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Registries or non-pharmacological observational studies? An operational attempt to draw the line and to provide some suggestions for the ethical evaluation of rare disease registries

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Abstract
Originally established to evaluate the ethical aspects of clinical trials, Ethics Committees (ECs) are now requested to review different types of projects, including, among others, observational studies and disease registries.
In Italy, clinical trials on medicinal products for human use and on medical devices are regulated by EU Regulation 536/2014, EU Regulation 2017/745, and 2017/746 while pharmacological observational studies are regulated by the Italian Medicines Agency guidelines of 2008 and by Ministerial Decree of November 30th, 2021.
The other types of studies are not strictly regulated, causing discrepancies in their definition and assessment by the ECs, and slowdowns in the start of projects.
The present contribution aims to propose definitions and distinctions between non-pharmacological observational studies and disease registries, which constitute different entities but are often assimilated by ECs, and to formulate suggestions for the evaluation of rare disease registries, which are an expanding research area of interest.

Key words
- ethics committees
- ethical review
- observational study
- registries

ETHICS COMMITTEES' EVALUATION ACTIVITIES: INTERVENTIONAL, OBSERVATIONAL STUDIES, AND DISEASE REGISTRIES

According to the Italian law, an Ethics Committee (EC) is "an independent body whose responsibility is to protect the rights, safety and well-being of human subjects involved in a clinical trial and to provide public assurance of that protection (…). Ethics Committees (ECs) may also carry out advisory functions in relation to ethical issues related to scientific and welfare activities, in order to protect and promote the values of the person" [1].

Established to evaluate the ethical aspects related to clinical trials, ECs are now involved in the examination of different types of studies that include, in addition to clinical trials (CTs), observational studies with drugs and/or medical devices, population studies, disease registries and health surveillance activities, surveys, focus groups, studies based on the use and reuse of health data and/or biological samples, to name a few.

Clinical trials with medicinal products and medical devices are fully regulated by EU Regulation 536/2014 [2] and EU Regulation 2017/745 and 2017/746 respectively [3, 4].

Observational studies with drugs are regulated by the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA) "Guidelines for the classification and conduction of observational studies with drugs" [5] and, more recently, the Ministerial Decree of November 30th, 2021 [6], which provides for a standardised procedure for the submission of applications to the ECs and the forms to be attached [7, 8]. The aforementioned decree instructed AIFA to issue a measure aimed at defining the new guidelines for the classification and conduct of observational studies with drugs, within thirty days, which, however, has not yet been adopted.

The "other" types of projects evaluated by ECs are

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not specifically regulated. They may differ in the level of risk for participants and also in the methodology and criteria for their evaluation. For these projects there are no clear rules concerning the forms and documentation that should be reviewed by the ECs.

A further grey area arises from the lack of regulatory references to the possibility for these "other" studies to receive an opinion from a single Committee, rather than multiple ECs. Currently, a unique opinion is released only for clinical trials with medicinal products and medical devices and for prospective pharmacological observational studies [2, 5].

Unfortunately, the lack of regulation for studies that do not fall within the umbrella of Regulation 536 and Ministerial Decree of November 30th, 2021, in particular non-pharmacological observational studies and disease registries, is often the cause of confusion and procedural discrepancies in the assessment processes by ECs and delays in starting the projects [9].

Multicentre projects are often reviewed by different ECs, which may request implementations to the documentation submitted by the applicant, with the invitation to fill out centre specific modules, often borrowed from the forms used for clinical trials and observational studies with medicinal products.

These multiple requests have consequences in terms of time and resources for ECs, whose workload is unnecessarily aggravated, and represent a challenge for researchers whose chance to finalize the projects are put at risk.

Indeed, in non-pharmacological observational studies and disease registries, especially those focused on rare diseases (RDs), it is essential to involve as many centres as possible in order to achieve the highest coverage in the population of interest. The timing of involvement of the centres, which also depends on the time of approval by the ECs, is crucial for the possibility for a study or a registry to start in time. The timing of ECs approval directly affects the timing of centres' involvement. Both of them are crucial for studies and registries to start in a timely manner.

In order to streamline the assessment procedures of non-pharmacological observational studies and registries by ECs, it would therefore be necessary to: a) entrust a unique committee with the ethical clearance of these projects, as it already happens for the evaluation of clinical trials on medicinal products and medical devices and for pharmacological observational studies; b) standardise the evaluation procedures for these types of projects, taking into account their lower level of risk as compared to interventional studies, and promoting the adoption of simple and comprehensible standard forms, aimed at protecting and involving participants rather than defending researchers or institutions.

While the first point could be addressed easily through an adequate normative framework, the second one is more complicated since ECs often encounter difficulties in classifying the different types of projects, and thus also in their evaluation. The boundaries between registries and non-pharmacological observational studies may be blurry and may generate a procedural confusion that affects the whole research process.

Given this framework, the aim of this paper is to shed light on the difference between the two types of projects. Starting from the literature, the paper proposes a distinction between non-pharmacological observational studies and registries and presents some aspects that should be considered in the intent to correctly classify them.

Specific proposals for the evaluation of observational studies will not be discussed in this work, which only aims at introducing suggestions for the evaluation of registries and on the documentation to be submitted to the ECs, with specific focus on registries dedicated to RDs.

NON-PHARMACOLOGICAL OBSERVATIONAL STUDIES AND DISEASE REGISTRIES: DEFINITIONS, SIMILARITIES, AND DIFFERENCES

Although non-pharmacological observational studies and disease registries both belong to the category of "non-interventional" projects and have a similar low risk-benefit profile, they constitute two distinct types of initiatives, with different objectives and methodologies to be considered in the assessment criteria and different documentation to be submitted in support for an ethical review.

Observational studies

Regulation 536/2014 defines the observational (or "non-interventional") study as "a clinical study other than a clinical trial" (Article 2, paragraph 2, point 4). Beyond EU Regulation 536/2014, the definition of "observational study", as well as the regulatory framework governing the conduct of such studies and the terminologies used to describe them, vary from country to country and are not harmonised internationally [10].

In the Italian legislation, the category of "observational studies" only includes studies in which a medicinal product is prescribed [5, 6, 11].

However, observational studies are not limited to those focused on prescription of medicines or medical devices. There may be different kinds of observational study, with different designs and methodologies [12]. Unlike what happens in interventional research, these are investigations in which the assignment of the patient to a specific diagnostic/therapeutic/care strategy or exposure to a situation/risk factor are not conditioned by the researcher, but fall within normal behaviour or clinical practice, without applying procedures that may present an experimental character.

According to a recent work an observational study may be defined as "collection and analysis for scientific purposes of epidemiological, administrative, clinical and biometric data related to single human subjects" [13].

Observational studies may include so-called "additional procedures" namely procedures that deviate from standard care. These procedures (like blood sampling, swabs etc.) are aimed at answering the study questions and may involve minimal risk for the subject (for instance swelling, redness, and pain at the site of sampling).

In this regard, the EC responsible for evaluating an observational study that involves "additional procedures" must determine whether they are acceptable or not in terms of invasiveness/dangerousness, and verify whether the information collected through these procedures can in some way influence the subsequent management of the patient: any additional and low-risk procedures (with possible insurance coverage) should not lead to the loss of the observational nature of the study [14]. The EC must also verify that additional procedures are adequately introduced and explained in information sheets for participants.

Registries

Registries are, by definition, instruments of an observational nature. According to the well-known definition of Gliklich *et al*., a patient registry is "an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes" [15].

A slightly different definition comes from Corrao, who defines a registry as "a file for the collection of data, records, administrative, accounting, financial, personal and legal records" [16].

According to the Decree of the President of the Council of Ministers (DPCM) of March 3rd, 2017: "Identification of surveillance systems and registers of mortality, cancer and other diseases" (DPCM March 3rd, 2017), there are different types of registries of health interest, including: disease registries; mortality registries; registries of treatments consisting of cell and tissue transplants; registries of treatments based on advanced therapy medicinal products or tissue engineering products; registries of implantable prostheses.

According to the definition of this law a "disease registry" is "an active system for the systematic collection of personal, health and epidemiological data to record and characterise all cases of risk to health or a particular disease or a relevant health condition in a defined population" [17].

The definitions for "registry" reported here, and there are many others, are not univocal. The paragraph dedicated to RD registries and *Table 1* will highlight that there are many different kinds of registries according to their sponsors, aims and design. This aspect further complicates the effort to find a valid and comprehensive definition. Nevertheless, despite their discrepancies, different definitions share the idea of systematic data collection, aimed at registering most, if not all, cases with a similar condition or exposure in a specific coverage area in a standardised way.

Observational studies and registries: main similarities

Compared to interventional studies, observational studies and registries rarely offer the chance of direct clinical benefit to the participant. However, the risks arising from participation are also low.

Rather than direct for the participant, the benefits of participation in observational studies and disease registries are of a collective nature, and derive from an increase in the scientific knowledge available on certain diseases, exposures, protective factors, or risk factors.

In some cases, collateral benefits of an individual nature are foreseeable, for example if participation in an observational study or a registry provides for the pos-

Table 1
Elements for the definition of a registry (modified from Addis *et al.* 2015 [31] and Kodra *et al.*, 2017 [32])

Field	Elements to be considered
Sponsor	Public, private, patients associations, mixed
Study objective	Single pathology or groups of pathologies
Aim	Natural disease history, genotype-phenotype correlations, epidemiological surveillance, efficacy assessment, cost effectiveness or safety of interventions
Scope and coverage	Hospital, territorial, regional, national, international; coverage of population or non-population
Stakeholders	Regulatory authorities, healthcare companies, pharmaceutical and device companies, patients, scientific societies, clinics, universities
Design	General purpose or comparative efficacy-oriented registries
Outcome	Outcome (e.g., mortality), intermediate, subjective, surrogate, process
Costs	Direct and indirect costs of the registry and the subject matter of these
Data source	Professionals, patients, existing databases, mixed
Data type	Relevant data for the evaluation of the results, periodicity, methods and tools of collection (paper, computer)
Standard	Regulatory Documents, Guidelines
Database	Data management and storage, data security, backup
Quality control	Audit, random checks, clinical monitor
Coding system	Existing coding systems, possible correlations with other databases
Dissemination of data	Open access vs restricted access, publication of reports
Lifecycle of the registry	Expected duration, stopping rules

sibility to come in contact with research groups that could initiate clinical trials for the pathology under investigation.

In addition, if the data and/or the samples collected for an observational study or a registry are periodically re-analysed, new information relevant to the participant may become available (for example, if a participant's genetic sequencing data includes variants initially classified as "variants of unknown significance", VUS, and, in subsequent analysis the variants themselves are attributed significance for certain conditions).

The most common foreseeable risk for those participating in both an observational study or disease registry is related to the processing of personal data, resulting from the accidental disclosure of personal data with possible repercussions for the social, occupational, and emotional sphere of the participant.

These risks must be carefully evaluated by the ECs and by the Data Protection Officer (DPO), also in relation to the level of data sensitivity, the possibility of tracing back the identity of the participant

and the inherent risk of stigmatisation arising from the dissemination of research data and results.

In addition, there may be psychological risks or discomforts, in particular in studies involving the use of questionnaires on particularly sensitive issues that may require psychological support at the time of the interview or immediately after.

The risks described above may require mitigation measures, as well as a specific and detailed description in the participant information documents and informed consent forms.

Observational studies and registries: main differences

Although observational methodology is common, according to Bruzzi, observational studies and disease registries are different entities and should be assessed differently (*Table 2*) [18].

An observational study, like any "study", is intended to address an open question and should be designed with this aim in mind.

Following the definition adopted by the Italian DPCM of March 3rd, 2017, a disease registry is "an active system for the systematic collection of personal, health and epidemiological data to record and characterise all cases of risk to health or a particular disease or a relevant health condition in a defined population" [16], it is not designed to address specific questions and thus it cannot be considered as a "study", even though registries focused on medicinal products or other devices usually aim at evaluating specific outcomes (*Table 1*).

Therefore, the ethical evaluation of observational studies and disease registries should be based on different criteria and require the filling of different study documents.

In this work, we will propose evaluation criteria and documents that ECs should review in the assessment of registries, in particular focused on RDs. Indeed, RD registries are an expanding area of interest for clinicians and researchers and, with increased frequency, researchers are requesting ECs to evaluate these types of proposals.

Rare disease registries

In some areas of research, particularly in RDs, registration activities have grown exponentially in recent years.

In 2021, Orphanet registered a total of 812 RD registries [19], most of them with national (561) coverage, but also European (97), regional (78) and international (76) registries.

The majority of the registries identified by Orphanet is public (84%); however, there are also private non-profit (12%) and private for profit (4%) registries.

In Italy, there are a total of 95 registers recorded by Orphanet, 70 of which with national coverage, 11 with regional coverage, 6 European registries and 8 international registries.

In a work by the EPIRARE (European Platform for Rare Disease Registries) project, which analysed the different regulatory, ethical, technical, and financial issues related to the development of RD registries [20], the latter were classified into three groups:

1) public health registries for epidemiological research, health service planning and disease surveillance. These are population registries and often collect information on more than one disease or condition, such as tumours or congenital anomalies [21, 22];
2) clinical and genetic registries that collect information on phenotypes, genotypes, family history, and clinical data;
3) treatment records aimed at the evaluation and monitoring of orphan drugs in post-marketing surveillance that collect information on the outcomes of the patients taking them.

The three types of registries described above, present very different peculiarities and problems to be analysed, also from an ethical point of view.

Table 2
Main differences between observational studies and registries (modified from Bruzzi, 2015 [18])

Observational study	Registry
Has one or more precise research/evaluation objectives	Can be multipurpose
Has a time limit	Does not have a time limit
Can provide for the *ad hoc* collection of data (e.g., questionnaires) and sometimes additional procedures (e.g., withdrawals)	Usually includes data collected for other purposes (clinical, administrative)
Data collection is aimed at the objectives of the study	Data collection is about information that "might" prove useful
Provides a research protocol with a statistical analysis plan	Should facilitate observational studies or even clinical trials

In fact, public health registries, as well as drug or medical device registries, are usually set up by law, provide almost exhaustive coverage of the phenomenon under consideration, rely on an infrastructure with a capillary network of data collection centres and are provided with long-term financial coverage. Usually, these registries do not require the collection of informed consent for participants, as participation is mandatory. Nevertheless, an information sheet is discussed with participants.

On the contrary, clinical and genetic registries are often initiated spontaneously by individual clinicians or small groups of clinicians in collaboration with patient associations (and in some cases by private sponsors) to collect as many cases as possible with a given disease or condition, in order to survey and compare the cases, their phenotypic and genotypic characteristics, their natural history, to name but a few objectives.

These initiatives are not established by law or decree, they do not include all the cases present in the territory, they do not have an infrastructure and a capillary network of centres for the collection and insertion of data, and they do not have long-term financial coverage. Informed consent of participants is always requested for this type of projects.

However, researchers usually define these initiatives as "registries" as they are aimed at a "systematic and continuous" collection data and share most of the characteristics of the registries listed in *Table 1*.

The rarity of certain diseases or conditions makes these types of activities necessary, and the establishment of such registries is encouraged, among others, by the European Commission already in a 2008 communication, "On Rare Diseases: Europe's challenges" [23], which states "paragraph 5.11, Registries and databases": "Registries and databases constitute key instruments to increase knowledge on rare diseases and develop clinical research. They are the only way to pool data in order to achieve a sufficient sample size for epidemiological research and/or clinical research. Collaborative efforts to establish data collection and maintain them will be considered, provided that these resources are open and accessible. A key issue will also be to ensure the long-term sustainability of such systems, rather than having them funded on the basis of inherently precarious project funding".

The Council of the European Union underlines the importance of rare disease registries in the Council Recommendation of June 8th, 2009, on action in the field of rare diseases [24], referred to in paragraph "II. Adequate definition, codification and inventorying of rare diseases, point 5," is recommended: "Consider supporting at all appropriate levels, including the Community level, on the one hand, specific disease information networks and, on the other hand, for epidemiological purposes, registries and databases, whilst being aware of an independent governance".

Since 2015, the European Medicines Agency (EMA) also recognises the importance of disease registries and, through the "Initiative for patient registries", encourages the regulatory use of existing patient registries and promotes the establishment of new registers where not available or inadequate, in order to collect and analyse high-quality data that can inform regulatory decisions (https:///www.ema.europa.eu/en/human-regulatory/post-authorisation/patient-registries).

More recently, clinical centres across Europe specialised in RDs research and care have built the European Reference Networks (ERNs). The first ERNs were launched in March 2017, involving more than 900 highly-specialised healthcare units in 26 EU countries. 24 ERNs are working on a range of thematic issues including bone disorders, childhood cancer and immunodeficiency (https://health.ec.europa.eu/european-reference-networks/overview_en).

ERNs aim to facilitate discussion on complex or rare diseases and conditions that require both highly specialised treatment, and specific knowledge and resources. The organisation of clinical centres in ERN is likely to foster the setup of new RD registries.

In our contribution, we will not refer to the evaluation of public health epidemiological RD registries, nor to the evaluation of safety, cost and efficacy of orphan drugs, but to RD registries, aimed primarily at describing the natural history of the disease.

CRITERIA FOR THE ETHICAL EVALUATION OF RD DISEASE REGISTRIES

In RD research, the continuous and systematic collection of health data in registries is an ethical imperative. This is particularly important because, compared to more common diseases, the rarity of conditions, the heterogeneity of their manifestations and the geographic dispersion of the cases involved limit the acquisition of useful information to the understanding of the pathological mechanisms and the therapeutic possibilities for the affected persons.

As already highlighted by Bruzzi [18], registries are not "studies" with specific cognitive objectives and structured hypotheses to be tested, but rather they are organized information systems for the census and monitoring of the conditions of interest, potentially useful for the conduct of study projects.

However, in RD research, especially when registration initiatives are undertaken by small groups of clinicians and/or patients' associations, the lack of long-term funding makes registries comparable in some respects to the category of "study projects".

Also, the lack of institutional or regulatory coverage makes these types of activities similar to study projects, for which the acquisition of consent is a necessary element for participation.

Due to the similarities that RD registries share with study projects, ECs may tend to apply to RD registries the same evaluation criteria that they apply in the evaluation of research projects like observational and clinical studies.

However, as already stated, the value of a registry does not lie in its ability to generate inferential knowledge, but in the ability to collect reliable and as complete data as possible, which may prove useful in the design and conduct of "registry based" studies [25]. The type of knowledge generated by a registry is therefore descriptive.

In addition, as compared to other projects and studies, RD registries must meet certain additional criteria and fulfil specific role requirements.

Therefore, in addition to the "traditional" criteria for the ethical evaluation of research with human beings: value, validity, equal selection of subjects, favourable risk-benefit ratio, independent review, informed consent, and respect for participants [26], ECs must consider other aspects [27] summarised in Box 1 available online as *Supplementary Material* [28-30; 33], which also determine the type of documentation to be submitted for evaluation.

EVALUATION OF RD REGISTRIES AND DOCUMENTATION TO SUBMIT TO THE ETHICS COMMITTEE

ECs should not evaluate the elements described above (Box 1 available online as *Supplementary Material*) through the same documents borrowed from clinical trials, but with *ad hoc* documentation, modulated on the purpose and specificities of the registries and possibly through checklists prepared *ad hoc*.

The documents that should be required and those that should not be required for the evaluation by an EC are mentioned below.

Documents required for the evaluation of a RD registry

The documents required for the evaluation of a RD registry are:

- letter of intent to the EC, dated and signed by the registry Sponsor, with the title of the project, the number of centres involved for multicentric studies, the duration of the project, the financial sponsor and the list of attached documents;
- project acceptance letter signed by local principal investigator (PI) and registry promoter for multicentric studies;
- information for participants and informed consent form (Box 2 available online as *Supplementary Material*);
- information and authorization for personal data treatment;
- (if applicable) information and consent form and revocation for: collection of biological samples; storage and conservation in a research biobank;
- Registry Protocol in which are explained (*Table 2*): identification of the promoters, sponsors, and PI of the registry; objectives of the registry; inclusion and exclusion criteria of participants; variables to be collected; data quality management; location of the server and security measures; governance, including the participation of patient organisations; presence of a coordinating committee (governing board) and, where appropriate, other committees (i.e. data access committee); methods of informing participants, including indications for the re-consent of participants under 18 years of age, ethical aspects and protection of privacy; project timeline with intermediate objectives;
- Case Report Form (CRF) with the fields to be completed and the distinction between mandatory and optional fields;
- Data Management Plan with a description of how data is managed during the lifetime of the project and possibly after its completion;
- (model) agreement between sponsor, institution and PI for the study including a detail of costs, availability of human and infrastructural resources;
- list of involved centres and local contacts, with letters of endorsement;
- opinion of the coordinating EC (if applicable);
- curriculum vitae of the PI with a list of relevant publications and declaration of potential conflicts of interest.

Documents not required for the evaluation of RD registries

The following documents are usually required in the evaluation of observational studies, but they are not relevant in the evaluation of RD registries and should not be requested; if deemed necessary, they should be reformulated and adapted to the specificities of the registry:

- statement on the observational nature of the clinical trial (AIFA Determination March 20th, 2008): registries, by definition, are not clinical trials and are not observational studies and the "Statement on the observational nature of the study" does not apply. Instead, it could be useful to add to the study documents a declaration that the parameters required as fields in the registry CRF are normally collected in clinical practice and the request to perform certain examinations for the individual patient is independent of the request to include the patient in the registry;
- declaration on the non-profit nature of the study, if this is the case. This document, often required by the EC amongst the documentation to be attached to the application, may include a request to declare that "the study is not finalized to the industrial and/or commercial development of the medicinal products in study, or however to economic exploitation of the same and/or of the data and results of the same experimentation";
- letter to the general practitioner (GP): generally, data recording activities do not have clinical consequences, so the general practitioner should not be involved. A document dedicated to the involvement of the GP could make sense if the GP was involved in the collection and sharing of patient data;
- statistical analysis plan: unlike clinical studies, which involve the formulation of clear and specific questions to be verified through a study design and a plausible statistical analysis plan, in RD registries the type of analysis envisaged is predominantly descriptive. The request for a statistical analysis plan may not be relevant.

Monitoring of the progress of the registries

Following the approval of a RD registry, the EC should be able to monitor its progress, in order to verify the good performance and compliance with the feasibility and sustainability requirements of the projects.

For this purpose, ECs may request the Promoter or registry PI to submit to the Committee a note docu-

menting the progress of the project on an annual basis. The note could include details on the number of cases entered, possibly indicating the contribution of each participating centre.

The PI may also provide other information documenting the development of the registry, for example, by reporting to the EC any scientific publications generated by the processing of registry data.

If the registry does not achieve the intended objectives in terms of patient inclusion and the completeness of the data collected for each patient, it is conceivable to propose an amendment to the study protocol that goes in the direction of simplification, for example a reduction of the fields in the CRF.

Once the funding period is over, the project should be concluded if it is no longer able to remain operational, if other sources of funding are not available, or if a proper coordination is not feasible.

However, keeping the collected data and making them accessible is crucial for further research projects or for the opportunity to merge the register with other registers dedicated to the same disease or groups of similar diseases.

If the registry is hosted on a platform for RD registries, the platform itself could decide on the operation of the collected data.

In the event of a change of governance of the registries, patients should be informed of the decision with the possibility of continuing or withdrawing participation.

This information should be indicated in the Data Management Plan and shared with participants.

CONCLUSIONS

In RD research there is a huge need of quality data to be collected and made available for researchers to conduct valid research on individual RDs or groups of diseases, potentially leading to scientific discoveries and/or other improvements in the life of patients.

The importance of RD registries is underlined by several recommendations at international and European level and the establishment of new RD registries should not be halted or delayed for unjustified procedural reasons. At the same time, registration activities constitute an expanding area of work and investment on the part of clinicians, institutions, and patient associations. Registries should be conducted following the right criteria and safeguards, otherwise they risk to produce useless data (lacking quality, not accessible or not interoperable), or, lacking a long-term vision and sustainability plan, to be prematurely interrupted with a consequent loss of time, energy, and financial resources.

If RD registries data are intended to support RD registry studies, the registrars responsible for their conduct and management must assure their reliability in term of timeliness and completeness of data. This aspect not only has a practical value, but also ethical implications, particularly regarding the value and validity of the study: ensuring the quality of the data and the study is a duty towards patients.

It is therefore crucial for new registration activities to be guided by tailored criteria. Within this framework, ECs would play a unique role in the evaluation of RD registries, including an assessment of their design, governance and organization. By rationalising the evaluation process and avoiding time-consuming procedures, ECs will be increasing opportunities for RD research.

Conflict of interest statement

The Authors declare that there are no conflicts of interest.

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