RWE page for information on RWD and RWE at the Oncology Center of Excellence.

See Advancing RWE Program page for information describing one of the Prescription Drug User Fee Act VII commitments related to RWE.



Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

August 2023
Real-World Data/Real-World Evidence (RWD/RWE)

Real World Data – Real World Evidence

Some definitions

- Real World Data : Multiple definition *(Makady, Value in Health 2017)*
  - Data collected in a non-RCT setting
  - Data collected in a non-interventional / non-controlled setting
  - Data collected in a non-experimental setting
  - Others

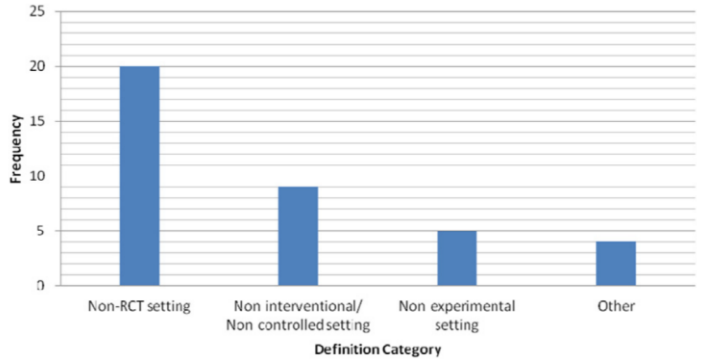


Fig. 1 – Overview of the total number of definitions classified under each of the four definition categories created. RCT, randomized controlled trial.

- FDA definition: “data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources”

- Categories of RWD sources:
  - Patient registries, electronic health records (EHRs), administrative claim, PRO
  - Observational studies,
  - Pragmatic clinical trials
  - Early Access program

- Real World Evidence is the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD.

What for and how to use RWD?

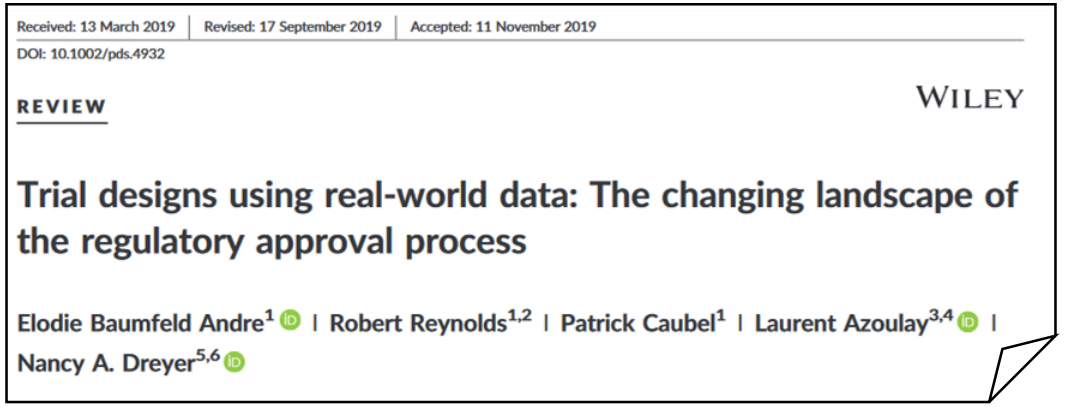
What for?

Leverage limitations of RCTs
Closer to reality
Rapid access for patients

How?

- Pragmatic clinical trial designs
- Single-arm trial with external comparator
- Emulated trial using RWD

…



Received: 13 March 2019 | Revised: 17 September 2019 | Accepted: 11 November 2019
DOI: 10.1002/pds.4932

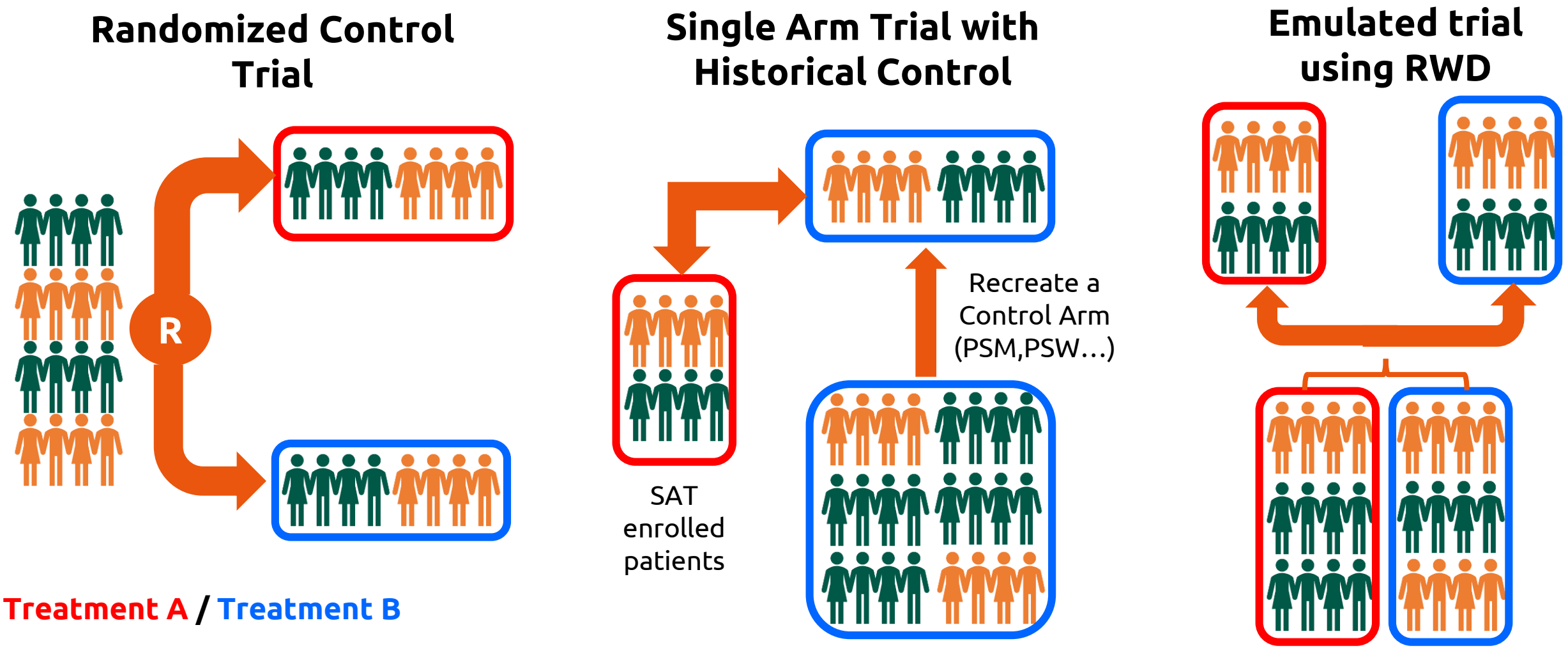
REVIEW

WILEY

Trial designs using real-world data: The changing landscape of the regulatory approval process

Elodie Baumfeld Andre[1] | Robert Reynolds[1,2] | Patrick Caubel[1] | Laurent Azoulay[3,4] | Nancy A. Dreyer[5,6]

Schematic representation



Focus on external control arms

Accelerating clinical developments using historical clinical trial data or real-world data for single-arm trials

What is it?

Also called **Synthetic Control Arm**, it is a control group that is derived from external sources, such as published data, previous clinical studies, or population-level databases, such as **Real-World historical Data**.

What for?

To conduct **externally controlled trials** in order to estimate a new treatment or health product effects and strengthen regulatory submissions.

As an alternative to randomized clinical trials (RCT), it allows to **accelerate clinical developments** and then the health technology access to patients.

When is it particularly relevant?

In case of difficulty for recruitment, as in rare diseases or uncommon conditions, or if it is deemed unethical to randomize patients to no-treatment (or placebo) group for a life-threatening condition.

How?

To reduce the potential bias and increase confidence in the interpretability of the study results, it is recommended to finalize the study protocol, including selection of the external control arm, **before initiating the single arm externally controlled trial.**

Several steps are mandatory, and each presents its own challenges:

- Anticipation (during the phase II or III design)
- Design to insure **rigorous methodology**
- Data selection and collection with sufficient **quality**
- Relevant analysis
- Transparent reporting and communication

HTA bodies are working on guidelines.

Focus on external control arms by HTA bodies

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

Reflection paper on establishing efficacy based on single-arm trials submitted as pivotal evidence in a marketing authorisation

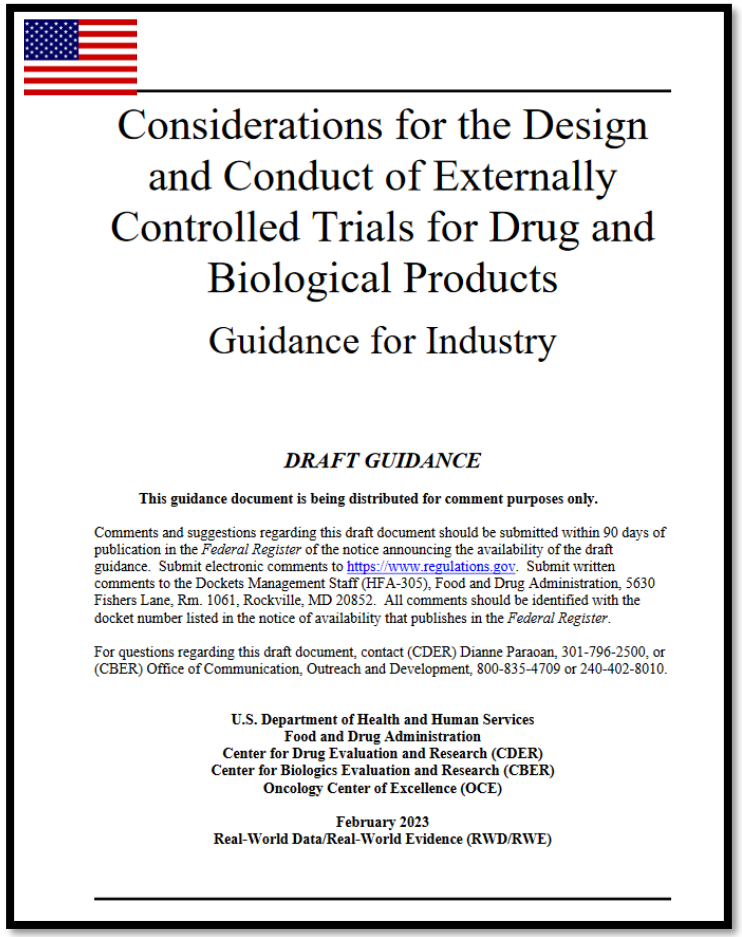
Considerations on evidence from single-arm trials

Draft

Draft agreed by Drafting Group on single-arm trials	27 January 2023
Adopted by CHMP for release for consultation	17 April 2023
Start of public consultation	21 April 2023
End of consultation (deadline for comments)	30 September 2023

Comments should be provided using this template. The completed comments form should be sent to RP-SATs@ema.europa.eu

Keywords	Single-arm trials, non-randomised trials, regulatory decision making



Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Dianne Paraoan, 301-796-2500, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

February 2023
Real-World Data/Real-World Evidence (RWD/RWE)

EBM analysis

Rapid access to innovative medicinal products while ensuring relevant health technology assessment. Position of the French National Authority for Health

Antoine Vanier,[1,2] Judith Fernandez ,[1] Sophie Kelley,[1] Lise Alter,[1] Patrick Semenzato,[1] Corinne Alberti,[3,4] Sylvie Chevret,[5] Dominique Costagliola,[6] Michel Cucherat,[7] Bruno Falissard,[8] François Gueyffier,[9] Jérôme Lambert,[5] Etienne Lengliné,[10] Clara Locher ,[11] Florian Naudet ,[12,13] Raphael Porcher,[14] Rodolphe Thiébaut,[15] Muriel Vray,[16] Sarah Zohar,[17,18] Pierre Cochat,[19] Dominique Le Guludec[19]

Box 1 Methodological points of attention HAS should consider when assessing an external comparison between an uncontrolled trial and an external control

Review | Open Access | Published: 20 May 2021

The Use of External Controls in FDA Regulatory Decision Making

Mahta Jahanshahi, Keith Gregg, Gillian Davis, Adora Ndu, Veronica Miller, Jerry Vockley, Cecile Ollivier, Tanja Franolic & Sharon Sakai

Therapeutic Innovation & Regulatory Science **55**, 1019–1035 (2021) | Cite this article

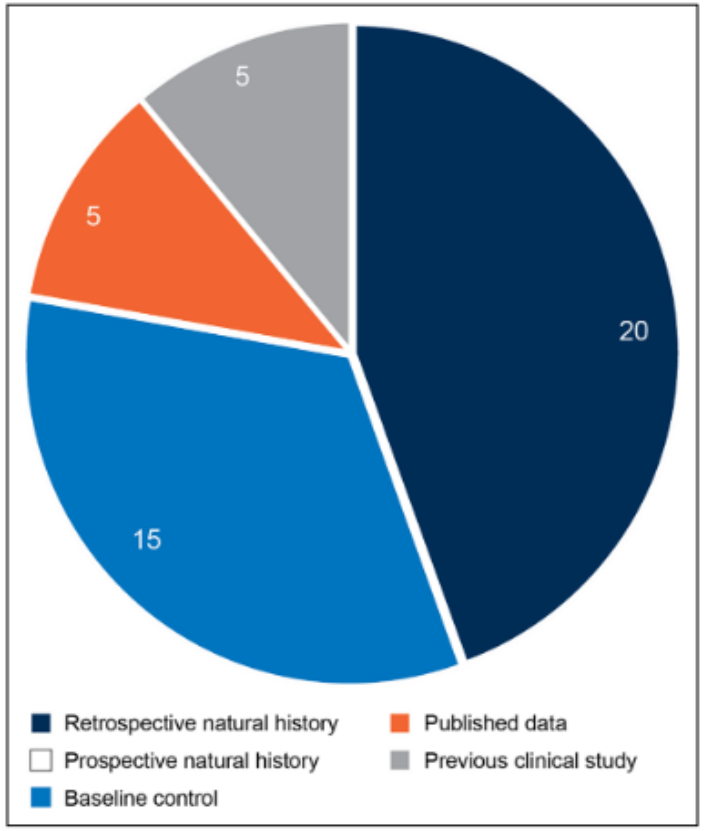


Fig. 3 Categories of external controls to support product approval by the US FDA (2000–2019, select therapeutic areas)

The Use of External Control Design is Most Persuasive When:

(Note: In many cases not all of these themes will be met and FDA will consider the totality of evidence)

	FDA Guidance	ICH E10
• It is not possible and/or ethical to run a placebo control[1,2,4]	✓	✓
• There is no available therapy for comparison (usually the case for rare diseases)	✓	
• The disease progression is well understood or predictable[1,4,9]	✓	✓
• The outcome measure is objective[1,3,4–9,11]	✓	✓
• The treatment effect		
- is large/dramatic[1–4,9,11]	✓	✓
- is not affected by patient or investigator motivation or choice of subjects for treatment[3]	✓	
- has a strong temporal association with administration of the investigational product[3,4]	✓	
- is consistent with the expected pharmacological activity based on the target and perhaps shown in animal models[3]	✓	
- is measured in a manner that reasonably manages and minimizes bias[3]	✓	
• The control population closely resembles the treatment group including setting for and manner of treatment (i.e. standard of care)[1,2,4,8,10,11]	✓	✓
• Covariates influencing the outcomes of the disease are well characterized[1]		✓
• The control group is a well-documented population with access to individual patient records[1]		✓
• The results provide compelling evidence of a change in the established progression of disease[2]	✓	

Focus on external control arms in oncology

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

REVIEW

External control arms in oncology: current use and future directions

P. S. Mishra-Kalyani[1*], L. Amiri Kordestani[2], D. R. Rivera[3], H. Singh[2,3], A. Ibrahim[2], R. A. DeClaro[2,3], Y. Shen[1], S. Tang[1], R. Sridhara[3], P. G. Kluetz[2,3], J. Concato[4], R. Pazdur[2,3] & J. A. Beaver[2,3]

[1]Office of Biostatistics, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring; [2]Office of Oncologic Diseases, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring; [3]Oncology Center of Excellence, U.S, Food and Drug Administration, Silver Spring; [4]Office of Medical Policy, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, USA

CHECK FOR UPDATES

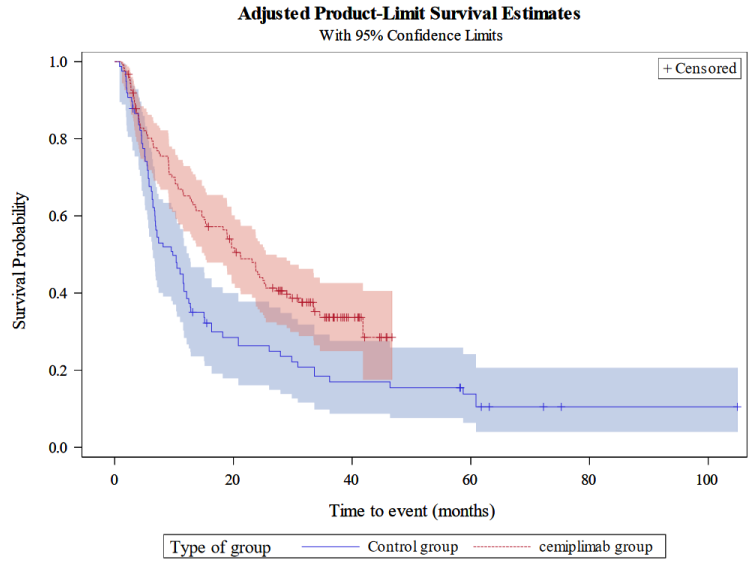
Available online 10 January 2022

External Control Arm

A recent example: Libtayo

- August 2023: HAS Favourable opinion for reimbursement in the subgroup of patients with metastatic or locally advanced cutaneous squamous cell carcinoma (mSCC or lSCC) who are not candidates for curative surgery or curative radiotherapy and who are not eligible for chemotherapy (chemotherapy failure or contraindication).
- Based on an indirect comparison (TOSCA) comparing indirectly data:
  - from patients treated with cemiplimab between April and October 2019 under its early access cohort (n=147),
  - and a historical cohort of patients treated in France in the same expert centers with systemic treatments used off-label before cemiplimab became available between August 1, 2013 and August 1, 2018 (n=133).
- Method: Inverse probability weighting on cofounding factors selected by systematic literature review (excepted ECOG)


HAS
HAUTE AUTORITÉ DE SANTÉ
ÉVALUER LES TECHNOLOGIES DE SANTÉ
AVIS SUR LES MEDICAMENTS
cémiplimab
LIBTAYO 350 mg,
solution à diluer pour perfusion
Réévaluation à la demande du laboratoire
Adopté par la Commission de la transparence le 30 août 2023
Carcinome épidermoïde cutané métastatique ou localement avancé (CECm ou CECla)
Adultes
Secteur : Hôpital



External Control Arm

Other example: Kymriah

- June 2018: CHMP positive opinion for granting a marketing autorisation to Kymriah on, indicated for the treatment of:
  - Paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse.
  - Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.
- Based on indirect comparison of:
  - JULIET single-arm trial
  - Vs SCHOLAR-1 cohort
- Method: Matching adjusted indirect comparison (MAIC)
  - Application of the same selection criteria
  - Weighting, taking into account 3 variables
  - Comparison after “matching”


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

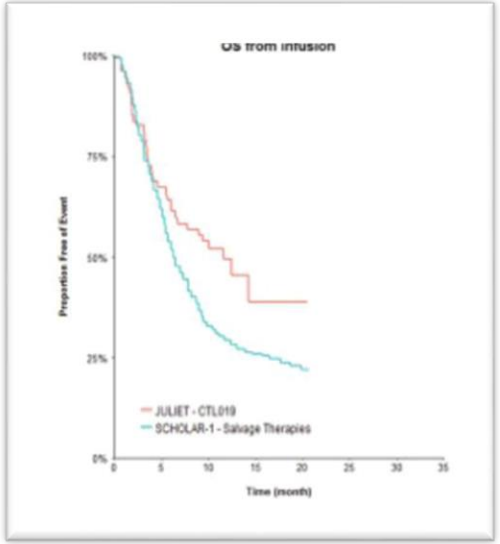
28 June 2018
EMA/485563/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kymriah

International non-proprietary name: tisagenlecleucel

Procedure No. EMEA/H/C/004090/0000

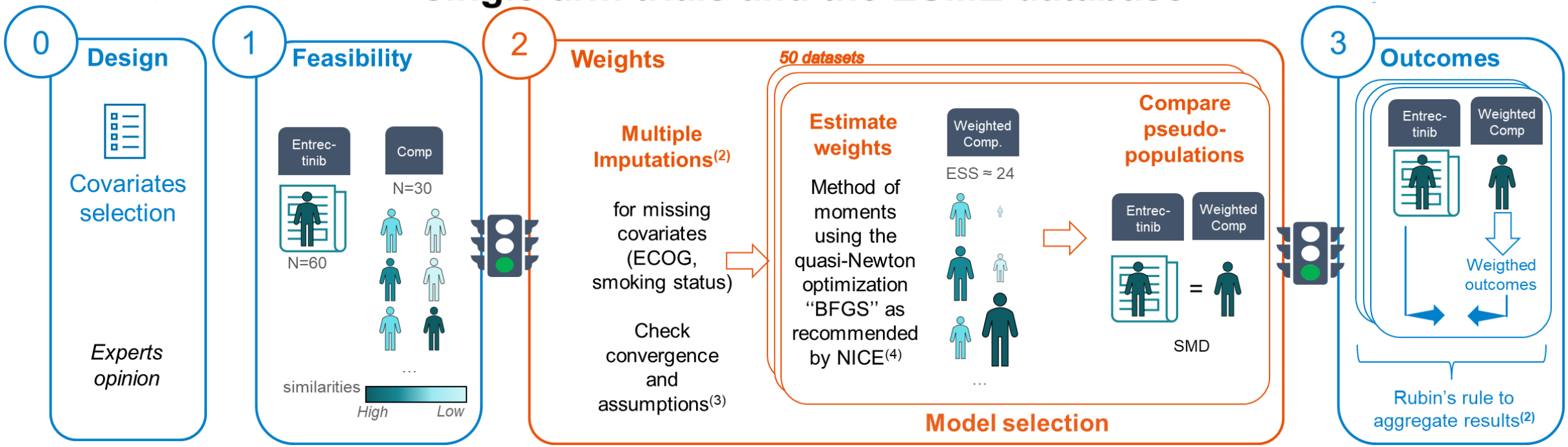


External Control Arm

ESMÉ unicancer

A workflow to perform matching-adjusted indirect comparisons with multiple imputation of missing data illustrated on aggregated single-arm trials and the ESME database

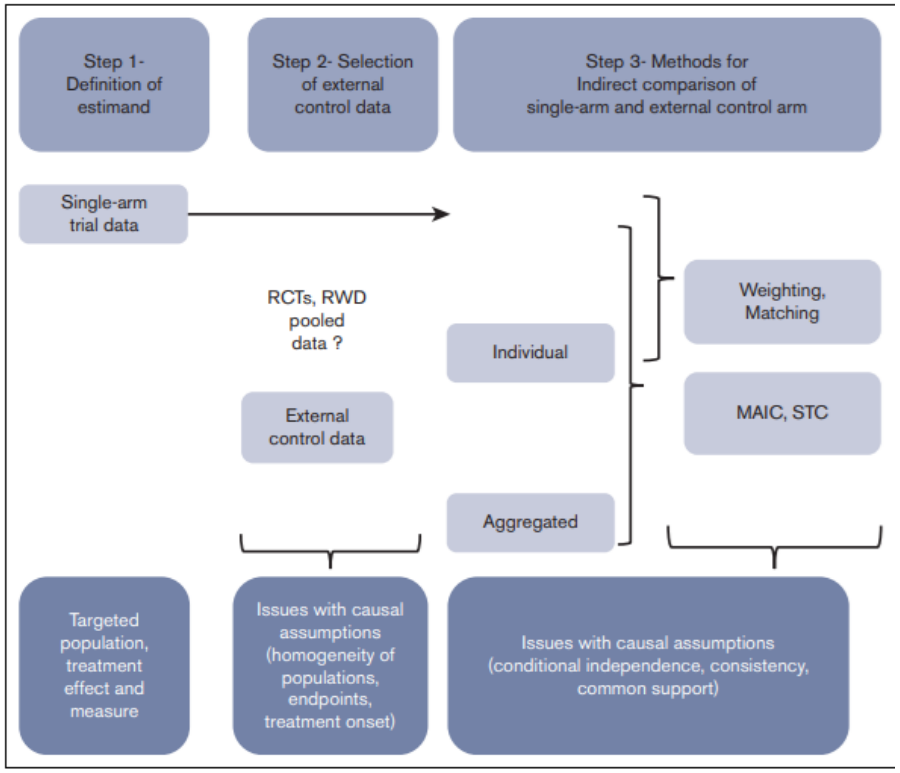
Roche



Esnault, Cyril, Vanessa Barbet, Thomas Filleron, Gaëlle Chenuc, Maurice Pérol, Didier Debieuvre, Nicolas Girard, Louise Baschet et al. *A workflow to perform matching-adjusted indirect comparisons with multiple imputation of missing data illustrated on aggregated single-arm trials and the ESME database*, 2022. https://doi.org/10.13140/RG.2.2.26237.84969/1.

External Control Arm

Schematic 3-step process

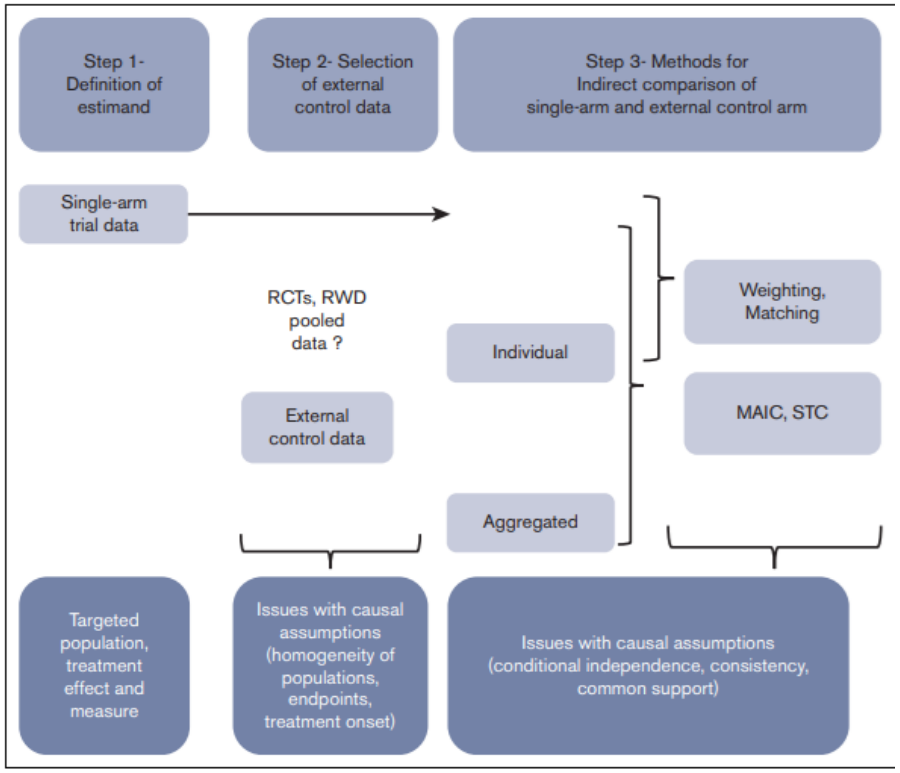


(Lambert, Blood Advances 2023)

- Step 1- Definition of estimand
- Step 2- Selection of the external control data
- Step 3- Methods for indirect comparisons of single arm and external control arms

External Control Arm

Schematic 3-step process



(Lambert, Blood Advances 2023)

- Step 1- Definition of estimand
  - Equivalent to specifying the protocol of the analogous randomized trial explicitly
    - Ask a causal question
    - Target population
    - Treatment strategies
    - Outcome and Censoring rules (Inter-current event)
    - Strategy to mimic randomization
    - Treatment effect estimation (HR,….)

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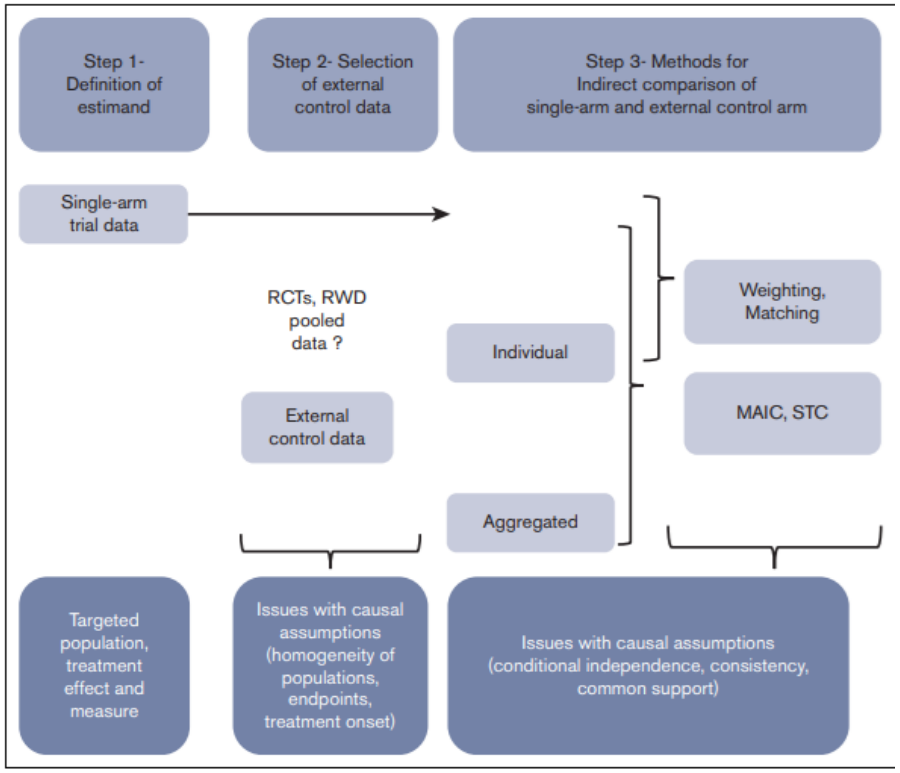

(Lambert, Blood Advances 2023)

- Step 1- Definition of estimand
- Step 2- Selection of the external control data
  - External controls should use predefined eligibility criteria for the inclusion of studies to ensure patient similarity, relevant end points, and pertinent comparators
  - Selected patients from the existing RWD who received therapy consistent with a trial's control arm

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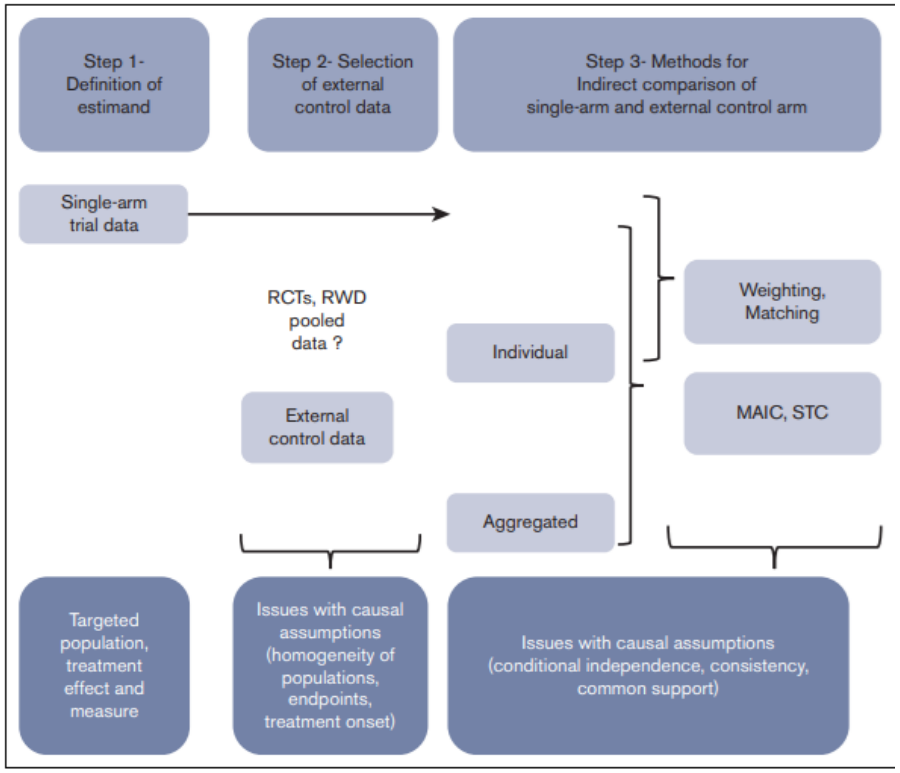


(Lambert, Blood Advances 2023)

- Step 1- Definition of estimand
- Step 2- Selection of the external control data
- Step 3- Methods for indirect comparisons of single arm and external control arms
  - To reduce the treatment assignment bias, and mimic randomization
  - To estimate relative treatment effect
  - Quantification of bias and robustness assessment

Methods for indirect comparisons of single arm and external control arms

Recreate the effects of randomization to get similar groups on their potential confounding characteristics (one by one or by propensity score)

Matching

To build pairs of similar patients

Adjustment

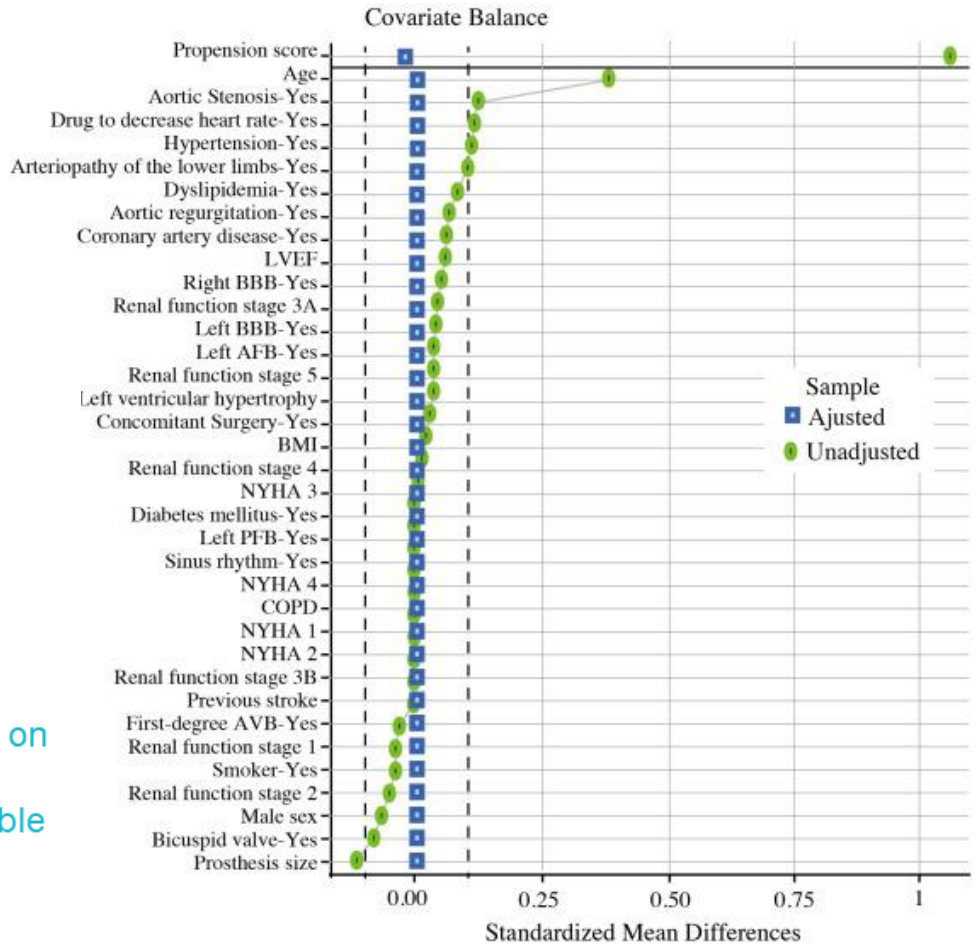
To remove the effect of covariates

Stratification

To cut into similar subgroups

Weighting

To put more or less weight on each patient so that on average they are comparable



Conclusion

- RWE has a place in HTA and can address inquiries related to the target population and the real-world utilization of therapeutic strategies.
- In particular, external controls arms may decrease the uncertainty of single arm trial.
- Indirect comparisons require a complex and rigorous implementation to be valid.
- This process would include considerations of data quality, data comprehensiveness and completeness, and comparability to a potential experimental arm (characteristics, temporality,…)
- Bias (confounding, selection bias, and survivor or lead-time bias) cannot be totally eliminated
- Study design elements can help to minimize bias, and statistical methods may address the influence of bias on the estimation of treatment effect.
- Development and appropriation of additional methods and bias quantification are needed to appropriately characterize use of RWD as substantial evidence in regulatory applications.

Thank you

Questions?

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