EMA/2020/46/TDA/19
Specific Contract 01

Comparative effectiveness and safety studies using the target trial emulation and estimand frameworks (TARGET-EU)

Study protocol: WP1 Objective 2 - Feasibility Assessment

EU PE&PV research network

Version 1.0

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Comparative effectiveness and safety studies using the target trial emulation and estimand frameworks

Title	**Comparative effectiveness and safety studies using the target trial emulation and estimand frameworks – TARGET- EU**
Study ID	**EMA/2020/46/TDA/19, Lot 5**
Framework contractor	European Pharmacoepidemiology and Pharmacovigilance (EU PE&PV) research network
Objectives	Objective 1: To develop an overview of advantages and challenges of combining target trial emulation with the estimand framework for comparative efficacy and safety studies Objective 2: To characterise which types of European RWD sources are suitable to be used in the context of TTE studies and key aspects that should be attended to in a feasibility assessment of data sources for running such a study Objective 3: To establish criteria for suitable regulatory cases, including PAES, PASS and clinical trials with external controls, that would benefit from TTE approach Objective 4: To develop good practices to aid in communication of the TTE studies for regulatory purposes
European RWD sources	The ten case studies in the proposal are going to utilise data sources, included in the EU PE&PV Consortium Framework Contract EMA/2020/46/TDA/L5.06, from the Netherlands, Spain, UK, Greece, Denmark, Italy, Finland, Belgium, Latvia and Norway.
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Amendments and updates

Date	Protocol version	Description
22/10/24	0.1	Creation of the First Draft of the Protocol
13/11/24	0.2	Establish feasibility assessment steps
03/02/25	0.4	Alignment with EMA new QC document
19/02/25	0.5	Open to review to the core team
26/02/25	0.6	Implement core team feedback and send for EMA comments
20/07/25	0.7	Address EMA comments
28/07/25	0.8	Answer comments and update text

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1. Title of the study

Comparative effectiveness and safety studies using the target trial emulation and estimand frameworks (TARGET-EU)

2. List of abbreviations

Abbreviation	Explanation
D	Deliverable
DEAP	Data Experts and Access Providers
DQ	Data Quality
EMA	European Medicines Agency
EF	Estimand Framework
ETL	Extraction, Transformation and Loading
GPP	Good Pharmacoepidemiology Practice
KPI	Key Performance Indicators
NIS	Non-Interventional Study
PAES	Post-Authorisation Efficacy Study
PASS	Post-Authorisation Safety Study
RCT	Randomised Clinical Trial
RWD	Real World Data
RWE	Real World Evidence
SLA	Service Level Agreement
SOP	Standard Operating Procedure
TTE	Target Trial Emulation
WP	Working Package

3. Milestones

An overview and timeline of project elements, including key milestones and deliverables, is presented below. Updates on progress will be communicated during bimonthly meetings between the research team and EMA.

Milestones (M) and Deliverables (D)	Date
Start of project	10 October 2024
D1: List of selected cases	**10 February 2025**
D2: Hypothetical target trial protocol	10 May 2025
D3: Feasibility assessment	**10 May 2025**
D4: Study protocol of target trial emulations	11 August 2025
D5: Study Report	10 June 2026
D6: Lessons learnt and recommendations	10 July 2026
D7: Webinar	10 September 2026
D8: Manuscript	12 September 2026

4. Abstract

Background
Continuous monitoring and evaluation throughout the entire lifecycle remain necessary for authorised medicines. Usually, efficacy and safety assessment for regulatory purposes for an already launched medicine are done via a mixture of interventional (RCT) and non-interventional studies (NIS) using real-world data (RWD). However, RCT cannot be performed in all cases and NIS does not always fill the gap of knowledge needed due to methodological reasons. The combined use of the target trial emulation (TTE) and estimand framework appears to be a promising approach to bridge between NIS and RCTs. The overarching goal of the project is to enhance the understanding of opportunities, limitations and challenges associated with using the TTE and EF frameworks to design and conduct NIS that support regulatory decision-making, using European RWD sources. Ten NIS with causal objectives to address comparative safety or effectiveness will be considered to develop this understanding. As the feasibility and timeliness of the data sources used for conducting each of those studies are essential, a feasibility assessment will be conducted. This deliverable outlines a series of steps to assess the feasibility of conducting the studies within the TTE framework using the envisioned data sources.

Methods
Prior to conducting the feasibility assessment, a set of potential case studies will be identified and agreed upon. Expressions of interest were then requested from data experts and access providers (DEAPs) partners belonging to our consortium. Based on this, a methodological framework will be established to select suitable European RWD for the case studies. The European Medicines Agency (EMA) data quality framework for medicines regulation applied to RWD will be used to assess the reliability of the selected data sources and their relevance for the selected case studies.

Results
Feasibility assessment will follow three key steps: I) Data sources' systems and processes characterisation, using the EMA checklist to evaluate foundational aspects and their maturity; II) Metrics for data reliability for each data source, based on published research and open-access catalogues; and III) Data relevance, assessing data source suitability for each case study based on question-specific determinants. Steps 1 and 2 are data source-specific, while step 3 is both data source- and case-specific, i.e. it can only be assessed in view of the specific research question to be addressed. From the previous steps, two tables containing qualitative information (I and III) and one table including quantitative metrics will be created (II). The overall feasibility of the case-studies using the candidate data sources will be derived by critically analysing the information gathered in the aforementioned tables. Every output will be revised by the DEAPs as needed during the feasibility assessment. All the information will be compiled in a report accompanying the generated tables and a narrative assessment.

Conclusions
Overall, this methodology is expected to provide a comprehensive, standardised, and adaptable framework for assessing the suitability of RWD for research purposes.

5. Rationale and background

In the evaluation of effectiveness of medicines, a well-conducted randomised controlled trial (RCT) has been widely accepted as the scientific and regulatory standard. For decades, the main application of non-interventional studies (NIS) using Real World Data (RWD) in regulatory decision-making has been the assessment of safety of medicines. However, there is an increasing demand to generate evidence on intended effects (effectiveness) of medicines in situations when an RCT is not feasible due to ethical, economical, or other constraints. Non-interventional cohort studies using RWD are the main alternatives to assess causal effects of medicines in routine clinical practice. The combined use of TTE by the hand of the estimand framework appears to be a promising approach to bridge the gap between RWD and RCTs in the context of regulatory assessment of applications using observational data. This approach will warrant a thorough understanding of opportunities and limitations, as well as operational and methodological challenges.

The design of the NIS should be primarily driven by the need to obtain reliable evidence regarding the research question [1]. To this aim, the availability of networks of RWD-sources where such studies are feasible and timely are essential. Generally, an RWD-source should be chosen to match the research question, rather than adjusting the research question to fit the RWD-source [2]. Usually, data are considered "reliable" if they represent the intended underlying medical concepts and thus are considered trustworthy and credible; and "relevant" if the dataset presents the necessary data elements to answer the research question in the clinical context of interest. The assessment of data source reliability and relevance is an important activity underlying study-level feasibility assessment [1].

A feasibility assessment is recommended after the research question is detailed and prior to writing the study protocol to guide its development and facilitate early discussions with regulatory authorities [1]. This step ensures that the proposed study is practical, achievable, and aligned with available resources, timelines, and infrastructure. It can provide valuable insights and help identify potential barriers and limitations early on. A thorough feasibility assessment ultimately supports the design of a realistic and robust protocol, increases the likelihood of successful study execution, and streamlines the approval process with regulators.

In this project, we propose a systematic workflow for feasibility assessment, which involves the characterization of multiple data sources and the evaluation of their reliability and relevance in the context of selected case studies.

6. Objective of this deliverable

We aim to characterise which types of European RWD sources are suitable to be used in the context of the 10 selected cases, and to identify the key aspects to pay attention to in the feasibility assessment of data sources for implementing the hypothetical target trial protocol in each case.

7. Research methods for the feasibility assessment

From the objective above, this deliverable will focus on outlining a series of steps to assess the feasibility of using specific European RWD sources—within the EU PE&PV consortium—to conduct TTE for selected case studies.

7.1. Study design

A feasibility assessment will be conducted for the data sources identified in D1 as potential candidates for the ten selected case studies. Among the potential contributors, we will implement a three-step process to determine their feasibility. First, we will characterise data sources by using the checklist proposed by the European Medicines Agency (EMA) [2] focusing on foundational aspects, together

with the level of maturity of each of the items of the checklist. The next step will be a reliability assessment using measurable metrics (intrinsic determinants) which will be completed using already published information, either from research papers or open-access catalogues. Finally, the relevance of each data source per case study will be evaluated (question-specific determinants). First and second steps are data source-specific, and step three is both data source and case-specific. By critically examining the information gathered in each step, we will make a final assessment of the suitability of each specific data source for each case study. It is important to note that all three steps are applied to each data source, without discarding sources between them. The steps of this process are outlined in **Figure 1.**

Information on data sources will be retrieved from the new HMA-EMA catalogues of Real-World Data sources [3], MINERVA [4] and complemented with information on foundational determinants of quality, retrieved from the VAC4EU Catalogue [5] and from previously published articles. Additionally, we will consult data experts and access providers (DEAPs) by asking targeted questions to gather any missing or unpublished information relevant to the steps outlined in this protocol. Free-text searches will be conducted if necessary to identify the limitations and strengths faced in studies including such data sources. Each of these steps will be discussed by two investigators to minimise subjectivity and increase information finding.

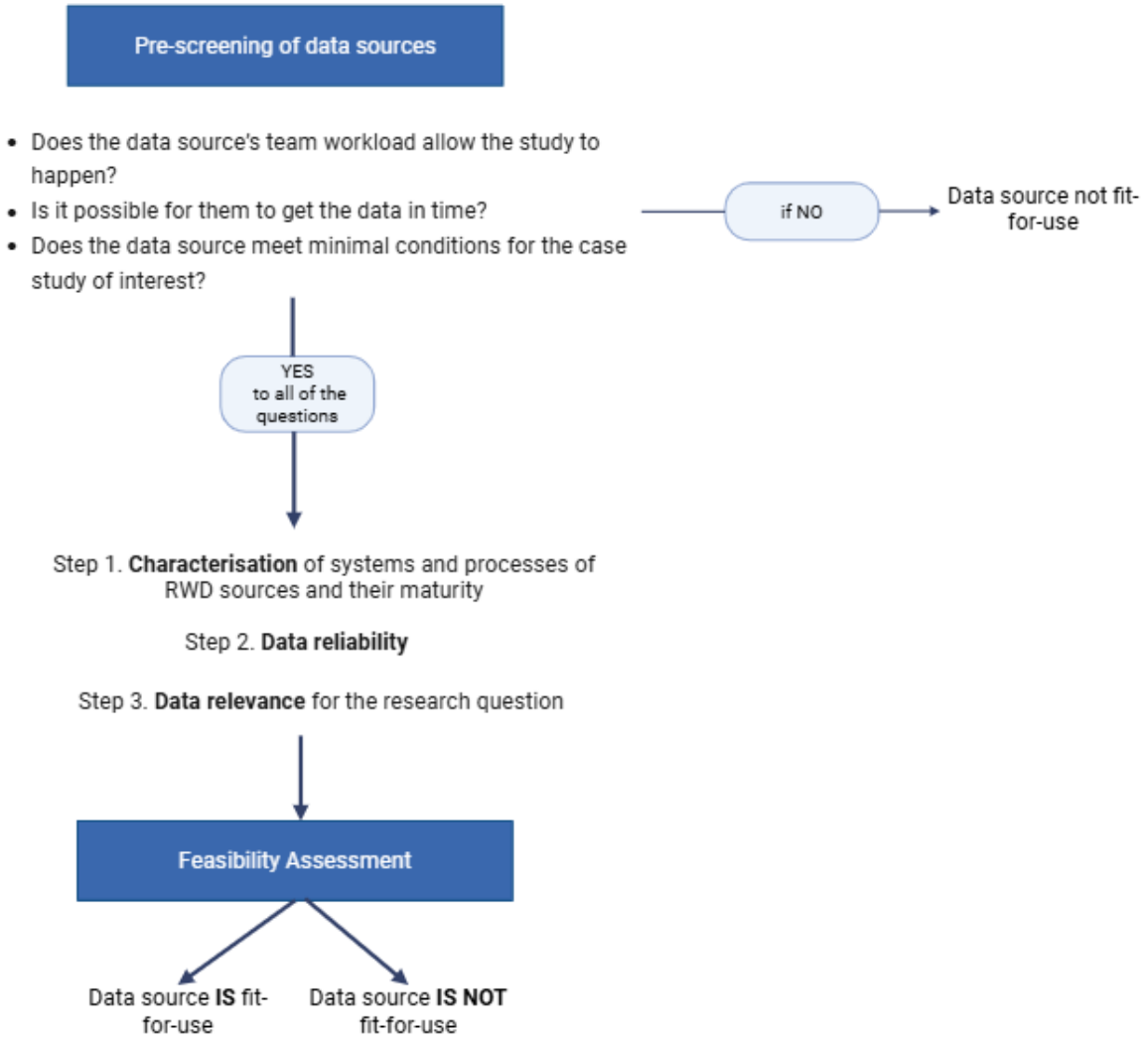

Figure 1. Steps for feasibility evaluation. RWD: Real-World Data

7.2. Selection criteria for data sources inclusion

We will conduct a standardised feasibility assessment of data sources previously identified as potential candidates for the ten selected case studies. A maximum of two candidate data sources per case study were selected to undergo the feasibility assessment after an initial pre-screening. In the event of no data sources being suitable for a case study, we will consider such a study not feasible and in consequence opt for a reserve case study.

We ensured that across all cases, these data sources represented at least six countries.

7.3. Steps to conduct the feasibility assessment

7.3.1 STEP 1: Characterisation of systems and processes of RWD sources and their maturity: data source specific

1. Items

In general, for data to be deemed reliable in the context of regulatory decision-making, the infrastructure and processes used to collect, store, transform, and transfer the data must be designed to ensure the data corresponds to the observed reality it represents, without any distortion or alteration. In our project, information on the candidate data sources for our case-studies can be retrieved from the new HMA-EMA catalogues of RWD sources [3], MINERVA [4] and complemented with information on foundational determinants of quality, retrieved from the VAC4EU Catalogue [5], or published articles.

For this deliverable, data source characterisation will follow the checklist proposed by the EMA shown in **Figure 2**, and will be conducted independently of the case studies to which each data source contributes to:

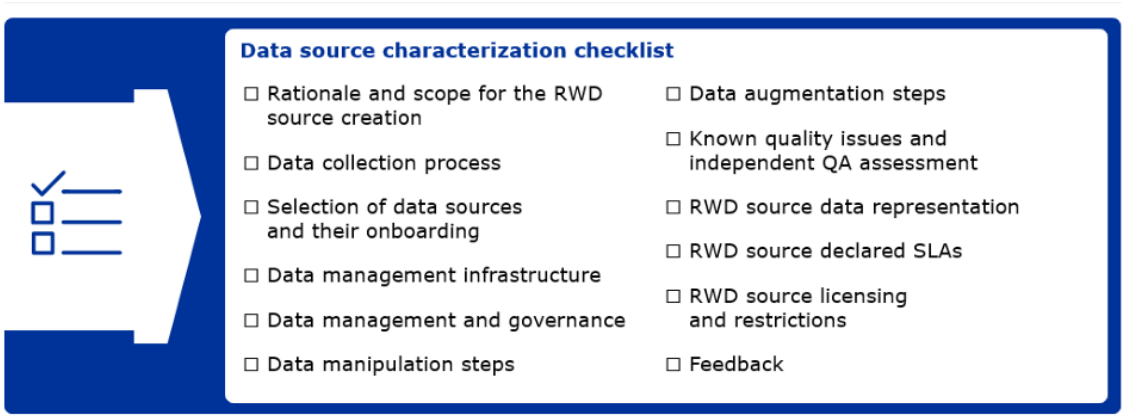

Figure 2. RWD source characterisation checklist overview, extracted from the Data Quality Framework for EU medicines regulation: applications to Real-World Data [2] SLA: Service Level Agreement

2. Rationale

For each item, a corresponding rationale is provided. This reflects the underlying justification for why the item is relevant, what specific data quality dimensions it informs, and how it contributes to a deeper

understanding of the strengths, limitations, and potential risks associated with a given data source. It helps understanding where scrutiny should be focused and aligning on expectations for each item.

The rationale for each of the items assessed can be found in **Table 1**.

3. Maturity

In addition to confirming the presence of the previous items, it is important to recognise that the manner in which they are reported can vary significantly in terms of depth, detail, and level of automation. Maturity depends on the level of automation, as automated DQ processes can be both more extensive and less subject to accidental or human errors. The maturity of reporting can be broadly categorised into three levels:

- **Level 1: Documented** – Basic information is provided through simple documentation or supporting links, with more extensive details available via standard operating procedures (SOPs), as well as key performance indicators (KPIs).
- **Level 2: Formalised** – Information follows established or emerging standards. SOPs and KPIs align with recognised standards.
- **Level 3: Automated** – Data quality is ensured by design, with information generated automatically by systems rather than entered manually. For example, in the case of data lineage, provenance information is generated by an ETL (extraction, transformation and loading) engine or derived from some executable electronic specification.

The following table (**Table 1**) includes the structure to gather the information in the checklist [2]. In **Appendix 1**, a ready-to-fill template is also provided. The maturity of each item will be evaluated based on the maturity model derived from the EMA Data Quality (DQ) Framework [6]:

Table 1. Data source characterisation checklist, adapted from the Data Quality Framework for EU medicines regulation: application to RWD [2]

General characteristics				
Item	**Rationale *("To know this is relevant because… "***	**Description**	**Origin of information**	**Maturity level***
0)Data base identification • Data base name • Country • Data Access Provider • Organisation type	*NA*	*NA*	*Publicly available (with references), obtained via targeted questions to the DEAP, or not found*	*NA*
I) Rationale and scope for the RWD source creation	*Relevant for all DQ dimensions as it provides a general understanding of the strengths and limitations of an RWD source.* *Knowing the triggers would ease the understanding of the content and motivations behind the data.*	*Purpose for data to be collected, prompt, publications, ...*	*Publicly available (with references), obtained via targeted questions to the DEAP, or not found*	*1: Documented,* *2: Formalised,* *3: Automated*
II) Data collection or recording process	*Essential to understand coverage and to assess reliability (that can be affected by errors or biases in the collection process). Also, essential to evaluate SOP for data collection or recording practices that may impact coherence (e.g., where "curation at source" is involved and provide hard constraints for timeliness).*	*Describe the data provider, and how data are recorded and SOPs are designed and implemented*	*Publicly available (with references), obtained via targeted questions to the DEAP, or not found*	1: Documented, 2: Formalised, 3: Automated

III) The selection of RWD sources and their onboarding	*When data are provided by a data aggregator, ensure that all the available evidence related to systems and processes potentially affecting DQ can be followed. Provide information of impact on both reliability and evidence (as well as other dimensions if relative constraints are formulated in inclusion/exclusion criteria)*	*(Applies to RWD sources that integrate or repurpose other RWD sources)*	*Publicly available (with references), obtained via targeted questions to the DEAP, or not found*	1: Documented, 2: Formalised 3: NA
IV) The data management infrastructure	*Essential for reliability regarding data alterations resulting from system accidents, software errors or malicious intervention*	*The software testing and QA processes in place. Measures to prevent accidental physical data alterations*	*Publicly available (with references), obtained via targeted questions to the DEAP, or not found*	1: Documented, 2: Formalised, 3: Automated
V) Data management and governance	*Data management and governance impact reliability, as well as all quality dimensions for metadata*	*Auditing, monitoring, metadata follows FAIR standards, ISO, ...*	*Publicly available (with references), obtained via targeted questions to the DEAP, or not found*	1: Documented, 2: Formalised, 3: Automated
VI) Data manipulation steps	*Impacts reliability both in terms of accuracy (possible errors) and precision (i.e., the degree of approximation by which data represents reality). Essential to ensure traceability of information. Also impacts coherence and potentially timeliness*	*Lineage information, data transformations performed, data cleaning steps, KPIs, ...*	*Publicly available (with references), obtained via targeted questions to the DEAP, or not found*	1: Documented, 2: Formalised 3: NA
VII) Data augmentation steps	*Data augmentation steps impact accuracy. We consider here data transformations that produce new information subject to reliability issues: e.g.: imputation of missing values, or extraction of codes via natural language processing.*	*Imputation, linkage, algorithms, ...*	*Publicly available (with references), obtained via targeted questions to the DEAP, or not found*	1: Documented, 2: Formalised, 3: Automated

VIII) Known quality issues and independent QA assessment of the RWD source	*Explicit description of known DQ issues, as well as external validation performed (all dimensions affected)*	*Known DQ issues (e.g., poor overall completeness in Q3 2020 due to COVID-19), validation studies, publications, ...*	*Publicly available (with references), obtained via targeted questions to the DEAP, or not found*	1: Documented, 2: Formalised, 3: Automated
IX) The RWD source representation	*Descriptive of the intended coherence of a dataset and its metadata*	*Data model or models used (OMOP, FHIR, ...), data dictionaries and vocabularies used, and if in standard formats that allow mapping across different languages (e.g., UMLS), ...*	*Publicly available (with references), obtained via targeted questions to the DEAP, or not found*	1: Documented, 2: Formalised, 3: Automated
X) The RWD source declared Service Level Agreements (SLA)	*Descriptive of guaranteed timeliness and possible variations of extensiveness/reliability provided*	*Frequency of updates, incident response, possibility to collect additional data, training materials, help desk, etc. important for timeliness.*	*Publicly available (with references), obtained via targeted questions to the DEAP, or not found*	1: Documented, 2: Formalised, 3: Automated
XI) The RWD source licensing and restrictions	*Descriptive of aspects that can limit extensiveness and coherence in downstream data aggregations*	*Limitations of use, accessibility policies, licensing constraints, standard policies of use, ...*	*Publicly available (with references), obtained via targeted questions to the DEAP, or not found*	1: Documented, 2: Formalised, 3: Automated
XII) Feedback	*Descriptive of feedback mechanisms in place to improve all aspects of DQ*	*Is there a data ecosystem in place so that quality assessment by data consumers can provide feedback to improve the data collection and production process, thus allowing a continuous monitoring and improvement of DQ?*	*Publicly available (with references), obtained via targeted questions to the DEAP, or not found*	1: Documented, 2: Formalised, 3: Automated

*EU: European Union; RWD: Real-World Data. *The definition of the specific maturity level for each of the items is established as per the EMA DQ framework for RWD document [5].*

In case we are unable to find the previous information, we will acknowledge it in the table accordingly. Additionally, we will ask DEAPs targeted questions to fill in any potentially missing unpublished information for the steps explained in this protocol, while keeping the information collected as broad as possible to collect useful information for future use. Free-text searches might be done, if necessary, to map the limitations and strengths faced in studies including such data sources.

7.3.2 STEP 2: Metrics for DQ for RWD dimension assessment (data reliability): data source specific

The reliability of the candidate data sources for our ten case studies will be assessed, by using a series of DQ metrics retrieved from the HMA-EMA catalogues of Real-World Data sources [3], MINERVA [4] and the VAC4EU Catalogue [5], or published articles. Concerning DQ metrics, there exists a set of DQ dimensions that are paramount from a regulatory perspective (see **Figure 3**): reliability, extensiveness, coherence, timeliness and relevance [6].

The dimension of reliability determines whether data represent the intended underlying medical concepts and are complete, trustworthy, and credible [1]. Reliability includes many subdimensions (**Table 2**), and together with extensiveness, coherence and timeliness, are data source specific. In Step 2, metrics to assess each of these dimensions will be collected.

Finally, the dimension of relevance (i.e., the extent to which a dataset presents the data elements useful to answer a given research question) is considered as something crosscutting through all DQ dimensions [1,6] and depends not only on the data source but also on research question. Hence, it will be addressed in Step 3 where a case-study and data source specific assessment are considered.

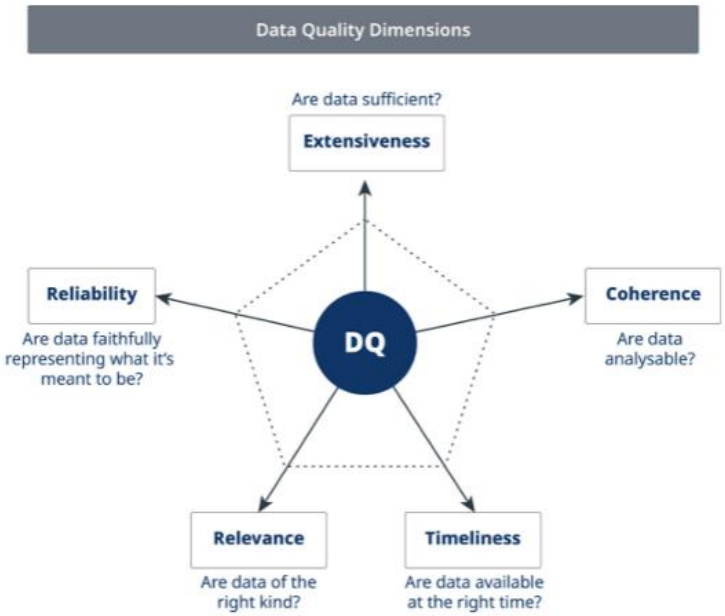

Figure 3. Data quality dimensions, extracted from the EMA DQ Framework [5]

DQ metrics will be retrieved from published information, either from research papers or open-access catalogues. No quantitative analyses will be performed on real data. Metrics will be selected per DQ dimension based on information availability elsewhere, and trying to cover to some extent the metric

groups as classified by the DQ Framework proposed by the EMA [2,6], i.e., independent data checks, plausibility checks, conformance checks, comparison to other data sources and checks on metadata (see **Table 2** and **Appendix 1**).

Table 2. Example metrics per dimension and sub-dimension of data quality, based on the EMA [6], to be performed by data source

Dimension	**Sub-dimension**	**Example Metrics**	**Origin of information**
Reliability	Accuracy	The population distribution in the data source aligns with that of the country Records of diagnostics, exposures or medical observations that do not agree with common expectations and knowledge or feasible ranges Variables that are based in imputation, derivation or inference	*Publicly available (with references), obtained thank to targeted questions to the DEAP, or not found*
	Precision	Exposures codes precision level, including medicines and vaccines Precision of date of the event/diagnosis	*Publicly available...*
	Traceability	Provenance of event records	*Publicly available...*
Extensiveness	Completeness	Percentage of subjects in the data with a recorded birth date Percentage of subjects in the data, irrespective of vital status, that have a recorded date of death	*Publicly available...*
	Coverage	Percentage of a target population present in a data source	*Publicly available...*
Coherence	Format coherence	For dates, formatting constraint being followed For sex, formatting constraint being followed	*Publicly available...*
	Relational coherence	Percentage of records with the Person ID in the PERSONS table	*Publicly available...*
	Semantic coherence	For relevant variables which employ code lists or data dictionaries according to external standards, % of patient records which use a given code list	*Publicly available...*
	Uniqueness	Number of records flagged as potential duplicates	*Publicly available...*
Timeliness	Currency	How often is the data source updated (i.e., frequency of updates) The time gap between the latest available data and date when data is delivered to user	*Publicly available...*

7.3.3 STEP 3: Data relevance: case-study and data source specific

Once the assessment of the reliability of data is performed and the DQ metrics of a RWD source are collected, the next step is to assess the relevance of the data source for the research question of interest. At a more detailed level, data relevance for a specific question is demonstrated if the data captures key data elements of the research to address such question (e.g., diagnosis, exposure, outcome, and covariates) in a reliable, coherent and timely way, or if the number of patients and follow- up time are sufficient to demonstrate the impact of the intervention/determinant under investigation. Once a research question has been defined, the data elements for the case-study need to be determined and operationalised into study variables. To assess the feasibility of conducting TTE for specific study cases, it is necessary to evaluate the availability and quality of the information related to the disease or exposure of interest, along with its covariates and potential confounders [7]. When used in combination with the EF, considerations may also be needed to the availability and quality of data on the occurrence of intercurrent events, depending on the strategies chosen to handle those. On the other hand, it is essential to determine whether it is feasible to operationalise the criteria required for TTE within each data source. The presence of some variables may be considered essential for determining whether a data source is relevant, while others may be viewed as advantageous to have, though not mandatory. With this purpose, a table like **Table 3** will be created (see also the template in **Appendix 1**), specifying the design elements applicable to the case-study and relevant aspects of the DQ dimensions they might be impacted by [2]. The completion of this table will be performed by one person and then reviewed by the team (including the corresponding case-study lead).

Table 3. Data relevance shell table with the list of design elements to be considered, their criticality, DQ they impact to and documentation for sources of information [2]

Scientific research question					
Design elements	**Operationalisation of definitions**	**Data elements for valid capture of variables**	**Criticality of the quality of the element (with justification): *High[A], Low[B]***	**DQ dimensions assessment (as applicable)**	**Documentation**
Study population					
Treatment or exposure					
Comparator group (if applicable)					
Key endpoint(s)					
Confounders					
Intercurrent events*					
Follow-up time needed per patient in the study					
Minimum time in the data source for lookback assessment					
Others*					

**These design items are not included explicitly in the EMA DQ Framework [2].*

[A] High criticality will be defined if the design element is essential to the design or integrity of the study. Includes: eligibility criteria, primary exposure, primary outcome, intercurrent events of a while on, principal stratum and/or composite strategy, time of follow-up and minimum time in the data source (related to eligibility criteria).
[B] Low criticality will be defined if the design element is a comorbidity, general demographic aspect, is descriptive or does not affect the viability of the study.

In **Table 4**, the specific exposure, comparators and outcomes of interest for the research question of each case-study can be found.

Table 4. Exposure, comparators and outcomes of interest for each of the ten case-studies

Case study	Exposure	Comparator	Outcome
1	SARS-CoV-2 mRNA vaccine (BNT162b2)	No vaccination	COVID-19 infection
2	Nivolumab plus ipilimumab combined with two cycles of chemotherapy (9LA regimen)	Pembrolizumab combined with two cycles of chemotherapy (KEYNOTE-189 and KEYNOTE-407 regimen)	Death due to any cause
3	Dapagliflozin	DPP4i	MACE (all-cause death, myocardial infarction or stroke)
4	Rivaroxaban	Apixaban	Safety (GI bleeding)
5	Vilanterol/fluticasone furoate	Inhaled corticosteroids (ICS)/Long-acting beta agonists (LABA)	Pneumonia
6	Sacubitril/valsartan	Angiotensine converting enzyme (ACE) inhibitors or angiotensin receptor inhibitors (ARB)	Angioedema
7	Valproate (paternal exposure)	Levetiracetam	Composite of autism, ADHD, congenital malformations, stillbirths, spontaneous abortions and post-birth death in offspring
8	Nirsevimab	No immunization	RSV-lower respiratory tract infection, RSV related hospitalization
9	Tolvaptan	Untreated	Hepatotoxicity
10	CapOx chemotherapy (capecitabine + oxaplatin) in combination with bevacizumab	CapOx chemotherapy (capecitabine + oxaplatin)	Progression free survival

ADHD: Attention-Deficit/Hyperactivity Disorder, CapOx: capecitabine and oxaliplatin, GI: GastrOintestinal, MACE: Major Adverse Cardiac Events, RSV: Respiratory Syncytial Virus

7.4. Feasibility assessment: putting evidence together

Since some research questions are time-sensitive or may require specific timeframes or population coverage depending on the research question, the overall characterisation of a source and certain data quality metrics can be a key criterion for its acceptability. The information gathered in the aforementioned steps will be assessed and discussed within the team. To decide the key aspects that are more likely to impact the feasibility of a data source to be used for any or a specific type of studies, team meetings with the core group and case-study leads will be held to reach consensus about which data sources are suitable for each of the selected case studies based on a comprehensive assessment (see **Table 5** and **Appendix 1**). Such assessment includes not only reliability and relevance, but also aspects relating to data accessibility, maturity (see **Table 1**), representativeness and sample size for the cohort and comparators.

Table 5. Final feasibility assessment table

Case study	RWD source	Sample size estimation from the hypotetical trial protocol	Feasibility assessment	Rationale for the feasibility assessmernt	Limitations identified during the feasibility assessment and categorisation	Description of potential impact of the identified limitations on the study results
Case study #1	**RWD source #1**	Estimated sample size for the TTE and likelihood of being reached based on data source characteristics	*Yes/yes, with limitations/no*	Justification of the feasibility assessment based on critical data elements, data recency, and sample size availability	Classification into minor/potentially major/major with a description of each limitation	Impact of each identified limitation
	RWD source #2 (...)	Estimated sample...	*Yes/yes, with limitations/no*	Justification of...	Classification into...	Impact of each....

RWD: Real-World Data

Based on the assessed variables, limitations will be identified and categorised as major, potentially major, or minor, as shown in **Table 6**. Each limitation will be described along with its potential impact on the study results. Finally, a feasibility assessment will be provided, categorised as 'Yes', 'Yes with limitations', or 'No', based on the issues identified. In cases with data sources where a major limitation is present, feasibility will be classified as 'No', and in case of potentially major limitations being present, it will be classified as a 'Yes with limitations'. All decisions will be discussed within the team and the relevance of each of the attributes and variables will be agreed with the case-study leads, on a case-by-case basis.

Table 6. Criteria for categorisation of the limitations identified during the feasibility assessment

Major:	• If the limitation significantly affects primary outcomes or key variables
	• If it affects statistical power or sample size
	• If data availability or quality limits the study's feasibility to address the research question
	• If the limitation may compromise the internal validity of the study
	• If the limitation affects the sample size estimation
	• If key subgroups (e.g., treatment-naive patients) are underrepresented
Potentially major:	• If limitations are major, but have a solution or reasonable approach
Minor:	• If the impact on the conclusions is small and can be mitigated
	• If the issue is easily addressable or quantifiable
	• If the impact on study timelines is limited and doesn't interfere with the key analyses
	• If the limitation affects non-critical aspects of the study design, like data extraction procedures or non-essential controls
	• If the limitation can be addressed using secondary analyses
	• If the study sample is mostly representative but some minor groups are underrepresented

Complete template tables for the whole feasibility assessment process and instructions can be found in **Appendix 1**.

7.5. Data management

We will ask DEAPs targeted questions to fill in any potentially missing unpublished information for the steps explained in this protocol. Free-text searches might be done if necessary to outline the limitations and strengths faced in studies including such data sources, to find previous data quality assessments and to help filling the table in Step 1.

We will create an electronic data collection form where the information from each data source used for the feasibility assessment will be stored. We will use the Excel for this purpose.

7.6. Quality control

7.6.1 General approach to quality management and control

The work in this proposal will be conducted according to the guidelines for Good Pharmacoepidemiology Practice (GPP) (International Society for Pharmacoepidemiology 2008) and according to the ENCePP code of conduct (European Medicines Agency 2018). All partners have experience in conducting pharmacoepidemiological research and research is done by researchers trained in pharmacoepidemiology.

Utrecht University and University Medical Center Utrecht are working according to a quality management system based on ISO 9001 principles. The quality management system is system and process oriented and based on continuous improvement. The system is based upon standard operating procedures implemented throughout the division with regular internal audits as well as external audits that lead to certification. The quality management system is based on national and international external quality requirements where available and pertinent, including the guidelines for Good Pharmacoepidemiological Practices, ENCePP Guide on Methodological Standards in Pharmacoepidemiology, Good Clinical Practice, and Good Clinical Data management. Practice as well national and international guidelines and legislation concerning data-handling and privacy issues. All deliverables will be reviewed by project partners.

7.6.2 Specific aspects of quality management and control

The protocol will be reviewed by the WP1, WP2 and WP3 members and the core team of TARGET-EU, Version control on SharePoint will be applied.

7.7. Limitations of the feasibility assessment method

While the approach outlined in this study provides a structured process for selecting and documenting the feasibility of RWD to be applied to specific research questions, there are several limitations that should be considered when applying this framework in practice.

The process itself is designed to be reproducible and adaptable, which, while a strength, also introduces variability in its application across different research questions and contexts. As such, the generalisability of the framework to all use cases may be limited, and its successful implementation will likely require customisation depending on the QC metrics of interest, and specific needs of a study or evolving research objectives (i.e., Step 2 and Step 3). However, the relevance of each element in these tables can be assigned differently depending on the context of application. This flexibility, while

beneficial, may also complicate its standardised application. Moreover, especially **Tables 1** and **2**, could become more extensive and deeper as experience increase, more evidence is generated, and revisions occur.

The framework places significant emphasis on due diligence in selecting appropriate data sources. However, this process is inherently time-consuming and resource intensive. Critical steps such as reviewing documentation, querying data owners, and obtaining cohort-specific estimates require substantial effort to ensure that the data is truly fit-for-purpose. Since we plan to use public information from relevant catalogues and data from similar case studies, we may miss out on more in-depth information. To mitigate the risk of overlooking key details, we will directly engage with DEAPs through targeted questions.

The framework also highlights the importance of carefully assessing data quality, but it may not fully address challenges related to the integration of data from multiple sources, such as the use of different formats or the compliance with different standards. In multi-data source studies, different estimates may be found even when the same protocol is applied across all data sources. Consistency or heterogeneity between data sources might be a source of confidence or uncertainties [1]. These should be considered in the earliest stages possible and be qualitatively or quantitatively discussed in study reports. However, mapping previous experience of RWD sources on CDMs and characterising those data sources in Step 1 may help shaping their integration and detecting potential sources of heterogeneity.

Additionally, the feasibility assessment process does not always account for the risks associated with data sources becoming obsolete or unavailable over time, especially in cases involving third-party data providers. Data errors or outdated information may not be immediately apparent during high-level assessments, yet it can significantly affect the usefulness of the data once implemented/extracted for a case-study. However, we plan to incorporate a high-level reporting of data missingness and timeliness of the variables relevant for the selected case-studies.

Another limitation is that some of the items are subjective and reported in a non-structured manner. To mitigate this, we created a table specifying a series of scoring criteria for each of the items and performed a double-blind assessment. Also, the framework does not always address the risks associated with data sources becoming obsolete or unavailable over time, particularly in cases involving third-party data providers.

Another important limitation to consider from the perspective of the data sources is that data silos within organisations or between institutions can restrict access to relevant data, even if the data appears fit-for-purpose on paper. These barriers can hinder the ability to use data effectively and could affect the overall quality of the case study results. Privacy concerns and legal compliance are also critical factors in data selection, particularly in sensitive domains such as healthcare or finance. While the framework emphasises the importance of data quality, Step 1 also reports on matters related to access restrictions and privacy laws such as GDPR or CCPA. These may impact relevance, as even if data meets the necessary technical and quality criteria, it may not meet legal or ethical requirements for use, which can restrict its application. This gap is especially significant when dealing with confidential or sensitive data, where additional safeguards and scrutiny are required.

In conclusion, while the proposed framework offers a structured approach to selecting fit-for-purpose data, its application is not without challenges. These challenges include difficulties in addressing evolving data needs, subjective judgments in data definition, issues related to data quality and integration, compliance risks, and the handling of unstructured and complex data types. To improve the utility and applicability of the framework, future work should focus on refining these aspects, with particular attention to data governance, compliance, and a more comprehensive assessment of data quality across diverse contexts.

8. Protection of human participants

This is a non-interventional study using secondary data collection and poses only very limited risks for individuals. Each research partner will apply for an independent ethical and/or institutional board review according to local regulations. Data protection and privacy regulations will be observed in collecting, forwarding, processing, and storing data from study participants.

Patient information

This study does not involve involves data that exists in a pseudonymised structured format locally and aggregated data centrally and contains no patient personal information. All parties will comply with all applicable laws, including laws regarding the implementation of organisational and technical measures to ensure the protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws. Patient personal data will be stored at DAPs in encrypted electronic form and will be password protected to ensure that only authorised study staff have access. DAPs will implement appropriate technical and organisational measures to ensure that personal data can be recovered in the event of a disaster. In the event of a potential personal data breach, DAPs shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

Patient consent

As this study does not involve data subject to privacy laws according to applicable legal requirements, obtaining informed consent from individuals is not required.

9. Management and reporting of adverse events/ adverse reactions

Not applicable

10. Plans for disseminating and communicating study results

As per EMA Good Pharmacovigilance Practices (GVP) Module VIII, the study and its protocol will be registered in the HMA-EMA Catalogues of RWD studies prior to the start of data collection. A template of the feasibility assessment steps will be also enabled publicly for its transparency and replicability (see **Appendix 1**). Results of analyses and interpretation will be delivered in report form. Study results will be published following guidelines, including those for authorship, established by the ICMJE. When reporting the results of this study, the appropriate Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist and the RECORD-PE extension will be followed. Independent publication rights will be granted to the research team in line with Section VIII.B.5. Publication of study results, of the EMA GVP Module VIII: Post-Authorisation Safety Studies. Upon study completion and finalisation of the study report, the results of this study will be submitted for publication, preferably in a relevant peer-reviewed journal and posted in the EU PAS Register. Also, study findings will be presented in national, regional and international conferences, when applicable. The study report will also be publicly posted on Zenodo (EU PE&PV) and cross-linked to the EU PAS register.

11. References

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