Author's response to reviews

Title: The EPIRARE Proposal of a Set of Indicators and Common Data Elements for the European Platform of Rare Disease Registration.

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Author's response to reviews: see over
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Dear Dr. Van Oyen,

The authors wish to thank the referees for their useful comments and observations, which helped to better explain and present the work done. They have been taken into consideration to improve the manuscript as will be indicated below.

From the overall consideration of the referees’ comments we have understood that the standardization goal of the platform in the registration of RD patient data, which is the main aim of the Common Data Elements, and a possible future function of the platform as a “mega-registry” was not clarified enough in the paper. Moreover, the bearings of the proposed CDE for registries and for the actual European RDR Platform were also not clearly distinguished.

Considering that the readers of the article will be essentially interested to the CDE from the standpoint of registry holders, we have deemed the light on the issues specifically regarding the data collection by the platform as follows:

a) Modified the title to make reference to the process of registration rather than to registries; this change makes the title more consistent with the wording in the introduction and with the wording used by the European Commission (ref. 3 of the paper)

b) Eliminated any reference to the requirements of platform indicators, since this issue was treated with reference to the features that should be fulfilled by the platform for it to provide meaningful indicators in the future and little likely case that it will actually collect data or will merge data from many registries. Although these requirements are considered by registry holders when planning their studies to provide meaningful indicators, it was not intended to propose that all registries should be population-based and prospective. Consistently, the “Additional file 2” is withdrawn.

c) The conclusions are redrafted distinguishing the different use of the CDE for registries and for the platform.

d) The reference to the disability profile and to metadata has been deleted from the table (domain 3 “Outcomes”) for the following reasons: 1) the actual disability profile based on a generic questionnaire, suitable (but most clinicians will find it unsatisfactory) for application across diseases, is rather lengthy to be compiled; 2) the reference to metadata is a point that pertains only to the data collection by the platform and not to registries.
Reply point-by-point to the referees’ comments is presented following the structure of the 1st referee report. Nonetheless, the relevance of the reply for the second referee’s comments is also indicated.

5th paragraph of the referee’s report: Methodology and experts participating in the discussion of CDE.

The “Methods” section now makes explicit reference to the published lists of the experts that have participated in the development of the EPIRARE activities (and specifically the identification of the stakeholders, their needs and the feasibility of the proposed CDE) and of the other activities on which the list of indicators has been built.

Numbered paragraphs of the referee’s report:

1) High number of variables (also commented by the 2nd referee)

The actual mandatory data, which can be regarded as the minimum set of CDE, are those of the domain 1 (Case characterization essentials), which contains data which are usually collected in regular medical practice plus data on the patient position regarding participation in research. This means that a registry could only provide the notification of the existence of an identified patient, with a defined disease and age, in a place, cared by a determined centre and willing (or not) to participate in a trial and recruited (or not) in a past trial. The deletion of the information on the patient position regarding participation in research, which can be regarded as unusual for a registry, actually provides an important support to research by facilitating patient recruitment and will be an important piece of information in case that data could be merged centrally (or queries could be sent to all registries adopting this CDE proposal).

In the new draft of the conclusion it is explained that the set of CDE should not be taken “in full” by a registry, but is a pick list, where the elements are selected on the basis of the purposes pursued, and the related indicators intended to be computed, by a registry. Consequently, the sentence in the first paragraph of page 5, which clearly was too weak in explaining this point, has been deleted.

Regarding the recommendation, made in the article, to collect all data indicated in the domain 3 (Outcomes) if outcomes are in the interest of the registry, a point can be made on the limited clinical relevance of health related quality of life (HRQoL) score as outcome. As explained in the paper (last paragraph of page 4), this information adds patient- and policy- focus to a registry beyond its clinical use. Moreover, the collection of this information requires few minutes of non-medical staff and could also be reported by the patient; and the frequency of collection of this information can be sufficiently reduced depending on the overall course of the disease.

2) Feasibility (also commented by the 2nd referee)

Having clarified that it is not necessary to collect the full set of the CDE, the concern regarding the feasibility of this data collection by registries should be reduced to the actual compliance with the specifications requested for each data element. Indeed, the variables to be collected will be tailored to the registry scope and its number will be strongly reduced. For example, a registry focused on the effectiveness of transplantation in the treatment of a disease should collect, beside the mandatory data set, the transplantation date, the transplanted material, the service were the transplant was carried out and, prospectively, the common data elements regarding outcomes. Such a set of data seems rather reasonable for such a study.

The reviewer also referred to the feasibility of a prospective collection of the full set of CDE data. As explained in item c) above, the requirement of prospective data collection has no longer been
dealt with in the paper, since it is not central in the definition of the CDE and especially is not a mandatory requirement for all registries. However, as in the example here above, the prospective collections of the selected CDE data will be, in our opinion, surely reasonable and feasible.

Regarding the feasibility, the EPIRARE project has carried out a survey among registries to study the actual use of the definitions (and formats) proposed for the CDE, the feasibility to change used definitions to the proposed ones, the usability of already collected data in the new framework of the proposed definitions. This survey showed that the vast majority of responding registries works with a prospective design of data collection. Most other CDE data, but for the outcome data and other data of services (as expected since not all of them are not relevant for all registries), are collected or can be collected as proposed by about 2/3 of responders (see the report at http://www.epirare.eu/down/del/D9.1_ReportontheSurveyonCDE_FINAL.pdf.) A manuscript on the results of this study is in preparation.

3) a) Purpose of CDE
This cannot be indicated. Indeed, as explained in the conclusions, the CDE is like a pick list, from where the elements relevant for the aims, which a registry intends to pursue, are selectively taken. The full set of CDE will be present only in the platform, in case that it will actually collect data, as explained in the conclusions. In this case too, however, the data to be collected on a specific disease, or from a specific registry will be limited to those relevant for that disease or available from that registry. The database of the platform will therefore need to accommodate all sets of CDE tailored to the features of many different diseases or selected by different registries. In this case, it will, and needs to, represent the “maximum possibilities offers by all the registries” as mentioned in the 6th paragraph of the reviewer report.

3) b) healthy carriers
Healthy carrier condition (questioned in the bullet point list) is taken away from the CDE list. The mistake was overlooked among the genetic information of the case family.

4) ORPHANET Code (indicated in pages 11 and 14)
The authors agree that the classification and coding of rare diseases is not satisfactory; correspondingly, registries use a variety of classification systems, giving rise to a rather fragmented situation (see reference 8 in the paper). Considering the OPHANET list of diseases overall the most detailed and most widely applicable, the attempt was done to propose it as an operative reference in the wait that a shared classification is agreed. However, as for some other elements of the CDE set, requiring expert agreement, we refrain from giving this indication and indicate now that multiple coding is recommended (to facilitate mapping of the disease in different classification systems).

Editor’s comments
The changes indicated are also considered fulfilling the editor’s comments 2 and 3. The final revised document contains also a revision of the references according to the journal style (comment 1), which however has not been recorded with the track changes function of Word.

A few minor editorial amendments have been done in Additional file 1.

Kindest Regards.
Yours

Domenica Taruscio and Luciano Vittozzi