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Methodology

Development and Pilot Test of the Registry Evaluation and Quality Standards Tool: An Information Technology–Based Tool to Support and Review Registries

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ABSTRACT

Objectives: Health technology assessment (HTA) bodies are increasingly making use of real-world evidence and data. High-quality registries could be an asset for this; nevertheless, there is a lack of specified standards to assess the quality of data in the registry, or the registry itself. The European Network for Health Technology Assessment Joint Action 3 led the work to develop a tool for the evaluation of clinical registries: the "Registry Evaluation and Quality Standards Tool" (REQueST).

Methods: REQueST was developed in 4 steps: (1) A partnership between HTA bodies across Europe drafted the assessment criteria. (2) Multiple rounds of consultation across HTA bodies and the public domain developed an Excel version of REQueST. (3) This version was transformed into a web-based application. (4) An external pilot tested this REQueST tool with SMArtCARE and NeuroTransData registries.

Results: Haute Autorité de Santé, the National Institute for Health and Care Excellence, and the Croatian Institute of Public Health led the development of REQueST. Another 4 HTA bodies contributed regularly to development meetings, and all European Network for Health Technology Assessment partners were invited to contribute. Eight methodological, 12 essential, and 3 supplementary criteria were identified. Both pilot registries scored well, fulfilling the requirements for >70% of criteria, with none failed. Feedback by registry holders led to streamlining of the process and clarification of the criteria.

Conclusions: The REQueST tool uses an iterative and collaborative methodology with registry holders. It has the potential to maximize the utility of registry data for decision making by regulatory and HTA bodies and provides a foundation for future research.

Keywords: European Network for Health Technology Assessment, evaluation, health technology assessment, registry.

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Introduction

The need for high-quality evidence and the complexity of randomized controlled trials (RCTs), combined with the pressure for rapid review and implementation of promising new treatments, have led to the need for health technology assessment (HTA) bodies and healthcare services to develop improved methods for the assessment of new technologies.

Although RCTs remain the gold standard in terms of evidence generation, there is increasing emphasis on the importance of real-world data (RWD) and real-world evidence (RWE). RWD are data collected to observe routine practice, whereas RWE is the clinical evidence derived from analysis of RWD. RWD and RWE are derived from real-life patient use of new technologies and can therefore provide external validation of clinical trial evidence; nevertheless, the inclusion criteria of RWE tend to be less strict than required for RCTs. Initiatives aimed at improving the quality and transparency of the implementation and reporting of RWD[1,2] and the challenges associated with the use of RWD have been outlined in the literature.[3]

Several frameworks with multiple aspects in common with high-quality trial methodology have proposed key factors for quality assurance of RWE.

For example, Finger et al[4] published a tool in 2020 that provides a simple method to support assessment of the strength of evidence and certainty of conclusions drawn from RWE in retinal disease, Schneeweiss et al[5] had also proposed in 2016 a set of principles to ensure that RWE is meaningful, valid, expedited, and transparent, and Gliklich et al[6] published guidance in 2020 to be used as a foundation for a unified set of quality criteria to be used across sources of RWD and RWE in medical product evaluation. Additionally, Reynolds et al[7] have recommended that when assessing the governance of RWE the provenance (eg, data collection, recording, storage, timeliness), access (eg, costs of data

access, barriers to access, and need for ethics approval), and curation (eg, presence of a data dictionary, data completeness, and data transformation) should also be considered.

For several years, HTA bodies have used RWD to provide complementary clinical and economic data for assessment and appraisal. RWD sources can include registries, electronic health records, medical claims data, and patient generated data, among others. These data can contribute to access schemes put in place by HTA bodies themselves or in collaboration with Pricing and Reimbursement decision makers. Although many HTA bodies do collect or use registry data as a source, the policies vary both across agencies and within agencies, based on the context of the technology being assessed.[8]

The use of high-quality registries is particularly interesting for assessing technologies for rare conditions, where patient base is small and there is paucity of evidence in the literature.[9,10] As understanding of diseases increases, new treatment targets are identified, and technological advancements are emerging but with an attendant decrease in the available data at the time of marketing authorization.[11] Registries may provide a platform for adaptive studies that overcome limitations of conventional trials.

Despite this potential, data quality has been identified as a major challenge and a limitation for usage of RWD or its derived RWE in HTA.[12] The National Institute for Health and Care Excellence (NICE) performed a review of the quality of registries recommended to fill evidence gaps relating to their Interventional Procedures program.[13] The results showed high variability in quality, with a split between large registries that scored highly across all standards considered and smaller registries that scored poorly across all of them. Another key issue reported was that relatively few of the registries had reached maturity, questioning their appropriateness for RWE in the short term.

The Institute for Quality and Efficiency in Health Care using literature reviews and interviews with experts concluded that routine data could not feasibly be collected from patient records or insurance claims for the assessment of the benefit of interventions (at least in Germany).[14] The findings supported use of registries as an alternative and identified key categories for registry quality assessment (including population and inclusions/exclusion criteria, data dictionary, governance, quality assurance of data, and funding) and suggested study designs and data collection requirements for analyses of RWD for drug effectiveness. They recognized that quality criteria would vary based on the specific research questions being asked. It should be acknowledged in addition that countries differ in the quality of data used in national insurance claims so the findings may not be generalizable.

Finally, a survey of multiple HTA agencies across Europe showed that although many made use of registries to provide data, less than half made use of specified standards to assess the quality of the data in the registry, or the registry itself.[15] In response, the European Network for Health Technology Assessment (EUnetHTA) Joint Action 3 led the work to investigate and develop Registry Evaluation and Quality Standards Tool (REQueST). This is a practical tool aiming to support HTA bodies, evidence developers, and regulatory bodies to guide and assess the quality of registries used for RWE generation.

This article lays out the design and piloting of this tool and the key learning points from the process.

Methods

Development of REQueST Content

Haute Autorité Santé, the Croatian Institute of Public Health, and NICE led the development of the tool, in collaboration with other 4 other HTA bodies (AIFA, AQuAS, INFARMED, and Avalia-t). The draft tool had its foundations in the survey of HTA agencies,[13] published guidance, [4-8,16] and research into specialized treatments in rare diseases[17-19] and presents a way to implement the results of the Patient Registries Initiative Joint Action.[20]

Consultation to Refine the Content and Produce a Publicly Available Excel Draft Version

The draft tool went through several rounds of review and testing to repeatedly upgrade it in all domains (the first 3 rounds correspond to HTA exclusive feedback and the fourth to a public round):

- The first consultation targeted WP5 EUnetHTA partners in April/May 2018.[20]
- The second consultation included 13 WP5 partners, 7 external EUnetHTA partners, and the European Medicines Agency (EMA) feedback (November to December 2018).
- In parallel, 3 volunteering agencies (Avalia-t, AQuAS, and INFARMED) tested the use of the draft tool in their HTA activities (mitral valve, hepatitis C, and arthroplasties registries) and made recommendations for improvement that were implemented to improve its utility (October 2017-January 2019).
- Finally, the near-final version was submitted for public consultation.

All comments received during the different consultations were collated in a document together with responses from the REQueST development team and shared with the consultees.

Development and Testing of Online Version

An Excel version of the tool was approved by WP5B partners after pilot testing but feedback indicated that an online version would be more useful and user-friendly. Therefore, a SharePoint version using PowerApps functionalities was developed and approved by WP5B partners.

External Piloting With 2 Existing Registries and Evaluator

The online REQueST tool was piloted with 2 registries, SMArtCARE and the NeuroTransData. SMArtCARE[21] is a registry for spinal muscular atrophy, collecting longitudinal data across all neuromuscular centers in Germany, Austria, and Switzerland. NeuroTransData[22] is a registry for a range of neurological conditions, including both mental health (bipolar and schizophrenia) and neurocognitive disorders (including epilepsy, multiple sclerosis, and Parkinson's disease). It collects data from 66 outpatient centers across Germany. The registries were chosen because they covered relevant technologies that are collecting RWD to assist in evaluation and had expressed an interest and understanding of the goals of the EUnetHTA registry evaluations.

For the pilot, evaluators were drawn from NICE (United Kingdom), the Robert Koch Institute (Germany's national Public Health Institute), and the University of Duisburg-Essen, Germany. The Croatian Institute for Public Health acted as the moderator. R-connect Ltd facilitated the registry submissions to the pilot study.

A total of 3 project meetings were held over a period of 6 months to explain the process to participants, to assess progress and address technological tool problems, and to discuss findings.

The tool includes a handbook of terms and user instruction, and an additional pilot user sheet was produced to clarify the project methodology and enable feedback from participants. These 2 products allowed the dual purpose of the pilot project, not just for registry owners to receive feedback via the REQueST tool but also to allow the feedback from the REQueST users on the design and functionality of the tool.

Table 1. Summary of the domains in each section of the REQueST tool.

Methodological section (used to review utility of registry for specific purposes)	
Type of registry	Specify the type of registry that defines the patient population, all the health interventions included in the registry, and the registry objectives (primary and secondary).
Use of registry	Can the registry be used as a platform for prospective registry-based studies? Provide weblink to publications.
Geographical and organizational setting	Specify the geographical area of the registry and organizational setting. List the data providers (type of providers and the number of sites) participating in the registry.
Duration	Specify the start and, if relevant, final date of data collection (duration). Indicate whether the content (eg, variables or coding) of the registry has changed in any significant way over time.
Size	Provide the total number of patients included in the registry. When was this number calculated? Provide the percentage of the patient population who meet selection criteria and who have participated in the registry.
Inclusion and exclusion criteria	List the inclusion and exclusion criteria.
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?
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.
Essential criteria (applicable to all registries)	
Registry aims and methodology and design including:	Registry has stated aims, objectives, and methodology. Registry has specified objectives, target population, exposures of interest, primary and secondary outcomes, data sources, and 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.
Governance	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.
Informed consent	The informed consent document should explain to potential participants: • The nature and purpose of the registry and whether secondary analyses may be undertaken • Why they are candidates for participating in the registry • What risks, benefits, and alternatives are associated with the participation • What rights they have as research subjects 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 an informed consent, describe authorization received for this.
Data dictionary	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. The data dictionary can be expanded as necessary for a specific purpose.
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.
Standard definitions, terminology, and specifications	Name of the standard, category of data (diagnosis, procedure, medication), and usage of the standard (organizing, storing, managing, or protecting the data sets) should be provided. Specify national/international data standards used for organizing, storing, managing, and protecting the data sets.
Data collection	Data collection methods are realistic (eg, software requirements acceptable to submitters) for the proposed population and treating centers with clear access rights. Describe the data collection procedure, pathway of submission, how data are submitted, and access rights to the registry.

Table 1. Continued

Data quality assurance	Specify the quality assurance activities. Provide at a minimum details of data validation methods, accuracy checks, routine completeness, and coverage estimates. Quality assurance activities relevant for the registry need to be described. The registry has a quality assurance plan including assured delivery of continuous and comprehensive data submission.
Data cleaning	There is a plan for cleaning the data that includes the time required for cleaning after closure to data submission.
Missing data	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?).
Financing including:	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. In addition, funding sources are identified, and the approximate proportions (%) of the total sum from each funding source are 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.
Protection, security, and safeguards	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.
Additional criteria for specific purposes	
Interoperability and readiness for data linkage	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 organizations. 4. Technical standards, data structure, and standard sets for measuring health outcomes and internationally agreed minimum data set are specified. 5. Existence of specific fees in providing access to data and data linkage are clarified.
Data sources	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.
Ethics	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.

HTA indicates health technology assessment; ID, identification; REQueST, Registry Evaluation and Quality Standards Tool.

Results

Development of REQueST Content

The recommendations generated from the literature, the previous pilots, and the discussions with stakeholders included a focus on clear registry definitions and classification, on strong governance, including finance and legal requirements, a standard set of data elements, and a data dictionary and data quality assurance. These were used to develop the key areas of the REQueST tool summarized in Table 1.

Consultation to Refine the Content and Produce a Publicly Available Excel Draft Version

The draft tool was upgraded in all domains in response to the following feedback:

- A total of 12 WP5 EUnetHTA partners during the first consultation
- A total of 13 WP5 partners, 7 external EUnetHTA partners, and EMA feedback during the second consultation
- Recommendations for improvement as a result of pilot testing by Avalia-t, AQuAS, and INFARMED
- Responses from 17 organizations during public consultation including HTA bodies (of which 3 were WP5 partners), regulators, patient organizations, industry, health professionals, academia, and clinical research organizations

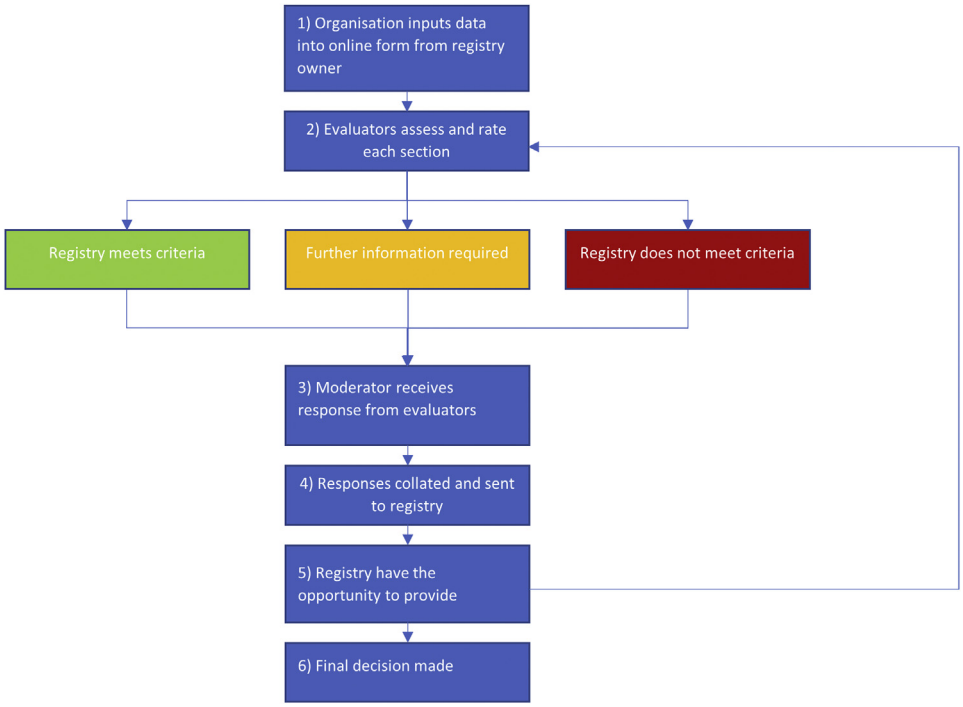
The final versions of the tool and of the accompanying vision article for future use of REQueST were published on the EUnetHTA website in October 2019.[23,24]

Development and Testing of Online Version

The REQueST evaluation online SharePoint platform uses PowerApps functionalities and is provided by EUnetHTA. It involves (1) a submission made by the registry owner responding to questions addressing the domains outlined in Table 1, (2) evaluation of the registry submission (typically by the HTA or other organization such as regulators wishing to use the data), (3) moderation of the assessment by a separate organization (in this case, an academic body) (the moderator's role is to provide a neutral party, collate the comments and rating for each section, and liaise with the registry), (4) a response to the registry owner from the moderator including clarifications and discrepancies, (5) collation by the moderator of registry answers, and (6) production of final feedback and decision to the registry. The process is summarized in Figure 1.

The REQueST output illustrates whether the registry meets each domain fully (green), partially (amber), or not at all (red), based on criteria laid out in the handbook. When partially met, the

Figure 1. REQueST workflow.



REQueST indicates Registry Evaluation and Quality Standards Tool.

REQueST assessors may ask for more information or make suggestions for further improvement. When the registry is assessed in the context of a specific health technology, detailed recommendations may relate to the need for a minimum data set with specific variables.

External Piloting With 2 Existing Registries and Evaluator

The 2 pilot registries generally performed well with no answers to sections failing absolutely to be suitable, and approximately 70% of the domains were rated "satisfactory" (17 of 24 items for SMArtCARE and 16 of 24 for NeuroTransData). Common domains that required more information were in the areas of governance, where additional information was needed particularly around the role of industry and quality assurance checks of the data, and in interoperability, particularly around semantic interoperability and coding.

There were substantial similarities between the areas in which further information was required. A summary of assessments given by the evaluators is presented in Table 2.[21]

Feedback from external piloting of REQueST

Both registry holders wished to provide their main information in attached documents and felt their answers to the questions within the tool would not be able to provide the full picture, corroborating the experience of the evaluators.

The extent to which the tool could accommodate the necessary information to fulfill the domains is difficult to resolve. Extensive references to linked articles gave the registries the ability to provide additional detail at the expense of more work for evaluators finding the information. A sensible compromise was agreed: proposing that registries should provide essential text in the tool with precise detailed references to additional relevant information in attached documents.

Another issue raised by the registry holders was that it was sometimes difficult to fully answer questions without the context of a specific technology and indication for which the registry data were to be used. All agreed that this would be preferrable for future pilot testing.

Feedback on technical issues

During this piloting process, a few technical issues were identified and solved, including the need to export and share the evaluators' outputs and some minor points including need to enlarge comment boxes that were too small for the more complex questions.

Although a handbook was written and provided alongside the tool, it was felt that this was often not used effectively and that a better system for both user and evaluators of REQueST would be to have help pop-up boxes or links directly related to the help and guidance on each section of the tool that was being used.

Discussion

The growing pressures and need for rapid assessment of innovative health technologies is increasing the need for integration of RWD evidence into the results from clinical trials in the evidence profiles. This has potential for a clash between the potential high standards set in clinical trials (in terms of the ability to reduce the effects of bias and confounding) and a tendency for lower standards in RWD.

The Patient Registries Initiative is the foundation for REQueST that is designed to be a way to implement its guidance. Other principles and standards published in existing guidelines, frameworks, and projects were used to refine the higher-level criteria in REQueST. It is the only tool currently available to bring together textual guidance and feedback to registry owners. It is designed to be used in several potential contexts, by registry owners to develop the quality of their registry and by international

Table 2. Key content discussion points with regard to the 2 included registries.

Topic	Key discussion points
Methodological criteria*	
Inclusion and exclusion criteria	SMArtCARE and NeuroTransData • Assessment comment: *More information needed on exclusion criteria; exclusion criteria should not be a description of the opposite of the inclusion criteria, and redundancy should be avoided.* • Registry response: *The included registries aim to include any patients fulfilling the relevant diagnostic criteria (spinal muscle atrophy or multiple sclerosis). This fulfillment of the relevant diagnostic criteria is the key inclusion criterion. No exclusion criteria are specified.* • Proposed resolution: *State that no exclusion criteria are defined.*
Geography description	NeuroTransData • Assessment comment: *How generalizable to other centers and patient demographics would this registry be? Could other sites be recruited, and how?* • Registry response: *Participating centers have to fulfill certain standard quality criteria such as, eg, DIN ISO 9001. Currently, NeuroTransData includes 66 certified centers. Other sites can be included if required quality criteria are fulfilled.* • *Noncertified centers can also use the registry as external sites, after comprehensive training and qualification. Data entry by external sites is also subject to the standard quality procedures implemented to ensure high data quality and density.* • Proposed resolution: *Specifically address the challenge of generalizability to noncertified centers when using the NeuroTransData registry data.*
Confounder	SMArtCARE and NeuroTransData • Assessment comment: *How have you approached/considered confounders in the analyses that have already been done/published?* • Registry response: *The NeuroTransData registry description includes an overview of key confounders such as selection bias, detection bias, observer bias, and recall bias. It further suggests that potential confounders are either added as predictors to statistical models or accounted for in propensity score weighting/matching. Previous analyses of both registries did not require detailed confounder assessments.* • *In previous NeuroTransData studies, specific sensitivity analysis and impact of unknown confounders were addressed using established statistical methods.* • Proposed resolution: *Contingent on the scope of requested analyses, a detailed description and discussion of confounders are recommended.*
Essential criteria†	
Governance	SMArtCARE and NeuroTransData • Assessment comment: *Please show working structure and sources of funding, role of manufacturers/industry within the registry to be clearly defined, and separation between data development and analysis and industry funding required.* • Registry response: *Working structure and sources of funding differ by specific project and analysis. For example, the German HTA body G-BA has mandated patients treated with onasemnogene abeparvovec to be included in the SMArtCARE registry.*§ *Funding will be partially derived by the industry; data development and analysis are conducted independently.* • *Two governing bodies (the Executive Steering Committee and the Registry Leadership Team) have been established to guide the NTD MS Registry to continuous success.* *The NTD MS Registry group is further organized in several layers of teams to provide for efficient flow of ideas, information, and decisions. The NeuroTransData registry database is entirely funded from the own resources of NeuroTransData GmbH.* • Proposed resolution: *Funding sources and in particular role of manufacturers should be provided for each analysis. Steps to ensure separation of data development and analysis from any conflict of interest should be clearly lined out.*
Data dictionary	SMArtCARE and NeuroTransData • Assessment comment: *Does data dictionary include any potential confounders? In addition, it is unclear how data dictionary would be expanded if needed.* • Registry response: *The data dictionary can be extended if needed, depending on the specific requirements of the respective scientific research question and protocol. See also response to methodological criteria "confounder." In addition, the list of confounding factors would need to be checked and—if required—amended by each analysis and project.* • Proposed resolution: *See proposed resolution to methodological criteria "confounder."*
Minimum data set	NeuroTransData • Assessment comment: *Unclear how the minimum data set would be expanded if needed.* • Registry response: *The NeuroTransData registry might be used for detailed analyses on 3 different levels: (1) planning and conducting clinical studies and noninterventional studies, (2) market and healthcare research, and (3) development of innovative database procedures (personalized medicine). The minimum data set may be expanded and additional data may be developed if required by any detailed analysis.* • Proposed resolution: *Each specific project to be conducted leveraging respective registry data should up front define required data set and determine optional additions to the minimum data set.*

continued on next page

Table 2. Continued

Topic	Key discussion points
Missing data	SMArtCARE and NeuroTransData • Assessment comment: *How much data are missing? How is the check for bias toward positive outcomes done? How are missing data reported?* • Registry response: *The SMArtCARE registry does provide information on data completeness (percentages of missing value).*‖ *Within NeuroTransData, missing data are notified in weekly reports and any missing data are flagged in query reports. Furthermore, it is important to notice that participation in registries is voluntary; ie, due to the "non-interventional character" of registries activities, missing data will always remain a key challenge with registries.* • *The proportion of missing data varies, depending on the protocol. Regarding the minimum data set, we observe < 10% missing data over the last 10 years. To identify possible bias toward positive outcomes, each analysis includes insight into data distribution and missing data.* • Proposed resolution: *Registry reports include information on missing data and information on how missing data were handled within the data analyses.*
Quality assurance	SMArtCARE and NeuroTransData • Assessment comment: *It would be helpful to see examples of external validation and case reports. Unclear whether any data linkage is conducted. The aim of data linkage is to check whether data triangulation is done against other sources as part of data validation.* • Registry response: *Both registries leverage various quality control mechanisms to ensure validity of data. Furthermore, NeuroTransData conducts an external audit process based on DIN ISO 9001 with each certification status lasting for 3 year.* • *Comparability between different registries is still at a very early stage due to different data definitions, data capturing procedures, and regional differences.* • Proposed resolution: *Registry reports and detailed analyses of data derived from the registries should include information on external validation and data linkage.*
Additional criteria‡	
Interoperability and readiness	SMArtCARE and NeuroTransData • Assessment comment: *A description of the system or standard guaranteeing the interoperability like SNOMED is missing* • Registry response: *No specific registry response* • Proposed resolution: *Registry reports and/or specific analyses based on the registries should provide information on applied standards regarding interoperability*

G-BA indicates Gemeinsamen Bundesausschusses; HTA, health technology assessment; NTD MS, NeuroTransData Multiple Sclerosis; SNOMED, Systematized Nomenclature of Medicine.
*No specific comments were raised with regard to the other additional criteria (type of registry, use for registry-based studies, duration, size, follow-up web link).
†No specific comments were raised with regard to the other additional criteria (registry aims and methodology, informed consent, standard definitions, data collection methods, data cleaning plan, financial security, security controls).
‡No specific comments were raised with regard to the other additional criteria (data sources, ethics, optional extra HTA-specific criteria).
§x-webdoc://FE950F40-D1FC-4033-B6CA-8289BE3E9BB9/www.g-ba.de/downloads/39-261-4702/2021-02-04_AM-RL-XII_awD_Onasemnogen-Abeparvovec_D-549_BAnz.pdf.
‖Pechmann et al (2019).[21]

organizations (HTA and regulatory) considering whether to use registry data in evidence development.

In practice, since its publication, the tool has been used in 2 EUnetHTA postlaunch evidence generation (PLEG) pilots, in EUnetHTA early dialogs/scientific advice to developers, and in several national PLEG activities. The EUnetHTA PLEG pilots used REQueST to assess the European Society for Blood and Marrow Transplantation registry and a product-specific PLEG pilot on left ventricular assist devices. In EUnetHTA early dialogs, HTA bodies used REQueST standards to give recommendations on usage of a specific registry for PLEG, whereas manufacturers used REQueST standards to discuss the rationale for choosing a specific registry for future PLEG. REQueST was also used in national PLEG activities; for example, in Spain, their HTA body (Red Española de Agencias de Evaluación de Tecnologías) has aligned their registry evaluation process with the REQueST framework.[25]

It is to be noted also that REQueST was referenced as a registry quality standard in the Report of the EMA[16] workshop on the use of registries in the monitoring of cancer therapies based on tumors' genetic and molecular features (held in November 2019). A checklist was subsequently added in appendix to EMA guidance, for evaluating the suitability of registries for registry-based studies.

Registries provide an important pillar of RWE, particularly in cases where the condition is rare or the technology is seldom used, providing observational data to evaluate current health technologies and as a platform for future research. The use and development of registries for specific HTA purposes require a set of standards to ensure and transparently assess the quality of the data collected. These should help to address the challenges of using RWD alongside clinical trials, namely:

- Differences in inclusion and exclusion criteria: registries aim to capture all patients with a condition, compared with a tightly controlled sample.
- Confounders: Registries will have to be pragmatic about which confounder data can be realistically obtained to cover a potential multitude of technology assessments or further research.
- Interoperability: Registry settings might differ considerably across regions and countries.
- Governance and financing: ensuring ongoing funding into the mid to long term is available, while ensuring the independence of the registry.

The last pilot of the online tool has highlighted key additional information that registries would need to provide, regarding

governance structures, independence, and funding. It also clarified issues regarding the assessment of registries as platforms for future research or technological assessment as opposed to their use to answer specific data collection objectives.

The pilot was vital in refining the tool itself, picking up on usability, technical, and functional issues, both from the side of the evaluator and from the user. By having an iterative and collaborative approach, these issues could be raised, discussed, and actioned.

Limitations

Although REQueST provides essential criteria for data quality assessment, the data may be used in a variety of ways with each type of study having its own specific quality requirements. Such studies may focus on natural history, clinical effectiveness, cost-effectiveness, safety, patient characterization, etc. Each use is likely to require additional quality criteria, and other tools such as Structured Template and Reporting Tool for Real World Evidence are likely to be needed for these cases.

The tool presented should not be considered a finished product. The iterations of consultations mainly included HTA bodies. It would benefit from ongoing iterations reflecting feedback from registry owners and health technology manufacturers. Feedback from registry owners has been limited to date, and no formal focus group or survey-based feedback from registry owners has been collected.

The 2 German registries for study in this pilot were especially adequate because they were well established, willing to take part in the pilot and were concurrently being considered for involvement in HTA (Gemeinsamen Bundesausschusses has subsequently mandated the SMArtCARE registry for Zolgensma gene therapy). Moreover, they have produced several publications and are not representative of younger less established registers that would be likely to find the REQueST process more difficult to engage in.

We have demonstrated that published guidance to registry owners and users of registry data can be consolidated into a user-friendly tool to produce a transparent and sharable assessment of the registry data for HTA and regulatory purposes. The tool will benefit from ongoing updates as experience with it develops. In particular, it will be useful to develop the tool further in consultation with health technology developers (not involved to date in its development). It provides a useful point of reference for research groups and healthcare providers setting up registries intended for future use in HTA and health technology regulation.

REQueST provides guidance in a tool that is easily accessible online and provides flexibility. It enables collaboration between multiple evaluators to assess the registry before the collated results and comments are sent back together to the registry for further improvements. The online tool enhanced the governance of the process in terms of version control and traceability, particularly during successive evaluations, when registries are updating their answers or providing additional information.

The tool can also support the Findability, Accessibility, Interoperability, and Reusability principles, a set of guiding principles,[26] widely supported, including by the European Commission,[27] providing data on registries that is easily findable, accessible, interoperable, and reusable.

The iterative and collaborative methodology with the registry holders maximizes the ability for data collected from registries to be better used by agencies for decision making and provides a strong foundation for future research and applications.

Article and Author Information

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