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Supplementary Materials for

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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Box 1
Some criteria for evaluation of rare disease registries

- *Novelty and added value of the register*
  New registration activities are in many ways desirable and necessary. However, it is important that new initiatives are not isolated but coordinated and interoperable with other related activities. The spread of scattered and disconnected data collection systems can lead to waste and loss of important information, as well as trust by patients. ECs should encourage research groups to coordinate their efforts with similar initiatives, including at international level, if any.
- *Definition of the registry*
  A registry can be defined on the basis of several elements (by type of sponsor, purpose, scope, geographical coverage, diseases being studied, methods used for data collection, etc. see *Table 2*). The type of registry should be clearly defined, in particular for what concern the nature of the sponsor and the sources of financial support.
- *Careful selection of data sources*
  The selection of data sources is crucil to the success of a registry. Primary data sources (ad hoc collections) are expensive and time-consuming but provide higher quality data than secondary data sources (administrative, hospital discharge forms, etc.). Before including a secondary data source in a registry, it is important to consider its ethical and legal feasibility and the potential impact on the overall quality of the registry data.
- *Clear definition of inclusion and exclusion criteria*
  Inclusion and exclusion criteria should be defined in advance to avoid selection bias. For RDs, a frequently adopted inclusion criteria is the presence of a molecular diagnosis. In the selection of participating centres (e.g., hospitals or local services), it is important to consider their representativeness and to ensure a satisfactory level of quality in the identification of all eligible patients.
- *Data quality (completeness, accuracy, no duplication and updating)*
  A function for data collection and "cleaning" (data manager), evaluation and analysis must be established. Registry documents should include standard operating procedures (SOPs) for quality control (how to deal with inconsistent, incorrect, missing data, etc.).
- *Data hosting and registry security*
  The location of the electronic system that collects and hosts the information and the name and contact of the person responsible for the storage, maintenance and backup of the database must be clearly indicated.
- *Compliance with the principles of availability, accessibility, interoperability and re-use*
  Findability, Accessibility, Interoperability, Reusability (FAIR) [28] and the adoption of Common data elements [29] and ontologies for the description and annotation of the collected data [30] which make the data themselves comparable with those collected from other registries.
- *Presence of an adequate system of governance*
  The project must have a strong commitment. There must be initial consensus among the community of researchers involved and it must be shared with the greatest number of reference centres for the disease in question distributed throughout the country. Patient organisations must be involved in the governance of the registry, the definition of funding sources, variables of interest and data access policies.
- *Informed consent*
  It must include the information necessary for participants to join in an informed manner (Box 2).
- *Sustainability*
  Disease registries must be assessed with respect to their sustainability and the real possibility of success in terms of results for scientific research.
  ECs must therefore assess the criticalities and real possibilities of achieving the proposed objectives, but also the possibilities of "survival" and reuse of registries, determined among other things by their level of representativeness, data quality, security, accessibility and effective usefulness for research.

Box 2
Comprehensive information for informed consent in biobanks and rare disease research

Relevant information in informed consent documents for biobanks and rare disease registries (modified from Gainotti *et al*. 2016 [33]):

- general information (name of principal investigator, PI, institution, financing, duration, centres involved); objectives, types of research (for example, research on cancer, rare diseases, etc.);
- voluntary participation and the possibility of withdrawal;
- procedures involved in participation, including interviews, examinations and samples;
- types of data and samples to be collected, prospective and retrospective (e.g., from medical records);
- potential physical, psychological and social risks, including information risks;
- potential benefits of participation;
- local protections to ensure confidentiality of data and samples;
- access to data/samples for research purposes: who can access, who will control and authorize access, procedures in place (e.g., presence of a data access committee);
- whom to contact to address any concern or question;
- access to data/samples for validation and quality control purposes;
- ethical review of the study;
- possibility of compensation/refunds;
- storage of data and samples;
- dissemination of results (articles in scientific journals/non-specialized press/publication of aggregated/disaggregated results/patient images and occasionally short video sequences).

Information for studies involved in international rare diseases (RDs) research:

- data sharing between national and international research groups;
- possible application of large-scale genome sequencing techniques;
- return of secondary results;
- data hosting on open access platforms;
- use of interoperable algorithms for pseudonymisation of participants;
- access by industry if foreseen and possibility of commercial or patent fallout by third parties;
- possible interconnection with other databases (registry, computerised medical records, clinical trials, etc.);
- procedures for withdrawal of consent, recovery and/or destruction of samples and impossibility of deletion of already published data;
- possibility to contact the participant again.