eunethta

EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

Joint Action 3

MILESTONE

Milestone 5.11 Options on the sustainable availability of the standards tool

Date of submission	30/09/2019
Work package	5
Activity Centre	Post-Launch Evidence Generation (PLEG) and Registries – Strand B2
Author(s)	National Institute for Health and Care Excellence, NICE (UK) French National Authority for Health (Haute Autorité de Santé), HAS (France) - *work package lead*
Dissemination level	Public

Co-funded by the Health Programme of the European Union

Revision History

Revision no.	**Date**	**Author**	**Organisation**	**Description** (first draft, final version, etc)
0.1	8/11/2017	Hannah Patrick (HP) (NICE)	National Institute for Health and Care Excellence (NICE UK),	First draft
0.15	09/04/2018	HP, Helen Powell (HeP) (NICE), Jae Long (JL) (NICE), Mirella Marlow (MM) (NICE)	NICE UK	Post partner consultation
0.2	21/05/2018	HP, JL, MM	NICE UK	Second draft
0.28	25/05/2018	HP, HeP, JL, MM	NICE UK	For second partner consultation
0.33	22/10/2018	HP, HeP, Irena Guzina (IG) (HAS)	NICE UK, Haute Autorité de Santé (HAS France)	For joint partner and EUnetHTA stakeholder consultation
0.36	30/04/2019	HP, HeP, JL	NICE UK	For public consultation
0.37	18/09/2019	HP, HeP, JL, IG	NICE UK and HAS France	Post public consultation
0.40	19/09/2019	HP, HeP, JL	NICE UK	For senior NICE UK review
0.42	**30/09/2019**	**Hannah Patrick (NICE), Helen Powell (NICE), Irena Guzina (HAS)**	**NICE UK, HAS France**	**Final version**

Vision paper on the sustainable availability of the proposed Registry Evaluation and Quality Standards Tool (REQueST)

Report produced as part of EUnetHTA Joint Action 3 Work Package 5B (Post-Launch Evidence Generation and Registries)[1]

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

Disclaimer: The content of this vision paper represents the views of the authors only and is their responsibility; it cannot be considered to reflect the views of the European Commission and/or the Consumers, Health, Agriculture and Food Executive Agency or any other body of the European Union. The European Commission and the Agency do not accept any responsibility for use that may be made of the information it contains.

Acknowledgements

The REQueST tool and vision paper have been developed by the following EUnetHTA partners:

Role	Organisation
Authors	National Institute for Health and Care Excellence, NICE (UK) French National Authority for Health (Haute Autorité de Santé), HAS (France) - *work package lead*
Co-authors	Italian Medicines Agency, AIFA (Italy) Agency for Health Quality and Assessment of Catalonia, AQuAS (Spain) Galician Agency for Health Technology Assessment, avalia-t (Spain) Croatian Institute of Public Health, HZJZ (Croatia) National Authority of Medicines and Health Products, INFARMED (Portugal)
Reviewers	Agencia Española de Medicamentos y Productos Sanitarios, AEMPS (Spain) Agenzia Nazionale per i Servizi Sanitari Regionali, Agenas (Italy) Agency for Health Technology Assessment and Tariff System, AOTMiT (Poland) Azienda Zero, AZIENDA (Italy) Ministero della Salute, DGFDM IT (Italy) National Evaluation Center of Quality and Technology, EKAPTY (Greece) Finnish Medicines Agency, FIMEA (Finland) Federal Office of Public Health, FOPH (Switzerland) Institute for Quality and Efficiency in Health Care, IQWIG (Germany) National Institute of Health, ISS (Italy) Public Agency of the Republic of Slovenia for Medicinal Products and Medical Devices, JAZMP (Slovenia)

	National Institute of Public Health, NIJZ (Slovenia) National Institute of Pharmacy and Nutrition, NIPN (Hungary) Norwegian Medicines Agency, NoMA (Norway) National School of Public Health Management and Professional Development, NSPHMPDB (Romania) Swiss Network for Health Technology Assessment, SNHTA (Switzerland) Dental and Pharmaceutical Benefits Agency, TLV (Sweden) University Hospital A. Gemelli, UCSC GEMELLI (Italy) National Health Care Institute, ZIN (The Netherlands)

The following external organisations provided comments on the REQueST tool and vision paper:

Role	Organisation
Stakeholder and/or public consultees	Alliance for Regenerative Medicine, ARM Analysis Group (USA) European Association of Hospital Pharmacists, EAHP European Coordination Committee of the Radiological, Electromedical and Healthcare IT Industry, COCIR European Federation of Pharmaceutical Industries and Associations, EFPIA European Federation of Statisticians in the Pharmaceutical Industry, EFSPI European Forum for Primary Care, EFPC European Free Trade Association, EFTA European Medicines Agency, EMA European Organisation for Rare Diseases, EURORDIS European Organisation for Research and Treatment of Cancer, EORTC European Patients' Forum, EPF European Public Health Association, EUPHA European Society of Cardiology, ESC European Union of General Practitioners, UEMO ICON Commercialisation & Outcomes (Ireland) Office for Life Sciences, OLS (UK) Red Argentina Pública de Evaluación de Tecnología Sanitaria (Argentina) Synergus RWE (Sweden) University of Manchester (UK) University of Zurich (Switzerland)

Contents

Abbreviations

AEG	Additional Evidence Generation
AHRQ	Agency for Healthcare Research and Quality
EIF	European Interoperability Framework
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EMA	European Medicines Agency
ERNs	European Reference Networks
EUnetHTA	European Network for Health Technology Assessment
HAS	Haute Autorité de Santé (France)
HTA	Health technology assessment
HZJZ	Croatian Institute of Public Health
IMDRF	International Medical Device Regulators Forum
NICE	National Institute for Health and Care Excellence (UK)
PARENT	PAtient REgistries iNiTiative Joint Action
PAS	Post-authorisation studies
PLEG	Post-launch evidence generation
REQueST	Registry Evaluation and Quality Standards Tool
RoPR	Registry of Patient Registries
RoR	Registry of Registries
SEED	Shaping European Early Dialogues for health technologies
ZIN	Zorginstituut Nederland

Glossary

Please refer to http://htaglossary.net/ for technical terms. This document has been written to be consistent with its terminology. The following is a list of terms that have been developed specifically to support the use of REQueST.

Term	Definition
Registry quality assurance mechanism	The combination of the REQueST tool and the infrastructure for its use including: • Operational delivery • Quality oversight, governance, methodological maintenance and development • Ownership and advocacy • Funding. See paragraph 4.
Quality assurance	Activities established before data collection. It aims to assure that the data will be collected in accordance with the plan previously agreed and that the data, which will be stored in the registry database, will meet the requisite standards of quality for intended purposes.
Minimum key documents	Registry owners are required to produce and make publicly available 4 documents relating to the registry aims and methodology[2], declarations of interest, data coverage and completion, and safety statement. For further information, see paragraph 32.
Tool output	See the 'Output' worksheet in REQueST.
Steering committee	Registry staff responsible for the major financial, administrative, legal/ethical, and scientific decisions.
Data quality team	Registry staff which ensures that the registry is outcomes-driven and that the data collected are disseminated effectively.

We recommend that this paper should be read after familiarisation with the Registry Evaluation and Quality Standards Tool (REQueST) itself. The tool provides an introduction explaining the aims of REQueST and how it was developed, instructions for use, sections to complete with information about the registry being evaluated, an output table and a glossary. The following text will be better understood with this knowledge.

[2] Documentation which specifies the objectives, target population, exposures of interest, primary and secondary outcomes, data sources, linkage (and analysis plans if any).

Aim of the project

1. The use of registries is becoming increasingly common in health technology assessment (HTA) and regulation. There is a growing interest in the role of observational data in complementing experimental data. This project aims to support best practice in the collection, use and re-use of real world data, and explore options to support sustainable multi-stakeholder collaboration.

2. The work proposed by this paper seeks to enhance the use of high quality registries in this context through the development of:

   a) A quality standards tool (REQueST), and

   b) A proposal for the long-term delivery, use and sustainability of the REQueST tool.

3. Appendix A presents a summary of the tool. This paper addresses the long-term sustainability of the tool by proposing a phased approach to its implementation.

4. This vision paper proposes:

   a) That the tool requires infrastructure for its use that provides the following components:
      - Operational delivery
      - Quality oversight, governance, methodological maintenance and development (including hosting the operational system)
      - Ownership and advocacy
      - Funding.

   b) A registry quality assurance mechanism[3] comprising the tool and the infrastructure for its use. It will be sustained and 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.

[3] For the purposes of this paper quality assurance includes all the essential dimensions of quality as outlined by the tool. This incorporates, but is not restricted to, data quality assurance which is the process of data profiling to identify inconsistencies and other anomalies in the data, as well as performing data cleansing activities (e.g. removing outliers, and applying missing data techniques) to improve the data quality.

Background

EUnetHTA Work Package 5

5. This vision paper has been produced for Work Package (WP) 5, Strand B (post-launch evidence generation and registries) as part of the European network for Health Technology Assessment (EUnetHTA) Joint Action (JA3). Managed by the Haute Autorité de Santé (HAS), WP5 coordinates the efforts of the 39 EUnetHTA partners to improve evidence generation throughout the life-cycle of a technology. It builds upon previous EUnetHTA experience in the area, including the JA2 WP7 subgroup (SG) 1 Early Dialogues and SEED project and the JA2 WP7 SG2 Additional Evidence Generation (AEG) work. While Strand A of WP5 is concerned with pre-launch evidence generation, Strand B concentrates on post-launch evidence generation (PLEG). Strand B is further broken down into 2 activities, including a specific activity on the quality of registries (this work), called Strand B2 (JA3 WP5B2).

6. The National Institute for Health and Care Excellence (NICE) in the UK and the Croatian Institute of Public Health (HZJZ) are leading WP5B2, which builds on the work of the PAtient REgistries iNiTiative (PARENT Joint Action). PARENT sought to support the EU Member States in developing comparable and interoperable patient registries (e.g. of chronic and rare diseases, and medical technologies) with the aim of rationalising the development and governance of patient registries, thus enabling analyses of secondary data for public health, policy and research purposes in cross-border settings. One of the key outputs, building on the PARENT framework concept, was the 'Methodological guidelines and recommendations for efficient and rational governance of patient registries' (1).

7. The first report for JA3 WP5B presented the results of a survey to examine the extent to which HTA agencies use registries and for what purposes (2). It also served to identify any existing quality standards in use by HTA organisations and agencies. This showed that many agencies, particularly in Europe, are drawing on a range of registries to provide data for their HTA evaluations. Less than half, however, currently employ criteria or standards to assess the quality of registry data before use in HTA. Of these, nearly all use criteria or standards defined by their own organisation, rather than a standardised tool defined by an external body. The survey showed variation in their understanding of the term 'registry', the types of registries used by organisations, and the way that they use them. The survey demonstrated a need for a standardised tool to promote best practice for the collection and use of such data. In addition to the survey, other initiatives that informed this vision paper are listed in Appendix B.

8. It is recognised that while no 'validated' set of standards to assess the quality of registries for HTA purposes has been identified, there are initiatives or mechanisms aiming at accrediting registries for general purposes.

Registries and registers - definitions

9. Registries have been defined as an "organized system that collects, analyses, and disseminates the data and information on a group of people defined by a particular disease, condition, exposure, or health-related service, and that serves predetermined scientific, clinical or/and public health (policy) purposes" (1)[4]. In addition, health institutions in France and the International Medical Device Regulators Forum (IMDRF) emphasise the importance of continuous and comprehensive data collection (3,4).

10. The term register generally relates only to the list of items, names or other data of interest.

The vision

11. The registry standards tool created as part of JA3 WP5B2 needs an agreed ongoing plan in order to make it available to registry owners, HTA agencies and regulators ('users' of the quality assurance mechanism[5]) on a sustainable basis after the end of JA3, and to keep it updated. It is intended that high quality registries would provide a useful platform for relevant registry-based studies.

12. It is proposed that making an international quality assurance mechanism for registries available on a sustainable basis would require 4 key components: a) operational delivery of the tool; b) quality oversight, governance, methodological maintenance and development; c) ownership and advocacy; and d) funding. These key components are now described in more detail.

Component A: Operational delivery of the tool

13. For HTA purposes, the Registry Evaluation and Quality Standards Tool (REQueST) is designed to be used in 3 steps (see Appendix A for more details on how the operational delivery would work):

    - Step 1: Initial screening of a potential registry for suitability. Standards currently presented in the 'Methodological Information' section of the tool

[4] A registry can support one or more registers. They can be designed to support evaluation of new technologies including devices, drugs and wider initiatives such as public health interventions.
[5] Industry will be welcomed as a potential user of the tool and as a collector of data.

are intended to enable a user to assess whether a registry can provide data that fulfil their needs[6].

- Step 2: All registries that are potentially suitable should then be assessed against 'Essential Standards' relating to registry quality.
- Step 3: Some registries will require assessment against additional criteria for specific purposes (e.g. international collaboration on data collection will require interoperability). This is assessed in the 'Additional Requirements' section of the tool.

14. The interaction process between HTA agencies/regulators and the registry will be further defined when developing the online version of the tool, however the outline interaction below should be followed:
    - HTA agency/regulator asks the registry owner to complete REQueST
    - Registry professional completes REQueST
    - HTA agency/regulator reviews the responses from the registry and asks for any additional information needed
    - HTA agency/regulator decides whether the registry is suitable and develops the collaboration.

15. The tool will produce an output table to assist users in rapidly understanding the quality of the registry and areas for improvement (see the 'Output' worksheet in REQueST).

16. It is expected that the nature and public availability of the output will change as the phases of implementation advance. In early phases the output is likely to primarily direct discussion with registry owners and may not be publicly available. By Phase 2B (for further information, see paragraph 27) the output may be in the form of accreditation which a registry may wish to advertise.

Component B: Quality oversight, governance, methodological maintenance and development (including hosting the operational system)

17. A registry quality assurance mechanism will require infrastructure to provide ongoing governance, maintenance and development. This could involve:

    Contributors

    - EUnetHTA (or an equivalent international collaborative structure)

[6] Issues related to the commercial sensitivity of data are considered to be outside the scope of this document.

- Academic support.

Process

- Annual general meetings to review and constantly improve the performance of the standards tool
- Consultation on key documents including methods and process guide updates
- A feedback mechanism for organisations using the tool to deliver continuous improvement.

Requirements

- Methodological capability and capacity to update standards
- Transparent declaration of relevant interests[7] (see Appendix C for an example declaration of interest and confidentiality undertaking (DOICU) form).

18. See Appendix D for further considerations on sustainable governance and ownership.

Component C: Ownership and advocacy

19. The REQueST tool and its related infrastructure needs to be owned and promoted beyond its host organisation, to ensure that the progress and impetus of the EUnetHTA collaboration is maintained at the end of JA3. This needs to include:

- Systemic support and advocacy for the tool and its infrastructure requirements, which could be included in plans for strengthening EU cooperation on HTA.
- Collaboration with similar international initiatives on registry quality such as those being considered by IMDRF, the European Medicines Agency (EMA) and the European Reference Networks (ERNs), and others.

Component D: Funding

20. Collaborating partners need to decide how they wish to balance the cost of the mechanism against the level of confidence required in the quality of data collected by registries. The cost of implementation will be proportional to the resources necessary to deliver the level of confidence that is required in the quality assurance mechanism. A self-assessment procedure would be

[7] The EUnetHTA procedure for Declaration of Interest and Confidentiality Undertaking is available at: https://www.eunethta.eu/doicu/.

relatively inexpensive but may allow variation in the practice and application of the standards that would not deliver great confidence in data quality, at worst leaving people with minimal confidence in the process. An intensive, full assurance mechanism delivered by a lead organisation with regular review of all recommended registries may deliver more confidence but be too expensive to be affordable on a sustainable basis. It is likely that a pragmatic phased approach is required, that allows recruitment of funding in proportion to usefulness of outputs from the quality assurance mechanism.

Proposal: A phased approach to REQueST tool implementation

21. Four phases are envisaged graduating from the least resource intensive to the most sophisticated and costly. The speed at which progress is made through the phases should be flexible, reflecting funds available and feedback received from users. Components of each phase need not progress in parallel as some will be easier to arrange than others. So, for instance, arrangements for ownership and advocacy may make more rapid progress than those for operational delivery and should not be held back by work needed on operational issues.

22. Whatever the phase, the tool will be used as a quality standard by HTA agencies in their everyday work when dealing with registries, as described in paragraph 13.

Phase 1A

23. The registry owner carries out a self-assessment by completing the ‘registry owner’ column in the ‘Essential Standards’ worksheet of REQueST. This information together with a summary of the registry methodological information and the minimum key documents (listed in paragraph 32) are presented on the registry’s web site. These may be reviewed at any point by organisations considering whether to use the data in evidence development for HTA and regulatory monitoring to check if the information meets their needs. Components B, C and D (quality oversight, ownership and advocacy, and funding) would rely upon voluntary contributions by interested agencies. The REQueST tool would be accessed through the website of a host organisation who would maintain and update the tool.

Phase 1B

24. The registry owner carries out a self-assessment by completing the ‘registry owner’ column in the ‘Essential Standards’ worksheet of REQueST. This information together with a summary of the registry methodological information and the minimum key documents (as required for Phase 1A) are submitted to a central portal, for presentation on a web site owned by third party independent of the registry (for example an academic body). The central

portal could provide access to the REQueST tool itself and information on all registries that have committed to the process using a standard format (making the output easier to search than in Phase 1A). This would allow comparison between registries covering similar topics and facilitate learning between registries. HTA agencies would use the information provided to assess whether a registry meets their requirements in terms of scope and quality. Components B, C and D could be managed by elected representatives of interested organisations on funded secondment.

Phase 2A

25. The registry submits the minimum key documents to a central portal for assessment by an independent third party. Over time, and according to the resources available, registries may be asked to submit more documentation to enable the independent third party to provide increasingly sophisticated evaluation. The exact nature of the independent body needs discussion, but it is likely to take the form of an academic or similar body, providing skills in critical appraisal, information technology, financial analysis and ethics review. The independent body would a) comment on registry adherence to the 'Essential Standards' (step 2 of the tool) and b) generate the REQueST output.

26. In both Phase 1B and 2A the HTA agencies would need to assess the suitability of the registry for their specific technology assessment purpose themselves (i.e. complete step 1 of the tool) and whether 'Additional Requirements' should be addressed (step 3 of the tool). Components B, C and D would be managed as for Phase 1B.

Phase 2B

27. The registry submits the relevant documents to an independent third party with academic support. The service provided by the third party would be to screen the registry using step 1 of the tool (not including items relating to specific purposes) and then, if the basic requirements are in place, assess the registry against the 'Essential Standards' (step 2 of the tool). HTA agencies (and other possible users e.g. regulatory bodies) would identify the specific purpose for which a registry is proposed and would use steps 1 and 3 of the tool to complete the evaluation in order to make a final decision.

28. Components B, C and D would be managed through user collaboration led by an individual organisation on a voluntary and rotational basis. If possible, a more stable supporting structure would be funded by users and allow for the creation of an elected management committee.

29. Agreement is needed for both Phase 2A and B as to who may be given access to the REQueST output. This could require some form of membership and funding contribution or be a free service available to any interested party.

Output review

30. In general, assessment of the quality of a registry cannot be done as a one-off event; ongoing quality needs to be demonstrated and the tool output will require periodic review[8].

31. It should be noted that the 'Methodological Information' and 'Additional Requirements' sections of REQueST include questions that relate to specific uses of a registry. Users of REQueST may therefore need to run the tool more than once for an individual registry, and only the 'Essential Standards' would be transferrable between assessments.

32. All phases require the registry owner to produce and make publicly available the following 'minimum key documents':

- Registry aims and methodology including minimum data set and data security policies.
- Declarations of relevant interests.
- Demonstration of continuous and comprehensive data collection (exact format and periodicity to be agreed but this is likely to include regular reporting on coverage, completeness and validation of data). Where a registry is federated between many countries, a report would be required from every participating registry.
- Safety statement detailing any alerts that have been raised (initiated by the registry owner and jointly publicised with the regulator/assessor).

33. Initially registry owners may be reluctant to take on the extra work involved in submission for REQueST assessment, but they will be encouraged by stakeholders because of the following potential incentives, all of which will bring benefits to patients, industry, and the HTA and research ecosystems:

- Manufacturers will be encouraged to fund registries by HTA agencies and regulatory bodies that use the evidence in their HTA processes.

[8] Criteria for the frequency of registry review could include the:

- Maturity of the registry and technology (e.g. national joint registries dealing with established technologies and governance would require less frequent review).
- Production of peer-reviewed publications based on the registry (e.g. if at least one peer-reviewed publication per technology is produced in an acceptable time interval, the REQueST review could be less frequent).
- Purpose of the registry (e.g. if it is bespoke, that is, to meet specific regulatory or technology assessment objectives, quality should be assessed at the beginning and at the point of data use).

- Researchers and registry owners who comply with the requirements of REQueST could be recognised as producing high quality data and therefore be more likely to be successful in submitting reports for publication.
- Clinicians who use the data in audit work could be recognised by professional bodies to be compliant with Continuing Professional Development, Appraisal and Revalidation requirements.
- Organisations funding research will be supported by a mechanism that provides independent data quality assessment.
- Research ethics committees considering studies involving data submission to a registry will likewise be supported by information quality assurance.
- Patients will be reassured that HTA agencies and regulators use up-to-date methods to develop evidence, monitor outcomes and provide them with complete information about new interventions.

34. These are possible supplementary benefits of the tool if fully implemented but the primary target of the tool is HTA agencies. Extra governance arrangements would be necessary for its use by professional bodies, research funders and other potential users.

Proposed interim arrangements pending full implementation of the vision

35. Once launched, it will be important to gather data on how the REQueST tool is used by which organisations, and to receive feedback on its utility and applicability. Online questionnaires or other activities (steering committees etc.) may be required to further refine and validate the tool before full implementation. This activity will need to be carried out within the existing resource level for EUnetHTA WP5B during the JA3 project lifetime, but such monitoring information will be the responsibility of the REQueST host organisation once the arrangements described in this vision paper are in place.

Conclusion

36. The REQueST tool has the potential to become a valuable element in the effective use of registry data by HTA agencies.

37. For the tool's potential to be realised it needs to be supported by an infrastructure that provides for a) operational delivery, b) quality oversight, governance, methodological maintenance and development c) ownership and advocacy and d) funding.

38. These components should develop progressively through phases which can be independent between each category to ensure the widest possible support for this important project.

Next steps

39. REQueST will be piloted until the end of JA3, at which point the ownership and continued development of the tool will be agreed.

References

(1) Zaletel M, Kralj MM (Eds) (2015). Methodological guidelines and recommendations for efficient and rational governance of patient registries. National Institute of Public Health, Ljubljana.

(2) Mandeville KL, Valentic M, Ivankovic D, Pristas I; Long J, Patrick HE (2018). Quality assurance of registries for health technology assessment. International Journal of Technology Assessment in Health Care. 34(4): 360-7.

(3) Epidemiology – France. Lexicon. Available at: https://epidemiologie-France.aviesan.fr/en/epidemiology/resources/lexicon

(4) International Medical Device Regulators Forum (2016). Principles of international system of registries linked to other data sources and tools. Available at: http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-160930-principles-system-registries.pdf

Appendix A: Brief overview of the Registry Evaluation and Quality Standards Tool (REQueST)

The REQueST tool supporting the use of registries in health technology assessment (HTA) has been developed by activity centre partners in support of the European network for Health Technology Assessment Joint Action Work Package 5B Strand 2 work.

REQueST will support consistent evaluation of the suitability of registries for HTA, and address concerns about the reliability of registry data for use in HTA. The tool uses criteria and standards published in existing guidelines, frameworks and projects, as well as several newly developed criteria.

The tool is designed to be used in 3 steps (see the 'Instructions for use' worksheet in REQueST for further information on how to complete the tool).

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 research methodology and which information is collected (research question, protocol and observational methods). This section provides an opportunity for the HTA agency to gather information about the data collected by the registry. Methodological information will be used to assess whether a registry is ready and able to answer a specific research question. There are 8 'Methodological Information' items covering the following areas:

- Type of registry
- Use for registry-based studies and previous publications
- Geographical and organisational setting
- Duration
- Size
- Inclusion and exclusion criteria
- Follow-up
- Confounders.

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 essential elements of good practice and evidence quality that can be used in the evaluation of the registry. Unless all essential criteria are demonstrably fulfilled, the

HTA agency should not use the registry for evidence evaluation. There are 12 'Essential Standards' items covering the following areas:

- Registry aims and methodology
- Governance
- Informed consent
- Data dictionary
- Minimum data set
- Standard definitions, terminology and specifications
- Data collection
- Quality assurance
- Data cleaning
- Missing data
- Financing
- Protection, security and safeguards.

C) Additional Requirements - Specific requirements for the evidence questions

'Additional Requirements' are elements of good practice and evidence quality which are not always practical or feasible to achieve but are useful to consider in planning and evaluating registries. Evaluation of the 'Additional Requirements' depends on the requirements of an individual HTA agency and the specific context or registry use (e.g. an international collaboration on data collection will require registry interoperability). There are 3 'Additional Requirements' items covering the following areas:

- Interoperability and readiness for data linkage
- Data sources
- Ethics.

Appendix B: Initiatives involving collaborative data collection and quality assurance

The European Medicines Agency (EMA) has set up an initiative to make better use of existing registries and facilitate the establishment of high quality new registries if none provide an adequate source of post-authorisation data for regulatory decision making. Launched in September 2015, it explores ways of expanding the use of patient registries by introducing and supporting a systematic and standardised approach to their contribution to the benefit-risk evaluation of medicines within the European Economic Area.

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) is a network coordinated by the EMA. The members of this network (the ENCePP partners) are public institutions and contract research organisations (CROs) involved in research in pharmacoepidemiology and pharmacovigilance.

ENCePP aims to strengthen the monitoring of the benefit-risk balance of medicinal products in Europe by:

- Facilitating the conduct of high quality, multicentre, independent post-authorisation studies (PAS) with a focus on observational research.
- Bringing together expertise and resources in pharmacoepidemiology and pharmacovigilance across Europe and providing a platform for collaborations.
- Developing and maintaining methodological standards and governance principles for research in pharmacovigilance and pharmacoepidemiology.

Its key outputs are:

- Database of Research Resources: A publicly accessible index of available European research resources.
- Code of Conduct: A set of rules and principles for pharmacoepidemiology and pharmacovigilance studies to promote transparency and scientific independence throughout the research process.
- Checklist for Study Protocols: A tool to promote the quality of studies.
- Guide on Methodological Standards in Pharmacoepidemiology: A resource for methodological guidance in pharmacoepidemiology.

The Registry of Patient Registries (RoPR) was established by the Agency for Healthcare Research and Quality (AHRQ) to complement ClinicalTrials.gov by providing additional registry-specific data elements.

It aimed to promote collaboration, reduce redundancy, and improve transparency among registry holders.

The RoPR data entry system allowed registry owners to provide information about the following:

- Classification and purpose: The type of registry and its purpose.
- Contact and conditions of access: Circumstances under which the registry can be contacted, and contact information for those interested in collaboration, participation and/or data access.
- Progress reports: Includes information about the growth of the registry and any relevant references to available progress reports.
- Common data elements: Descriptions of registry-specific standards, scales, instruments, and measures.

RoPR did not quality assure the registries that it listed. Funding of the RoPR project ended in April 2019. AHRQ is currently seeking a collaborator to re-launch the RoPR.

The Registry of Registries (RoR) was developed as part of the PARENT initiative. It is a web-based service designed to facilitate:

- Collection and access to reliable and up-to-date information about patient registry metadata.
- Efficient use of resources in setting-up and managing patient registries.
- Cross-border exchange of registry data for research and public health in the EU by establishing interoperability standards in data exchange.

RoR does not quality assure the registries that it lists.

The Integrated Research Application System (IRAS) is a single system for applying for permissions and approvals for health and social care/community care research in the UK. It enables:

- Users to enter information about projects in order to apply for permissions and approvals.
- Appropriate information submission through filters to ensure correct document collection and collation.
- Project leads to meet regulatory and governance requirements.

European Reference Networks (ERNs) help professionals and centres of expertise in different countries to share knowledge. ERNs should:

- Apply EU criteria to tackle rare diseases requiring specialised care.

- Serve as research and knowledge centres treating patients from other EU countries.
- Ensure the availability of treatment facilities where necessary.

Appendix C: Example declaration of interest and confidentiality undertaking (DOICU) form

Declaration of Interest and Confidentiality Undertaking (DOICU) Form

The undersigned,

Title:

Family name:

Given name:

Email address:

Organisation/Institution: <Enter 'none' if this point does not apply>

Address (street):

Postal code:

Town/city (country):

EUnetHTA Partner/Associate organisation or institution: Yes ☐ No ☐

Provided the following information to the best of his/her knowledge and belief.

SECTION 1. DECLARATION OF INTERESTS

Please provide details on your affiliations as far as three (3) years back from the time of filling the form and up until present. The DOICU form is valid for one (1) year. Please provide a new DOICU form after expiration of the validity.

If you choose the tick box 'NO' it means that you have no interest to declare at all. In case of potential interest to declare, please choose 'YES' and specify. Declaration of potential conflicts of interest does not automatically lead to an exclusion from the task, but to the evaluation on an individual level by the EUnetHTA COI Committee.

In case of potential interests that were not declared by the individual but become visible during the evaluation process, the respective individual can be excluded from the task. The decision on the exclusion of an individual from the task will be taken on an individual level by the EUnetHTA COI Committee.

1. CURRENT PROFESSIONAL ACTIVITY/ACTIVITIES

Description of the current professional activity/activities: *Please provide a brief description of your current professional activity/activities. If professional activity/activities do not apply, please specify.*

From Month/Year to Month/Year

2. TABLES OF INTERESTS

2.1 Employment with a Company/Institution

<'Employment with a company/institution' means any form of occupation, part-time or full-time, paid or unpaid, in the company/institution.>

For the purpose of this form, a company/institution means any legal or natural person whose focus is to research, develop, manufacture, market, and/or distribute medicinal products and/or medical devices. This includes companies/institutions to which activities relating to the research, development, manufacturing, marketing, and maintenance of medicinal products and/or medical devices (which might also be carried out in-house) are outsourced on a contract basis.
Contract research organisations (CRO) or consultancy companies providing advice or services relating to the above activities also fall under this definition of company/institution, given the remit of this form.

Employment with professional/clinical/patient organisations should be declared in 2.6.

Please provide for each company/institution you are/were employed at the information about your role/function, with which products and therapeutic indications (together with the name of the respective manufacturers) you were involved, and the relevant time period.

	No	Yes
Employment with company/institution	☐	☐

If 'YES', please provide details below:

Company/ Institution	Role/Function	Product, Therapeutic Indication, Manufacturer	Time Period MM/YYYY – MM/YYYY
			<Please add more rows if needed>

2.2 Consultancy

<'Consultancy' means provision of advice (including training on a one-to-one basis, preparation of HTA reports or HTA submission) to a company/institution (as defined in 2.1), regardless of contractual arrangements or any form of remuneration. Furthermore, advice on behalf of a public Health Technology Assessment body should be declared.>

Employment with CROs or consultancy companies should be declared in section 2.1. Employment with professional/clinical/patient organisations should be declared in 2.6.

Please state for each company/institution you provide/provided advice to, the information about your role/function, with which products and therapeutic indications (together with the name of the respective manufacturers) you were involved, and the relevant time period. Please state if the consultancy was associated with contractual arrangements or any form of remuneration.

	No	Yes
Consultancy	☐	☐

If 'YES', please provide details below:

Company/ Institution	Role/Function	Product, Therapeutic Indication, Manufacturer	Contractual arrangements/ remuneration (amount if applicable)	Time Period MM/YYYY – MM/YYYY
<Please add more rows if needed>				

2.3 Strategic Advisory Role

<'Strategic advisory role' means participation (with a right to vote on/influence the outputs) in a(n) (scientific) advisory board/steering committee with the role of providing advice/expressing opinions on the (future) strategy, direction, or development activities of a company/institution (as defined in 2.1), either in terms of general strategy or product related strategy, regardless of contractual arrangements or any form of remuneration.>

Please state for each company/institution you have/had a strategic advisory role to, the information about your role/function, with which products and therapeutic indications (together with the name of the respective manufacturers) you were involved, and the relevant time period. Please state if the strategic advisory role was associated with contractual arrangements or any form of remuneration.

	No	Yes
Strategic advisory role	☐	☐

If 'YES', please provide details below:

Company/ Institution	Role/Function	Product, Therapeutic Indication, Manufacturer	Contractual arrangements/ remuneration (amount if applicable)	Time Period MM/YYYY – MM/YYYY
<Please add more rows if needed>				

2.4 Principal Investigator

<'Principal investigator (/Co-Principal investigator)' means an investigator with the responsibility for the coordination of investigators at different centres participating in a multicentre sponsored trial, or the leading investigator of a monocentre sponsored trial, or the coordinating (principal) investigator signing the clinical study report. For the purposes of this form, a sponsor/instigator is a company/institution as defined in 2.1. Involvement in Data Monitoring Committees should be included in this section.>

Please state for each study you are/were a principal investigator (/Co-Principal investigator), the information about your role/function, with which products and therapeutic indications (together with the name of the respective manufacturers) you were involved, and the relevant time period.

	No	Yes
Principal investigator	☐	☐

If 'YES', please provide details below:

Study	Role/Function	Product, Therapeutic Indication, Manufacturer	Time Period MM/YYYY – MM/YYYY
<Please add more rows if needed>			

2.5 Investigator

<'Investigator' means an investigator involved in a sponsored trial at a specific trial site who can be the responsible lead investigator of the trial at that specific site or a member of the clinical trial team who performs critical trial related procedures and makes important trial related decisions. For the purpose of this form, a sponsor/instigator is a company/institution as defined in 2.1.>

Please state for each study you are/were an investigator, the information about your role/function, with which products and therapeutic indications (together with the name of the respective manufacturers) you were involved, and the relevant time period.

	No	Yes
Investigator	☐	☐

If 'YES', please provide details below:

Study	Role/Function	Product, Therapeutic Indication, Manufacturer	Time Period MM/YYYY – MM/YYYY
<Please add more rows if needed>			

2.6 Professional/Clinical/Patient Organisations

<'Professional/clinical/patient organisations' means any sort of organisation/institution in the healthcare sector that represents healthcare professionals and/or patient views. For the purpose of this form, a sponsor/instigator is a company/institution as defined in 2.1.>

Please state for each organisation/institution you are/were a member/staff, the information about your role/function, the respective sources of their funding, the percentage of sponsoring by companies/institutions (separate as well as the overall funding), and the relevant time period.

	No	Yes
Professional/Clinical/ Patient organisations	☐	☐

If 'YES', please provide details below:

Organisation/ Institution	Role/ Function	Sources of Funding	Percentage of sponsoring (separate, overall funding)	Time Period MM/YYYY – MM/YYYY
<Please add more rows if needed>				

2.7 Financial Interests

<'Financial interests' means any economic stake in a company/institution as defined in 2.1 including: 1) Holding of stocks and shares, stock options, equities, bonds and /or partnership interest in the capital

of a company/institution (as defined in 2.1); 2) Intellectual property rights including patents, trademarks, know-how and/or copyrights relating to a medicinal product/device owned by you or of which you are directly a beneficiary; 3) Compensation, fees, honoraria, salaries, grant or other funding (including rents, sponsorships and fellowships) paid by a company/institution (as defined in 2.1) to you in a personal capacity.>

Please state for each company/institution the description of the financial interest and respective time period.

	No	Yes
Financial interests	☐	☐

If 'YES', please provide details below:

Company/Institution	Description of the interest	Time Period MM/YYYY – MM/YYYY
		<Please add more rows if needed>

2.8 Grants and Funding

<'Grants and funding' means any funding (other than compensation for services provided) received from a company/institution (as defined in 2.1) by an organisation/institution to which you belong, or for which you perform any kind of activity, and which is used to support any of your activities whether or not they are related to research work. Any other funding received by an organisation/institution to which you belong, or for which you perform any kind of activity, do not need to be declared.>

Please state for each organisation/institution to which you belong, the purpose of the grant and funding, the names of the companies/institutions providing the grants and funding as well as the amount of the grants and funding and the relevant time period.

	No	Yes
Grants and funding	☐	☐

If 'YES', please provide details below:

Organisation/ Institution	**Purpose of the grant and funding**	**Company/Institution providing the grants and funding**	**Amount of grants and funding**	Time Period MM/YYYY – MM/YYYY
<Please add more rows if needed>				

2.9 Conferences/Meetings/Presentations

<'Conferences/Meetings/Presentations' means any sort of event where compensation, fees, honoraria, salaries, or other funding were paid by a company/institution (as defined in 2.1) to you in a personal capacity, including payment for or reimbursement of expenses directly related to conference/meeting/presentation attendance (i.e. accommodation and travel costs).>

Please state for each event, the name/title and hosting organisation, the information about your role/function in that event, the time period it took place and a description of the interest including information on the company/institution responsible for the payment/reimbursement and the amount of payment/reimbursement. In case you gave a presentation at a conference/meeting, please indicate the title.

	No	Yes
Conferences/Meetings/ Presentations	☐	☐

If 'YES', please provide details below:

Name/Title (Organiser)	Role/Function	Description of interest (company/institution, amount of payment/reimbursement, title of presentation (if applicable))	Time Period MM/YYYY – MM/YYYY
<Please add more rows if needed>			

2.10 Any other interest

Please state any other interests you might have that were not declared in the tables above.

3. FAMILY AND HOUSEHOLD MEMBERS INTERESTS

Please indicate if any family[9], partners, and/or household member[10] of yours has one or more of the following interests[11]:

	No	Yes	
Employment with a Company/Institution	☐	☐	<If yes, please provide a description with the same level of detail as per the table(s) of interests>
Consultancy	☐	☐	<If yes, please provide a description with the same level of detail as per the table(s) of interests>
Strategic Advisory Role	☐	☐	<If yes, please provide a description with the same level of detail as per the table(s) of interests>
Principal Investigator	☐	☐	<If yes, please provide a description with the same level of detail as per the table(s) of interests>
Investigator	☐	☐	<If yes, please provide a description with the same level of detail as per the table(s) of interests>
Professional/ Clinical/ Patient Organisations	☐	☐	<If yes, please provide a description with the same level of detail as per the table(s) of interests>
Financial Interests	☐	☐	<If yes, please provide a description with the same level of detail as per the table(s) of interests>
Grants and Funding	☐	☐	<If yes, please provide a description with the same level of detail as per the table(s) of interests>
Conferences/ Meetings/ Presentations	☐	☐	<If yes, please provide a description with the same level of detail as per the table(s) of interests>

[9] First degree family member.
[10] Household member is a person living at the same address as the individual who signs the DOICU form.
[11] See above for the definitions of employment, consultancy etc.

DISCLAIMER

a. **Review by EUnetHTA COI (Conflict of Interest) Committee:** The data provided by the individual in the DOICU form (including related annex and supporting documents) will be reviewed by the EUnetHTA COI Committee;
b. **Review by national authorities:** Additionally, the provided data will be made available for all partner organisations and members of EUnetHTA that have HTA implementing authority, for the purpose of reviewing the provided information against national provisions that need to be taken into consideration additionally to the guidelines and assessment of the EUnetHTA COI Committee. The information will be shared at the same time as with the EUnetHTA COI Committee. Findings by these partners must be shared with the EUnetHTA COI Committee by a fixed deadline to be included in the deliberations of the EUnetHTA COI Committee;
c. **Additional verification:** The EUnetHTA COI Committee can undertake additional research on the validity of the data provided by an individual and specifically can try to verify if no conflict exists beyond the data provided by the individual in the DOICU form;
d. **Decision:** Based on the data provided in the DOICU and possible additional findings the EUnetHTA COI Committee takes a decision on whether a conflict of interest exists that qualifies as critical and hence excludes the relevant individual from participating in the planned activity;
e. **Information of findings and decision:** The EUnetHTA COI Committee will inform the individual about all their findings (and provided information from relevant individual EUnetHTA partner organisations and members received by the applicable deadline). The individual will be informed about the decision of the EUnetHTA COI Committee and the reasoning for the provided decision;
f. **Storage of data:** The data provided by the individual and any additional findings made by the EUnetHTA COI Committee will be stored permanently in relation to the specific activity the DOICU was originally requested for, regardless whether the individual is considered as appropriate or to be excluded due to conflict of interest;
g. **Publication of data:** The individual's data provided can be made publicly available in parts or full depending on national and regional requirements of individual jurisdictions that are represented in the EUnetHTA consortium;
h. **Positive list:** Provided data will only be made publicly available in cases where an individual's input is actually used or of relevance in a procedure. If a conflict of interest is considered to be of substantial nature and hence prohibiting the participation of the individual in the planned activity, the submitted data will not be published;
i. **Completeness of data:** The individual testifies that he/she provided all requested information to the best of his/her knowledge and does not withhold any information that would have influence over establishing a conflict of interest in the specific case;
j. **Indemnification for false or incomplete reporting:** The individual will indemnify any loss made due to false or incomplete statements;
k. **Reminder to update DOICU:** The individual agrees to receive an automatic reminder to update his/her provided DOICU prior to expiration of the form provided;
l. **Expiration:** The provided DOICU form expires after a specific period mentioned in the form and based on the signature date of the individual;
m. **Renewal in case of changes or expiration:** A renewal of the information for conflict of interest needs to be submitted promptly by the individual in case of any occurring changes regarding the stated conflict of interest in the DOICU form and where the engagement of the individual surpasses the expiration date of the originally submitted form. Such renewal needs to take into consideration all additional data that have come to light since the original DOICU form was signed. In particular, attention will be payed to the acquisition of any additional interests by the individual (e.g. consultancy arrangements, etc.).

Place:

Date:

Signature: <Please return a Word version of the completed DOICU form together with a signed and scanned version of the completed DOICU form.)>

<SECTION 2. CONFIDENTIALITY UNDERTAKING>

In view of the following definitions:
"EUnetHTA"

"EUnetHTA Joint Action 3 Activities" encompass any meeting (including meeting preparation and follow-up), associated discussion or any other related activity of the EUnetHTA Joint Action 3 committees and governance bodies, its work packages, expert groups, stakeholder groups, or any other such meeting, work as an expert on assessments, and work as an expert on guidance development.

"Confidential Information" means all information, facts, data and any other matters which are indicated as confidential or, would reasonably, under the circumstances, be understood to be confidential information and of which I acquire knowledge, either directly or indirectly, as a result of my EUnetHTA Joint Action 3 Activities and related activities

"Confidential Documents" mean all drafts, preparatory information, documents and any other material, together with any information contained therein, which is indicated as confidential or, would reasonably, under the circumstances, be understood to be confidential information and to which I have access, either directly or indirectly, as a result of my participation in EUnetHTA Joint Action 3 Activities. Furthermore, any records or notes made by me relating to Confidential Information or Confidential Documents shall be treated as Confidential Documents.

Confidential Information and Confidential Documents shall not include information that: (a) is now or subsequently becomes generally available to the public through no fault or breach on part of the undersigned; (b) the undersigned rightfully obtains from a third party who has the right to transfer or disclose it to the undersigned without limitation.

The undersigned understands that he/she may be invited to participate either directly or indirectly in certain EUnetHTA Joint Action 3 Activities and hereby undertakes:

1. To treat all Confidential Information and Confidential Documents under conditions of strict confidentiality and shall use the Confidential Information and Confidential Documents for the sole purpose of and only in connection with the EUnetHTA Joint Action 3 Activities;

2. Not to disclose, publish or disseminate (or authorise any other person to disclose, publish or disseminate) in any way to any third party[12] any Confidential Information or Confidential Document;

3. Not to use (or authorise any other person to use) any Confidential Information or Confidential Document other than for the purposes of my work in connection with EUnetHTA Joint Action 3 Work Package activities;

4. Not to use or otherwise export or re-export any portion of the Confidential Information and/or Confidential Documents;

5. At EUnetHTA's option and (written) request to return Confidential Documents or to provide EUnetHTA with written certification that all tangible Confidential Documents have been destroyed within (10) business days of receipt of EUnetHTA's (written) request;

6. To compensate all damages, costs and expenses including reasonable attorneys' fees, as incurred by EUnetHTA, resulting from or arising out of or in connection with any unauthorized disclosure or use of the Confidential Information and Confidential Documents by the undersigned.

[12] Third party does not include employees of the National Competent Authorities who either have employment contracts that provide confidentiality obligations that prohibit unauthorized disclosure or use of the Confidential Information and/or Confidential Documents or are encompassed by confidentiality obligations under national legislation on professional secrecy.

This undertaking shall not be limited in time. Any termination of this undertaking shall not relieve the undersigned of its confidentiality and use obligations with respect to the Confidential Information and Confidential Documents disclosed prior to the date of termination.

Place:

Date:

Signature: <Please return a Word version of the completed DOICU form together with a signed and scanned version of the completed DOICU form.)>

Appendix D: Further considerations on sustainable governance and ownership

A sustainable model for quality oversight, governance, and methodological maintenance and development of REQueST is required to ensure that the standards tool continues to develop in practical use. Governance needs to be organised to incorporate multi-level decision making and guidance on the use of the tool. The model must ensure there is clarity over who is responsible for running and developing the tool, and disseminating information on its use.

Governance mechanisms need to facilitate cross-border collaboration between organisations that are responsible for the regulation and assessment of new health technologies and which therefore have an interest in the availability of high quality registry data.

A sustainable structure for REQueST will need an adaptive model that promotes learning, encourages continuous monitoring, facilitates broad participation in the policy making processes, encourages transparency, and as a result, delivers the expected level of value to stakeholders and users.

The model must be practical, robust and transparent, reinforcing collaboration between stakeholders, and meet public sector body standards of conduct.

Proposed operational and governance structure

A host organisation could be appointed to carry out the agreed tasks required for methodological maintenance and development of the standards tool.

A Governance Board could be established with responsibility for policy making and supervision. Decisions relative to membership, remit and organisation of the Governance Board should be taken in the light of the future European HTA collaboration. Academic and other stakeholder representatives should be invited to contribute. The Governance Board should hold annual general meetings to review and improve performance.

Staff from the host organisation should carry out activities involving methodological and process development of the REQueST tool, including:

- Consultation on key documents such as methods and process guide updates
- Developing a feedback mechanism for the tool to enable continuous improvement
- Updating methodological standards.

Other organisational and operational issues

Other issues to be addressed and formalised by the host organisation include:

- Terms of use
- Copyright terms
- Enforcement of rules (see EIF box below for example)
- Editorial and content management policy
- User support policy (tasks, responsibilities, minimal standards).

Box: European Interoperability Framework (EIF)-compliant decision making process

When an initiative for change gains acceptance on the policy level it is formally accepted and defined as a joint change action vision and included in a periodic plan. By acceptance of the joint change action vision on this level, each member of the policy board assumes responsibility to drive their subordinate team of experts on lower interoperability levels towards a functional change project specification.

Stakeholder legal representatives review the approved and articulated change action vision against the EU and national legal contexts (to determine actual or possible legal obstacles to goal achievement); if obstacles exist, they should harmonise a feasible legal change context, or define legal conditions the joint change action has to meet in order to be legally acceptable for all to proceed.

Legally approved change action vision is reviewed on the next level by stakeholder representatives responsible for related organisational/process systems; the outcome is either an acceptable mutual joint change organisational model, or an agreement on needed policy or legal model revisions that would lead to a jointly acceptable process and operations model for the change.

When the process/operations model is defined, stakeholder semantic experts need to harmonise a joint change semantic model compatible to their existing context. Any encountered difficulties that need resolution on higher levels are jointly articulated and communicated for modification.

Having agreed on the business specification, stakeholder technical experts review most adequate application or modification of their existing technical resources, determine a possible need to develop or source additional capacities and resources and define a virtually unified technical solution environment.

Layered functional and responsive change/supervision structure (policy/legal, organisational, semantic and technical) assures continuity of availability, operation and maintenance of the full scope of the REQueST tool according to priorities and accepted policies.