Joint Action 3

MILESTONE

Milestone 5.15 Final validated Standards Tool for Registries in HTA prepared

Date of submission	9/30/2019
Work package	5
Activity Centre	Post-Launch Evidence Generation (PLEG) and Registries – Strand B2
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Dissemination level	Public

Co-funded by the Health Programme of the European Union

Revision History

Revision no.	Date	Author
1	9/6/2017	Maja Valentić (MV) (HZJZ)
2	12/22/2017	MV, Hannah Patrick (HP) (NICE)
5	7/12/2018	MV, HP, Helen Powell (HeP) (NICE), Irena Guzina (IG) (HAS)
7	4/17/2019	HP, HeP
8	5/25/2019	MV, HP, HeP, Emmanuel Gimenez (EG) (AQuAS)
9.1	5/3/2019	MV, HP, HeP, IG, Jae Long (JL) (NICE)
9.7	9/30/2019	Maja Valentić (HZJZ), Hannah Patrick (NICE), Helen Powell (NICE),

Introduction to REQueST

Description of REQueST

The Registry Evaluation and Quality Standards Tool (REQueST) has been developed to support more systematic and wide-spread use of registry data in HTA and for regulatory purposes. It will support consistent evaluation of the suitability and reliability of registries for HTA . The tool uses criteria and standards published in existing guidelines, frameworks and projects, as well as several newly developed criteria. It is designed to be useful in several potential contexts; by registry owners to develop the quality of their registry, and by international organisations (HTA and regulatory) considering whether to use registry data in evidence development.

The tool is designed to be used in three steps (see 'Instructions for use' worksheet for more information):

A) 'Methodological Information' - Screening step to identify registries whose data and methodology match the requirements of the HTA/regulatory study or research question(s)

B) 'Essential Standards' - Assessment of registry governance to assure general data quality and protection

C) 'Additional Requirements' - Specialist requirements for the specific evidence questions

Note: Users may wish to add requirements into sections for their own purposes including for example required file format, timelines for response, content limits, colour coding etc.

Definitions

A patient registry has been defined as an organised system that collects data and information on a group of people defined by a particular disease, condition, exposure or health-related service and followed over time, and that serves a pre-determined scientific, clinical and/or public health (policy) purpose. Although the terms 'registry' and 'study' are sometimes used interchangeably, it should be noted that the tool is intended to be used for registries (data collection systems). Registry-based studies will benefit from quality assessment of the registry platform but will have other specific requirements that need additional review (a registry-based study is an investigation set up to answer a research question that uses data collected in a registry).

Patient registries can be used as a source of real world data for evidence generation for HTA purposes. In addition data from registries can be used for epidemiological and quality control aims and, if they are (nearly) completely recorded and monitoring is systematic, they can help in recording late-occurring or rare (unintended) events. The specific contribution to HTA of real world data lies in the potential to measure a technology's effectiveness (e.g. how well a technology performs as intended in the general population of patients, and in the less controlled environment of clinical practice), as opposed to clinical studies that measure efficacy (e.g. how well a technology performs in a setting of carefully selected patients and a controlled protocol). The REQueST tool is designed to support the collection of real world evidence whilst minimising potential bias.

Data from patient registries are used in two main ways. From pre-existing patient registries as a form of secondary data use and, new patient registries as a form of primary data use, in accordance with the HTA research question.

Although registries have been recognised as an important source of data and information, both during the pre- and post-launch phases of technology lifecycle and related assessments, until now only limited published examples are available on the use of registries by HTA organisations in Europe.

Development of REQueST

REQueST has been developed by activity centre partners in support of the European network for Health Technology Assessment Joint Action (EUnetHTA JA3) work package 5 strand B2 work. As part of this work, a survey was conducted to explore the current understanding and use of registries by HTA agencies and the employment of any standards/criteria or other tools to assess the quality and comparability of registries before their use in HTA. The results showed that the real world data from registries is used more extensively than previously described in the literature, and for more 'advanced' inputs into the HTA process (effectiveness and safety) than previously described (mostly 'basic' epidemiological data like prevalence and incidence). The results from the survey strengthen the need for developing a standardised tool to assess governance and data quality of registries before their use in health technology assessment.

This tool is part of the EUnetHTA JA3 project which has received funding from the European Union's Health Programme (2014-2020).

Instructions for use

Instructions on how to complete the evaluation by section

REQueST is designed to provide a framework for registry owners to demonstrate the quality of their data collection and for HTA/regulatory professionals to transparently as

The HTA agency/regulatory body may wish to provide an outline of the proposed use of the registry in order to help the registry owner to address the specific needs of the

The registry owner provides the information about the registry, and the HTA/regulatory professional evaluates the information supplied.

The evaluation should be done in 3 steps, in a consecutive manner:

A) 'Methodological Information' - Screen for registries whose data and methodology match the requirements of the HTA/regulatory study or research question(s)
'Methodological Information' refers to the methodology used and the data contained in the registry. This section provides an opportunity for the HTA or regulatory body to data collected by the registry. Providing methodological information demonstrates a registry's transparency and readiness, and the ability of the registry to answer a specifi

This information should be assessed by the HTA agency or regulatory body to make sure the data and methodology match the requirements of the HTA's evidence question methodology of the registry meet the user's needs, the registry quality should be evaluated against the essential standards.

B) 'Essential Standards' - Assessment of registry governance to assure general data quality and protection
'Essential Standards' are the minimum requirements for every registry. They are universal and essential elements of good practice and evidence quality. Unless all essential demonstrated to be met, the HTA should not use the registry for evidence development.
In this section the evaluation is done by comparing the information provided by the registry to the minimum essential standard.

C) 'Additional Requirements' - Specific requirements for the evidence questions
'Additional Requirements' are elements of good practice and evidence quality which are not always practical, feasible or necessary to achieve, but may be important to spe Evaluation of the 'Additional Requirements depends on the requirements of an individual HTA agency or regulatory body. Suggested basic standards are described here for meet the HTA agency or regulatory body's needs.
In this section the HTA agency or regulatory body judges whether the level of evidence provided is sufficient and whether the information meets the requirements of that H

Evaluation results are automatically generated by the tool and can be found in the 'Output' worksheet.

The definitions of the tool items as well as further explanation of how to use the tool for specific items are to be found in the 'Glossary and explanations' worksheet.

Implementation of this tool requires an infrastructure a 'vision' for which has been set out in an accompanying paper. Sections 19 to 23 of the vision paper describe seve delivery, use and sustainability of REQueST. Different organisations may complete the various sections of the tool, depending on the phase of the tool's implementatior will be developed to provide greater detail on requirements as the later phases of the vision are implemented.

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Methodological Information

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Registry Evaluation and Quality Standards Tool (REQueST)

Instructions on how to complete the evaluation for 'Methodological Information':

This section of the tool is designed to collect information on the methodology used and the data contained in the registry. It should be used by the HTA agency or regulator, to make sure the methodology and data match the requirements of the evidence gap or research question(s). Although the questions do not provide insight into the quality of the registry, they should be answered in order to allow the HTA agency/regulator to decide whether or not the registry is suitable for the evidence development required.

Item number	Area	Item and format required	Column completed according to the data provided in the IPIG PNH Registry Protocol and communication with IPIG and vendor [redacted]	Does the information meet the PASS requirements? (Select one option) *To be completed by the Novartis assessor*	Comments *To be completed by the Novartis assessor*	
1	Type of registry	Specify the type of registry which defines the patient population, all the health interventions included in the registry and the registry objectives (primary and secondary). Free text/short summary + online link	Disease Registry: Patients with PNH confirmed by flow cytometry who do not currently participate in an interventional PNH clinical trial. All patients with PNH will be eligible, regardless of the type of therapy they are receiving.	Satisfactory	Note: here and below all data is extracted from the IPIG PNH Registry Protocol	
2	Use for registry-based studies and previous publications	Can the registry be used as a platform for prospective registry-based studies? Provide weblink to publications. Free text/short summary + online link	Yes, access to data for patients treated with PNH-specific therapies may be provided to respective MAHs ("product-specific silo")	Satisfactory	Access may only be provided to data for patients treated with MAH's own product, comparative studies not possible	
3	Geographical and organisational setting	Specify the geographical area of the registry and organisational setting. List the data providers (type of providers and the number of sites) participating in the registry. Free text/short summary + online link	Currently planned: Australia, Brazil, Canada, China, France, Germany, Italy, Japan, South Korea, Spain, Switzerland, United Kingdom, United States	Satisfactory	Further countries may be added. Participating HCPs are selected among the PNH KOLs that are treating several patients in their practice. In the extremely rare disease setting this is considered to be an acceptable approach	
4	Duration	Specify the start and, if relevant, final date of data collection (duration). Indicate if the content (e.g. variables or coding) of the registry has changed in any significant way over time) Numeric and free text	FPFV: Q4 2023 End of data collection: currently not defined, however, each patient is expected to be followed up for up to 5 years	Satisfactory	Planned duration of follow-up is satisfactory to conduct a safety study	
5	Size	Provide the total number of patients included in the registry. When was this number calculated? Numeric and date Provide the percentage of the patient population who meet selection criteria and who have participated in the registry. Percentage and free text explanation if necessary	Expected total enrollment: 2000	Needs development / clarification	Some concerns exist on how this number is expected to be reached, e.g. not all sites in all countries were initiated as planned. Topic needs further clarification	
6	Inclusion and exclusion criteria	List the inclusion and exclusion criteria. Free text/short summary + online link	PNH confirmed by flow cytometry, signed ICF. Exclusion: participation in an PNH clinical trial.	Satisfactory	Broad inclusion criteria serve to maximise patient population	
7	Follow-up	Describe the methodology for the follow-up. What is the average follow-up period per patient in months? How do you predict and prevent loss to follow-up? Free text	Study visits expected to be approximately every 6 months; follow up for up to 5 years	Satisfactory	Data is collected by specialized hematology centers so LTFU is expected to be a relatively minor issue	
8	Confounders	Are data relating to potential confounders collected and identified for a specific registry use as appropriate. Specify techniques to prevent or control the potential confounders. Free text	Detailed patient history, laboratory values, pregnancy history is collected	Satisfactory	All key variables relevant to PNH history and treatment as well as the outcomes are collected in the registry	FALSE

Essential Standards

Instructions on how to complete the evaluation for 'Essential Standards':

If the data and methodology of the registry meet the HTA agency/regulator's needs, the registry is being evaluated against the 'Essential Standards'.
'Essential Standards' are the minimum requirements for every registry. They are universal, essential elements of good practice and evidence quality. Unless all essential criteria are satisfa
In this section the evaluation is done by comparing the level of evidence given to the minimum essential standard.

Item number	Area	Minimum standard	Assessment criteria	Item and format required
9	**Registry aims and methodology**	Registry has stated aims, objectives and methodology.	Registry has specified objectives, target population, exposures of interest, primary and secondary outcomes, data sources, linkage (and analysis plans if any). If the documentation is more than 5 years old, the current status should be checked with the registry coordinator or participant.	Provide the registry documentation of aims, objectives and methodology. Document file format
10	**Governance**	Registry governance is in place.	An independent steering committee or a governing body and a data quality team with specified responsibilities are in place. These should include patient representation. Registry governance should have an audited process for declarations of interest covering all financial contributions to the work. Employees of the relevant manufacturers, close relatives who have a position of responsibility within these manufacturing companies or close relatives with financial interests in the capital of these manufacturers could have a declared role in data analysis for the specified HTA project as long as the declared interests are considered not to affect the validity of the data.	Describe the registry governance structure. Provide documentation of the research ethics approval (or equivalent as appropriate) and all declarations of interest. Free text
11	**Informed consent**	Protection of privacy rights is assured for the persons whose health-related data is recorded.	The informed consent document should explain to potential participants • the nature, purpose of the registry and whether secondary analysis may be undertaken, • why they are candidates for participating in the registry, • what risks, benefits, and abernatives are associated with the participation • what rights they have as research subjects. If the documentation is more than 5 years old, the current status should be checked with the registry holder.	If the registry requires individual informed consent for recording personal data (registry's primary purpose), provide the consent document (document file format). Or, if regulations exist for the management of data in the absence of informed consent, describe authorisation received for this. Free text
12	**Data dictionary**	The data set has a data dictionary or similar.	The data dictionary should contain identifying attributes (name, ID), definitional attribute (definition of data element, where also the purpose of the data element is described), and representational attributes (permissible values, representation class, data type, format). The data dictionary defines terms needed to answer the registry's research questions and objectives. If the documentation is more than 5 years old, the current status should be checked with the registry coordinator or participant.	Provide a documented data dictionary. Check that the data dictionary can be expanded as necessary for a specific purpose. Document file format
13	**Minimum data set**	The registry has a defined minimum data set.	The registry has a defined minimum data set that is able to answer the registry's research questions and objectives. If new fields are required for a specific purpose, the registry is able and willing to make the necessary changes. If the documentation is more than 5 years old, the current status should be checked with the registry coordinator or participant.	Provide a minimum data set. Document file format
14	**Standard definitions, terminology and specifications**	Standard definitions, terminology and specifications are being used.	Name of the standard, category of data (diagnosis, procedure, medication) and usage of the standard (organising, storing, managing or protecting the data sets) should be provided.	Specify national/international data standards used for organising, storing, managing and protecting the data sets. Free text
15	**Data collection**	Data collection is described.	Data collection methods are realistic (e.g. software requirements acceptable to submitters) for the proposed population and treating centres with clear access rights.	Describe the data collection procedure, pathway of submission, how data are submitted and access rights to the registry. Free text/flow chart
16	**Quality assurance**	The registry has a quality assurance plan including assured delivery of continuous and comprehensive data submission.	Quality assurance activities relevant for the registry need to described.	Specify the quality assurance activities. Provide at a minimum details of data validation methods, accuracy checks, routine completeness and coverage estimates.
17	**Data cleaning**	A plan for cleaning the data is described.	There is a plan for cleaning the data that includes the time required for cleaning after closure to data submission.	Describe the data cleaning plan. Free text
18	**Missing data**	A plan to manage missing data is described.	The percentage of missing data for the core outcomes has been provided. An explanation is given for whether missing data may potentially bias results.	Describe the analytical plan for missing data (complete analysis or imputation?) Free text
19	**Financing**	The financing of the registry is transparently presented.	Financial security to the end of the evidence development period should be demonstrated in the financial plan, solvency with a summary of income and expenditure for the previous 2 years is recommended. Also, funding sources are identified and the approx. proportions (%) of total sum from each funding source is indicated. If the documentation is more than 5 years old, the current status should be checked with registry coordinator or participant.	Provide a financial plan (or similar) of the registry. Demonstrate financial security for proposed evidence development period. Document file format
20	**Protection, security and safeguards**	Data security risks, policies and procedures are described. The registry has a policy for data sharing.	The security controls specific for the registry should be specified. Risks should be identified and appropriate mitigation described.	Describe in detail the data security risks, policies and procedures specific to the registry. Free text

Additional Requirements

Instructions on how to complete the evaluation for 'Additional Requirements':

'Additional Requirements' are useful extra items of information, relevant to evidence quality but which are not always practical or feasible to achieve. They may be useful to consider in planning and evaluating registries for specific purposes.
Evaluation of the 'Additional Requirements' depends on the requirements of an individual HTA agency or regulator and the specific evidence gap.
In this section the HTA agency/regulator judges whether the level of evidence given is enough and whether the information meets its requirements.

Item number	Area	Standard/requirement and format of the requested data	Assessment criteria	Column completed according to the data provided in the IPIG PNH Registry Protocol and communication with IPIG and vendor [redacted]	Does the information meet the HTA agency/regulator's needs? (Select one option) *To be completed by the Novartis assessor*	Comments *To be completed by the Novartis assessor*
21	**Interoperability and readiness for data linkage**	Registry shares data with interested parties. 1. Document file format 2. Data format: CDISC 3. AE reporting in the study database and forwarding to Novartis according to standard timelines 4. Data is provided to Novartis at least 3 times per year at previously agreed milestones 5. Free text	1. Data access and sharing procedures documentation are uploaded. 2. Average time to answer an information query and to undertake data linkage is specified. 3. Statements regarding usage of data and consent for data sharing (and with whom) are provided. These cover sharing of registry data with interested parties from other countries and/or international organisations. 4. Technical standards, data structure, and standard sets for measuring health outcomes and internationally agreed minimum data set is specified. 5. Existence of specific fees in providing access to data and data linkage are clarified.	1. Data access and sharing procedures documentation have not yet been provided to Novartis 2. Data format: CDISC has been agreed and confirmed by all stakeholders 3. AE reporting data format and modality: discussions with [redacted] ongoing 4. Data transfer frequency has been agreed with IPIG	Needs development / clarification	Data linkage: not applicable Further clarification on the data management aspects is pending from [redacted] as summarized to the left
22	**Data sources**	All data sources are identified. Predefined, multiple choices. If 'Other' - Free text	Sources of data are identified. If the sources of data for the registry are not listed, please select 'Other' and describe the data sources in text.	Data source: hematology specialists that agreed to participate in the registry data collection. No linkage planned	Satisfactory	
23	**Ethics**	An ethical committee is involved in governing the usage of data. Free text	Consideration of research ethics requirements has been reported. If a research ethics committee approved the working procedures/ methodology of the registry, the process of obtaining approval is described.	Protocol: the registry shall be conducted in compliance with ISPE GPP guidelines, the ethical principles of the Declaration of Helsinki, the EU GVP, European and National laws in terms of data protection and all	Satisfactory	Study is submitted to the relevant IRB/IEC for approvals before starting the patient enrollment

Output

Registry Evaluation and Quality Standards Tool (REQueST)

Instructions

Individual scores are automatically copied from the 'Methodological Information', 'Essential Standards' and 'Additional Requirements' worksheets. The area score is automatically generated by the tool.

Registry name: **IPIG PNH Registry**
Date of assessment: **10-Sep-23**

Satisfactory
Needs development / clarification
Not suitable

Area	Item	Colour rating
Methodological Information	1. Type of registry	
	2. Use for registry-based studies and previous publications	
	3. Geographical and organisational setting	
	4. Duration	
	5. Size	
	6. Inclusion and exclusion criteria	
	7. Follow-up	
	8. Confounders	
Essential Standards	9. Registry aims and methodology	
	10. Governance	
	11. Informed consent	
	12. Data dictionary	
	13. Minimum data set	
	14. Standard definitions, terminology and specifications	
	15. Data collection	
	16. Quality assurance	
	17. Data cleaning	
	18. Missing data	
	19. Financing	
	20. Protection, security and safeguards	
Additional Requirements	21. Interoperability and readiness for data linkage	
	22. Data sources	
	23. Ethics	

Glossary and explanations

Term	Area	Definition	Explanation for use in REQueST	Reference source
Registry	**General**	An organised system that collects data and information on a group of people defined by a particular disease condition exposure or health-related service and followed over time and that serves a pre-determined scientific clinical and/or public health (policy) purpose.	'Registry' is the organisation and system that supports one or a number of individual databases or 'registers'. In the EUnetHTA JA3 WP5B deliverables the term 'register' will be used only to indicate the list of items names or other data of interest.	Zaletel M Kra j M (Eds). Methodological guidelines and recommendations for efficient and rational governance of patient registries. 2015. National Institute of Public Health Ljubljana. Available from: https://ec europa.eu/health/sites/health/files/ehealth/docs/patient_registries_guide ines_en.pdf https://www.ema.europa.eu/en/human-regulatory/post-authorisation/patient-registries
Registry-based study protocol	**General**	The plan or set of steps to be followed in a study.	The methodology of registry-based studies should be consistent with the registry policies and procedures.	http://htaglossary.net/protocol ENCePP European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. ENCePP Guide on Methodological Standards in Pharmacoepidemiology. Available from: http://www.encepp.eu/standards_and_guidances/methodologicalGuide.shtml
Type of registry	**Methodological Information**	REQueST uses the following patient registry classifications: • A disease or condition registry is a registry defined by patients with a common disease or condition. • A pharmaceutical registry is a registry defined by patients who take or have taken a particular pharmaceutical product. • A medical technology registry is a registry defined by patients who have been exposed to a particular device or diagnostic technology. • A procedural registry is a registry defined by patients who have	Specify the type of registry which defines the patient population all health interventions included in the registry and the registry objectives (primary and secondary).	Methodological information - REQueST. Categories developed for this programme of work. ENCePP European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. ENCePP Resources Database. Available from: http://www.encepp.eu/encepp/resourcesDatabase.jsp
Use for registry-based studies and previous publications	**Methodological Information**	The registry should have primary and secondary objectives.	The registry objectives may include the possibility of running a registry-based study which would have its own aims and objectives (consistent with those of the registry but usually answering a specific research question or evidence gap).	Zaletel M Kra j M (Eds). Methodological guidelines and recommendations for efficient and rational governance of patient registries. 2015. National Institute of Public Health Ljubljana. Available from: https://ec europa.eu/health/sites/health/files/ehealth/docs/patient_registries_guide ines_en.pdf http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-160930-principles-system-registries.pdf
Geographical and organisational setting	**Methodological Information**	The geographical area and organisational setting from which the registry recruits investigators and patients as well as collects data. Examples of types of data providers: Clinical units (within hospitals practices outpatient clinics etc); Laboratories/central services (biochemistry pathological services genetic Rx etc); Discharge registries; Patients and families; Patients' groups (associations/federations); Disability registries; Centres of expertise; Birth registries; Cause of death registries; Insurance funds (public and private). REQueST was originally designed as a tool for Health Technology Assessment (HTA) but its principles are applicable to regulatory and academic work and therefore it may be used in wide contexts.	Specify whether the registry is run on local national or international level and which geographical area the registry covers. Also provide the type of data providers participating in the registry.	https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/registries-guide-2nd-edition_research.pdf
Duration	**Methodological Information**	Specify the start and if relevant final date of data co lection (duration). Indicate if the content (e.g. variables or coding) of the registry has changed in any significant way over time).	No additional explanation.	https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/registries-guide-2nd-edition_research.pdf
Size	**Methodological Information**	Description of the absolute number and proportion of the eligible population which is recruited into the registry.	No additional explanation.	https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/registries-guide-2nd-edition_research.pdf
Inclusion and exclusion criteria	**Methodological Information**	The inclusion criteria are the set of conditions that a patient must meet to be eligible for inclusion in a registry and generally include geographic demographic disease-specific time-specific laboratory-specific and other criteria. The exclusion criteria are the criteria that disqualify patients from inclusion in the registry.	An example of how to answer this item: Registry example: The Pulmonary Fibrosis Foundation Patient Registry (source: https://www.pulmonaryfibrosis org/medical-community/pff-patient-registry) Inclusion criteria: 1. 18 years old or older. 2. Understand and sign the informed consent document. 3. ILD diagnosis must be made/confirmed at a participating Registry center. a. The diagnostic evaluation must include at a minimum a medical history physical examination pulmonary function testing and a computerized tomography (CT) scan of the chest. b. If patients exhibit another pulmonary disease (such as emphysema or asthma) the primary disease must be ILD. 4. Anticipated additional follow up at the Registry center within one year. Exclusion Criteria 1. Diagnosed with: a. Sarcoid b. Lymphangioleiomyomatosis (LAM) c. Pulmonary alveolar proteinosis (PAP) d. Cystic fibrosis (CF) e. Amyloidosis.	Zaletel M Kra j M (Eds). Methodological guidelines and recommendations for efficient and rational governance of patient registries. 2015. National Institute of Public Health Ljubljana. Available from: https://ec europa.eu/health/sites/health/files/ehealth/docs/patient_registries_guide ines_en.pdf
Follow-up	**Methodological Information**	The period of patient observation for a registry. It can be sub-classified as follows: • Active fo low-up is the period of registry patient observation where information is obtained directly from the registry patients. • Passive follow-up is the period of registry patient observation where information is obtained from linkage to existing database.	The methodology for the follow-up can be described as active follow-up passive follow-up or mixed follow-up.	Zaletel M Kra j M (Eds). Methodological guidelines and recommendations for efficient and rational governance of patient registries. 2015. National Institute of Public Health Ljubljana. Available from: https://ec europa.eu/health/sites/health/files/ehealth/docs/patient_registries_guide ines_en.pdf
Confounders	**Methodological Information**	Confounding factors are variables that influence both the exposure to treatment and the outcome in the analyses and can confuse analysis results and interpretation of causality.	Confounding can include patient factors provider factors and system factors. Control of confounding factors can be done in the design and analysis phases. While it is not possible to identify all confounding factors in the advance of data construction it is desirable to give serious thought to what will be important and how the necessary data can be collected.	https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/registries-guide-2nd-edition_research.pdf
Registry aims and methodology	**Essential Standards**	The stated aims objectives and methodology of the registry.	Documenting registry policies and procedures enables the registry to become more process dependent than person dependent potentially enhancing data quality stability and reliability.	Zaletel M Kra j M (Eds). Methodological guidelines and recommendations for efficient and rational governance of patient registries. 2015. National Institute of Public Health Ljubljana. Available from: https://ec europa.eu/health/sites/health/files/ehealth/docs/patient_registries_guide ines_en.pdf
Governance	**Essential Standards**	An organisational foundation of patient registries mostly concerned with guidance and decision making.	Registries fulfil governance roles in a variety of ways for example through a project management team clinical/subject matter board scientific committee data collection and database management board legal/patient privacy team quality assurance team etc. Many of the roles could be assumed by a single committee (e.g. a steering committee). Whichever model is adopted it must accommodate all of the working constituencies and provide a mechanism for those individuals to work together to achieve the goals of the registry. Managing conflicts of interest is vital to transparency of governance.	Zaletel M Kra j M (Eds). Methodological guidelines and recommendations for efficient and rational governance of patient registries. 2015. National Institute of Public Health Ljubljana. Available from: https://ec europa.eu/health/sites/health/files/ehealth/docs/patient_registries_guide ines_en.pdf
Informed consent	**Essential Standards**	A person's agreement to allow personal data to be provided to the registry.	Securing the privacy of the patients or research subjects is an essential task when establishing and maintaining a patient registry or when conducting registry-based research. Moreover when processing personal data the data controller has to take into account not only legal but also ethical perspectives. Informed consent refers to a person's agreement to allow personal data to be provided for the registry.	Zaletel M Kra j M (Eds). Methodological guidelines and recommendations for efficient and rational governance of patient registries. 2015. National Institute of Public Health Ljubljana. Available from: https://ec europa.eu/health/sites/health/files/ehealth/docs/patient_registries_guide ines_en.pdf
Data dictionary	**Essential Standards**	Set of information describing the data elements and how those data elements are interpreted. The data dictionary contains a detailed description of each variable used by the registry including the source of the variable coding information if used and normal ranges if relevant.	Data elements should be well-documented and readily accessible to everyone who is interested in a registry's data set. Well-documented and transparent data elements give an understanding of the collected data and ensure consistency in the data collection process. Therefore it is important that a registry establishes an inventory of all data elements/variables included in the registry. The data dictionary should define elements needed to answer the research questions and objectives.	https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/registries-guide-2nd-edition_research.pdf
Minimum data set	**Essential Standards**	List of data elements/variables that are essential to collect the data for any case/subject.	As a minimum registry planners must account for the minimum data set when calculating the resource needs and overall design of the registry. It is recommended that a minimum data set should contain the following information: identifying attributes (name ID) definitional attribute (definition of data element where also the purpose of the data element is described) and representational attributes (permissible values representation class data type format).	Zaletel M Kra j M (Eds). Methodological guidelines and recommendations for efficient and rational governance of patient registries. 2015. National Institute of Public Health Ljubljana. Available from: https://ec europa.eu/health/sites/health/files/ehealth/docs/patient_registries_guide ines_en.pdf https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/registries-guide-2nd-edition_research.pdf
Standard definitions, terminology and specifications	**Essential Standards**	Essential standards are common registry data elements which facilitate consistency comparability data exchange and reuse.	It is important to ensure that the specifications of the data are consistent with national and international data standards. This avoids duplication of effort and the development of conflicting data standards. Designing the registry with respect to national and international standards is essential for improving data quality. Some examples of data standards are: terminology standards (CTS2 standard SNOMED-CT ICD10 ATC LOINC ICPC-2 ICHI ICF DRG) structure/exchange standards (OpenEHR HL7 RIM CDA C-CDA HL7 FHIR I2b2 ISO/CEN 13606 Clinical information modelling initiative) metadata standards (ISO/CEN Metadata standard 11179 Dublin Core Metadata).	Zaletel M Kra j M (Eds). Methodological guidelines and recommendations for efficient and rational governance of patient registries. 2015. National Institute of Public Health Ljubljana. Available from: https://ec europa.eu/health/sites/health/files/ehealth/docs/patient_registries_guide ines_en.pdf https://www.ichom.org/
Data collection	**Essential Standards**	The process of gathering data to get a complete and accurate picture of an area of interest of the registry.	The registry should have a detailed procedure plan for the entire data collection and provide methodological guides/standard instructions and rules for data collectors/providers and other data users. This typically includes information on reporting dynamics which data need to be collected and how means of data transmission established controls for the acquired data (e.g. readability of data adequacy of records and their number) and access rights. The registry should find resources for continuous data collection.	Zaletel M Kra j M (Eds). Methodological guidelines and recommendations for efficient and rational governance of patient registries. 2015. National Institute of Public Health Ljubljana. Available from: https://ec europa.eu/health/sites/health/files/ehealth/docs/patient_registries_guide ines_en.pdf https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/registries-guide-2nd-edition_research.pdf
Quality assurance	**Essential Standards**	Quality standards for the registry data procedures and computerised systems to be followed in order to meet the quality requirements.	Registry planners should consider how to ensure quality to a level sufficient for the intended purpose(s) and how to develop appropriate quality assurance plans for their registries. Those conducting the registry should assess and report on those quality assurance activities.	ENCePP European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. ENCePP Guide on Methodological Standards in Pharmacoepidemiology. Available from: http://www.encepp.eu/standards_and_guidances/methodologicalGuide.shtml https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/registries-guide-2nd-edition_research.pdf
Data cleaning	**Essential Standards**	Data control and cleaning of patient registries is the process by which erroneous data are removed or fixed.	The plan for cleaning the data should take into account the following types of data anomalies: lack of data duplicates data inconsistency and out-of-range values. Data quality reporting should include assessments of population coverage validity and reliability of measurements.	Zaletel M Kra j M (Eds). Methodological guidelines and recommendations for efficient and rational governance of patient registries. 2015. National Institute of Public Health Ljubljana. Available from: https://ec europa.eu/health/sites/health/files/ehealth/docs/patient_registries_guide ines_en.pdf
Missing data	**Essential Standards**	The process by which missing data are filled.	Missing data should be treated with care to avoid the potential introduction of bias. The analytical plan for missing data (complete analysis or imputation) should take into account the size of the data set and the reasons why data are missing (random or otherwise). Linking to external databases can provide a source to fill missing values. Special codes or flag variables should be set to distinguish corrected fields.	Zaletel M Kra j M (Eds). Methodological guidelines and recommendations for efficient and rational governance of patient registries. 2015. National Institute of Public Health Ljubljana. Available from: https://ec europa.eu/health/sites/health/files/ehealth/docs/patient_registries_guide ines_en.pdf
Financing	**Essential Standards**	Financial resources used to ensure the sustainability continued relevance and maximum impact of the data for which the registry coordinators are responsible.	The financial plan should take into account initial development of the registry including infrastructure database user training costs etc. and longer-term maintenance including periodic evaluations and additional analyses.	Zaletel M Kra j M (Eds). Methodological guidelines and recommendations for efficient and rational governance of patient registries. 2015. National Institute of Public Health Ljubljana. Available from: https://ec europa.eu/health/sites/health/files/ehealth/docs/patient_registries_guide ines_en.pdf
Protection, security and safeguards	**Essential Standards**	Measures implemented in order to maintain the privacy of participants enrolled in a registry and data confidentiality.	All security measures should be contained in a document that describes in detail the data security risks policies and procedures specific to that registry. International standard ISO/IEC 27002 includes a range of activities related to security policies processes procedures organisational structures software and hardware. Some of the controls are: a) Administrative information security policy controls which provide direction and support for information security in accordance with business and legal requirements and initiate the implementation and operation of information security within registry systems; (b) Human resource security controls which ensure that staff and contractors understand their responsibilities; (c) Access controls which limit access to information and information processing facilities; (d) Cryptography controls which ensure proper and effective use of cryptography in order to protect the confidentiality authenticity and/or integrity of information; (e) Physical and environmental security controls which prevent unauthorised physical access and damage to as well as interference with information and information processing facilities.	https://www.iso27001security.com/html/27002.html#StructureAndFormatOfISO17799
Interoperability and readiness for data linkage	**Additional Requirements**	In the broadest sense stands for "ability to operate with others". It can be applied to any situation where two or more entities achieve their goals or purpose by successfully interchanging services.	Sharing registry data with other interested parties signifies the registry's willingness to connect with others for mutual benefit along with a certain level of interoperability. Procedures for granting access to or sharing data in a cross-border context must be in place preferably including pre-defined response time targets. An organisational culture oriented towards as well as appreciative of data utilisation beyond its own remits combined with appropriate resourcing are essential elements in achieving a high level of preparedness. Collaboration with other registry holders is advisable in order to exchange experiences advice and ideas.	Zaletel M Kra j M (Eds). Methodological guidelines and recommendations for efficient and rational governance of patient registries. 2015. National Institute of Public Health Ljubljana. Available from: https://ec europa.eu/health/sites/health/files/ehealth/docs/patient_registries_guide ines_en.pdf
Data sources	**Additional Requirements**	Modes of data co lection for the registry.	The registry should take into account the technological aspect of data collection (e.g. paper-based forms web-based data entry) and be aware of advantages and disadvantages of both paper-based and electronic approaches. Important characteristics of paper-based methods is that they are inexpensive and easy to create and develop but in the registry's whole process they involve a substantial cost because they need to be recorded in an electronic way. Although the design of bespoke electronic solutions can be expensive their advantages are those of connectivity error minimisation and reduction of duplication.	Zaletel M Kra j M (Eds). Methodological guidelines and recommendations for efficient and rational governance of patient registries. 2015. National Institute of Public Health Ljubljana. Available from: https://ec europa.eu/health/sites/health/files/ehealth/docs/patient_registries_guide ines_en.pdf
Ethical committee	**Additional Requirements**	Group of people whose role is advising on the efficient and secure collection and sharing of health information evaluating information resources and publishing information about the delivery and performance of a registry	While this aspect is not critical in a functional sense there is an obligation to ensure that the registry complies with relevant ethical requirements.	Zaletel M Kra j M (Eds). Methodological guidelines and recommendations for efficient and rational governance of patient registries. 2015. National Institute of Public Health Ljubljana. Available from: https://ec europa.eu/health/sites/health/files/ehealth/docs/patient_registries_guide ines_en.pdf

Registry Evaluation and Quality Standards Tool (REQueST)

FAQs

Question	Response
Who by, and for what purposes, is the tool designed to be used?	REQueST is designed to be used by i) registry owners to assess the quality of their registry, and ii) international organisations considering whether to use registry data in evidence development for HTA and regulatory monitoring. The purpose is to highlight areas of a registry that need improvement in order to maximise the quality of its data and ensure that those data can be used for HTA and regulatory purposes.
Will REQueST be used to generate evidence for HTA agencies or regulators, or to evaluate evidence submitted by others to those bodies.	REQueST is designed to enable registry owners to develop robust data collection and analyses for use by HTA agencies and regulators. In line with this it should be used by HTA agencies and regulators to transparently assess the quality of data from registries.
What should the requirements for acceptance of criteria be?	Evaluation is done by comparing the information provided by the registry to the standard set out in the tool. The rigor of requirements should be appropriate to the nature of the technology and circumstance. They may increase as the phases of development are implemented. NB the reader should consult the vision paper for more information on the phases.
Are confounding data considered in REQueST, and how?	It is not possible to identify specific confounders for a whole registry. Confounders apply rather for registry-based studies addressing specific research questions. However, there may be cases in which confounders can be identified a priori. In registry-based studies, data are needed to distinguish between objectives of a descriptive nature like treatment patterns or prevalence or incidence of a condition, and studies with comparative effectiveness purposes where confounding is an important consideration.
Is REQueST evidence based?	PARENT is the main evidence reference for REQueST - further explanations are provided in the 'Glossary and explanations' worksheet.
Is REQueST designed to assess registry-based studies or Registries?	REQueST is designed to assess the quality of registries. Additional work would be required to review a proposed registry based study.
How does REQueST fit into the landscape of emerging guidance on registries?	REQueST is designed to be a simple tool that is based on international published guidance on registry methodology. It provides a transparent, clear summary of the strengths and weaknesses of a registry that users may wish to approach for purposes such as registry based studies, audit, simple data collection etc.
The 'Additional Requirements' should be essential. Why are they not all listed under 'Essential Standards'?	The issues are covered at a basic level in Essential Standards but more, study-specific requirements may be required e.g. not all registry data are intended to be shared across borders and not all registry data require research ethics approval (if intended for audit purposes only).