Towards the Standardization of Disease Registry Form Structure

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Abstract: This paper presents a set of specifications for disease registry forms that vary from one registry to another, emphasizing their standardization to ensure better interoperability and data analysis. After an in-depth review of the state-of-the-art disease registry forms, we introduce a standardized structure adhering to the essential data standards set by EPIRARE (Taruscio et al, 2014), a project funded by the European Union to improve standardization and data comparability among patient registries, while respecting all question suggestions provided by the Patient Registry Item Specifications and Metadata for Rare Disease PRISM project (Richesson, Shereff and Andrews, 2012). This structure has been validated on several registries currently in use, demonstrating a high level of accuracy.

1 INTRODUCTION

A disease registry (DR) includes information about patients suffering from the same disease in order to collect and track data related to their diagnoses, treatments, outcomes, and demographics for research, monitoring, and improving the understanding and management of the condition. The information collected by these registries becomes increasingly meaningful depending on the protocols they follow. It is necessary to establish standardized protocols for diagnosis and treatment, which contributes to making the collected data more reliable and comparable, thereby enhancing the robustness of research findings. Protocols can vary from one country to another due to economic, demographic, and even genetic differences.

Different national and international experiences have been conducted. The latest report from Orphanet (Orphanet Report Series, 2023) indicates a total of 827 registries, cohorts, and databases worldwide: 11% regional, 66.5% national, 11% European, and 11.5% global. Germany has the highest number (171 disease registries), followed by France (117 disease registries).

There are many forms and structures which can be included in disease registries. The main component is the disease sheet (i.e. disease form), which is our focus in this paper. Disease registry form includes general data about the patient, circumstance of discovery, clinical and analysis symptoms, treatment and evolution. More information can be added depending on physicians' needs.

The content of the disease registry form varies across registries in terms of the data collected and the structure, types, and presentation of that data.

There are several standardization efforts in the creation of registries, defining essential data that should be included in the registry form. (Aktaa et al, 2023) going further to specify the data type and how it should be retrieved. There are also efforts to group the questions/fields to be collected by registries (Richesson, Shereff and Andrews, 2012), which can be shared across various disease types. This is driven by the fact that standardizing disease registry forms will enhance the interoperability of health and research data (Richesson, Shereff and Andrews, 2012). This, in turn, widens the scope of analyses and research on diseases worldwide.

However, standardization efforts do not encompass the standardization of the structures and representation of registry forms, leading to multiple implementation approaches for these registries. Each registry has its unique way of implementing and representing its forms. The Standardization of the structure and representation of registries proposed in this paper would not only reduce the design and implementation efforts for registry forms but also unify the structure of gathered data, even for registries that do not adhere to a standard. For example, we would no longer find registries with three levels of organization alongside others with four levels, and we would no longer encounter entire sections lacking

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fields specifying the collected data. These structuring issues, often overlooked, can impact the automation of disease registry implementations that comply with global standards.

In this paper, we base our work on established standards to introduce a well-defined structure and representation for the sections of disease registry forms. This is a crucial step for all who aim to generate registry forms that comply with global standards in terms of organization and structure. The structure we have established has been validated against seven resources, including standards and currently used registries, and has yielded an average accuracy of 0.88 and an accuracy of 1 for the two standards used.

This paper is organized as follows: Section 2 delves into related work regarding the standardization of disease registry forms, highlighting our specific contributions in this area. Section 3 outlines the skeleton and structure of disease registry forms. Moving to Section 4, we introduce a theoretical and conceptual representation of disease registry forms, discussing its validation. Finally, in Section 5, we conclude our work.

2 RELATED WORK

Data collected from disease registries represent a valuable source for clinical research. However, despite the availability of a large amount of data from registries worldwide, the utility of this data remains limited due to the lack of interoperability and consistency among these registries. For example, the same question may be asked in multiple registries, but it is formulated differently, and the types of responses vary from one registry to another (Spisla and Lundberg, 2012). Therefore, the standardization of disease registries is a necessity to enhance the quality of medical research and care globally (Computerized Disease Registries | Digital Healthcare Research). This underscores our commitment to this standardization effort by establishing a uniform structure for all registries, clearly defining the diverse components of registry forms and their appropriate relationships.

The PRISM project, funded through an American Recovery and Reinvestment Act (ARRA) grant administered by the National Library of Medicine (NIH), serves as a valuable resource for standardizing questions in rare disease registries. It encompasses over 2,200 questions (Richesson, Shereff and Andrews, 2012). Each question is indexed by one or more keywords that characterize its general content category, such as demographic information, medication details, medical history, and special histories. Additionally, EPIRARE, funded by the European Commission, presents a collection of indicators and common data elements for the European platform dedicated to the registration of rare diseases (Taruscio et al, 2014). These are based on the indicators identified by the EUROPLAN project (Posada, Carroquino and Pérez, 2011) and the EU Rare Disease Task Force (RDTF). The FHIR® (Fast Healthcare Interoperability Resources) standard, developed by HL7® (Health Level Seven), facilitates easier and faster healthcare data exchange. It defines a set of standardized formats, known as resources, to represent various healthcare data types such as medications, allergies, and diagnoses. These standardized formats (FHIR® resources) enable seamless exchange and sharing of data between different healthcare systems and applications. Similarly, SNOMED CT (Systematized Nomenclature of Medicine Clinical Terms) provides standardized terminology that can be utilized in healthcare-related information systems, ensuring consistency and interoperability across various clinical specialties within healthcare systems. However, despite this extensive collection, the number of questions, indicators, and elements provided by these initiatives remains limited when compared to the diverse array of inquiries pertinent to rare diseases. Consequently, disease registries employing PRISM or common data elements for the European platform, resources of FHIR®, or standardized terminology of SNOMED CT may have multiple sections lacking coverage by these established questions, indicators, or elements, resulting in an absence of complete standardization.

(Aktaa et al, 2023) undertook the standardization of TAVI (Transcatheter Aortic Valve Implantation) related data variables (i.e., data fields to be collected) to address registry heterogeneity, facilitating international comparative analyses and the development of comprehensive valvular heart disease registries, regardless of the treatment approach. These variables were classified into two levels: Level 1 for essential quality assessment data and Level 2 for supplementary information useful in quality evaluation and research but not universally required. The selection of these variables was accomplished through a modified Delphi method, with the Working Group voting on a list of candidate variables identified through a literature review. This effort resulted in 93 Level 1 and 113 Level 2 variables across ten TAVI care domains, including patient characteristics, comorbidities, prior interventions, and pre-procedural tests. This could be regarded as a

general standardization of TAVI registries, particularly as it takes into account demographic differences. However, this applies only to a specific procedure used for treating aortic valve disease, Transcatheter Aortic Valve Implantation (TAVI). Similarly, (Fulvio and Mantegazza, 2014) present the European database for Myasthenia Gravis (EuroMG-DB) as a model for an international disease registry. The structure of EuroMG-DB follows a schematic representation, including the Patient main page linked to: (1) referring physicians and MG patients, (2) diagnostic criteria, (3) thymus, (4) biological samples, (5) other diseases, and (6) follow-up visits.

The RoPR project (Gliklich, Leavy and Dreyer, 2020) introduces an Outcome Measures Framework that organizes disease registries into three hierarchical levels: domains, subcategories of data elements, and data elements. These domains encompass: (1) Characteristics, which are further divided into three main categories: Participants, Diseases, and Providers. (2) Treatments, which can be categorized into two main groups: Type and Intent. (3) Outcomes, consisting of five main categories: Survival, Clinical Response or Status, Events of Interest, Patient-Reported, and Resource Utilization. Finally, at the third level, you'll find subcategories of data elements that are used to define an outcome measure, including those that capture physical findings and diagnoses. This project defines the outcomes to be extracted from disease registries, considering the variations among diseases and the specific details they require. It goes further by providing examples of these details for several diseases, yet it does not specify the method or structure for collecting this data.

All these standardization initiatives aim to establish standardized disease registries. They do so by either concentrating on specific aspects of disease registries, emphasizing registry content and offering useful yet limited collections, or by centering efforts on standardizing the extracted outcomes. Nevertheless, these approaches frequently result in an inability to maintain a consistent standardized format for disease registry forms. Alternatively, certain initiatives offer a structured set of variables for collection, but this is limited to a single disease.

The absence of standardization in the formats and representation of disease registry forms renders discussions on interoperability and comparability between registries impossible and would necessitate extensive reformatting of collected data (Fulvio and Mantegazza, 2014). This drove our research efforts to explore the standardized representation of disease registry forms.

3 STRUCTURE AND CONTENT OF A DISEASE REGISTRY FORM

Disease registries can vary significantly based on their intended purpose, context, and the overseeing organization.The specific structure and content of a registry depend on the registry's purpose (Gliklich, Leavy and Dreyer, 2020). Regardless of the registry's design, an electronic disease registry provides healthcare professionals with a disease registry form containing predefined options for its various sections.

The disease registry form acts as a key source of input data, typically organized into sections or domains (Item groups). The titles of these sections may vary across registries. Each section consists of a series of subsections (Item concepts), and within each subsection, there is an array of fields (Questions) that represent the data elements to be collected. These fields may contain subfields (Content coding) delineating the method or specifics of data collection, as outlined in the Data Set for Rare Disease Patient Registries Recommended for European Cooperation (Version 3.0) (Berger et al, 2021). “Figure 1” illustrates an example of this structure within a portion of the "Malformation Syndrome" section of the TFAR registry (Bellaaj et al., 2017).

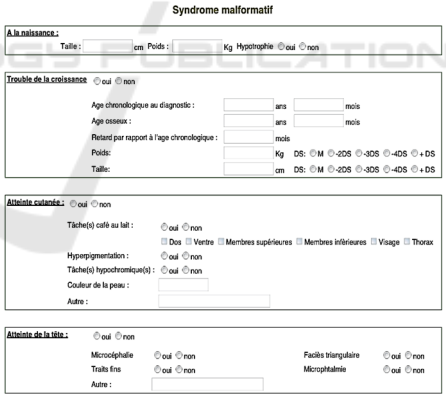

Figure 1: Example of Registry Form Section Structuring.

Different content of disease registry form experiences are presented in the literature. For instance, (Salenius et al, 1992) includes the “Patient's History”, “Clinic Statistics” and “Progress Note”. This last consists of four sections: (1) vital signs, allergies, average weekly glucose measurements, and any point-of-care values (2) eye, foot, and psychological screening information, (3) smoking history, medication compliance, and activity (minutes per week) and (4)

SOAP (subjective, objective, assessment, and plan) note.

On the other hand, the Electronic Disease Form (EDF) within the TFAR (Bellaaj et al, 2017) encompasses 11 distinct sections: Register Identification, Patient Identification, Family history, Circumstances of discovery, Malformation syndrome, Cytogenetic study, Hematological signs, Molecular biology, Cell freezing, Clinical score and Treatment. Each of these sections is further subdivided into one or more subsections, totaling 37 subsections in the entirety of TFAR. For example, the Malformation syndrome component comprises 11 subsections, many of which align with specific medical specialties, such as Skin damage and Urogenital malformation. Each subsection contains various fields, including checkboxes and input fields. Additionally, some fields are initially hidden and are revealed only if the 'yes' option is selected.

The CASCADE FH Registry comprises four domains (sections). 'Enrollment information' encompasses the patient demographics section. 'Medical history' is divided into two subsections: patient history and family history. 'Treatment, laboratory, and examination' incorporates three subsections: FH treatment, Examination/laboratory, and Imaging/procedures (within 5 y). The 'Additional' domain includes Patient-reported outcomes subsection and an additional subsection for Clinical trial participation and Provider contact information (O'Brien et al, 2014).

The National Cardiovascular Data Registry (NDCR)® ICD Registry ™ utilizes the ACC/AHA Heart Failure Clinical Data Standards, clinical data standards created by the American College of Cardiology (ACC) for acute coronary syndromes, heart failure, and atrial fibrillation (WRITING COMMITTEE MEMBERS, Radford et al, 2005). These standards categorize the collected data into 11 sections: Patient Demographics, Medical History, Patient Assessment: Current Symptoms and Signs, Patient Assessment: Summary Assessment, Laboratory Tests, Diagnostic Procedures, Invasive Therapeutic Procedures, Pharmacological Therapy, End-of-Life Management, Patient Education: Assessment of Status and Patient Education: Intervention and Referral. For each of these sections, the standards specify subsections and the requisite data to be collected.

The structure of disease registry forms simplifies data collection and analysis. The level of detail and specialization, however, varies from one disease and organization to another. For instance, in the case of a Rare Disease Registry, more extensive and detailed data may be necessary due to the rarity of the conditions being studied. Conversely, for more common diseases, less extensive data may suffice, as a wealth of information about these conditions is already available.

4 REPRESENTATION OF DISEASE REGISTRIES FORMS

4.1 Definition

In our study, we investigated the contents of registry forms, encompassing their individual sections, the scope of data they cover, and the diversity in form representation across each registry. However, upon examining this structural representation, we observed its near uniformity across the majority of international and standardized registries. Nevertheless, not all registries adhere to or adopt this common structure, rendering the task of standardizing disease registries increasingly challenging. This is why the definition of formal representation is essential to guide the new work of creating registries, especially for small regional registry initiatives that generally do not adhere to a well-defined standard. This standardization of form format representation will enable them to adopt a format that aligns with international registries following standardization guidelines. Hence, our aim is to introduce a standardized theoretical and conceptual model for registry forms, offering a universal representation. This model holds significant value as it furnishes an all-encompassing framework, enabling automated systems to consistently interpret the diverse information types present within registries.

The disease registry form consists of multiple sections, each containing one or more subsections. Within each subsection, there exists a set of fields, which can have some subfields if needed.

So we can represent a registry like $S = \{S_i \mid i \in 1..m\}$ with S_i is the section number i of registry form, m is the number of sections in the form and each section S_i can be represented as shown in "Figure 2". with:

- $\boldsymbol{\Lambda}$ is the set of subsections of S_i , $\boldsymbol{\Lambda} = \cup_{j=1}^{n} \lambda_j$, n = $|\boldsymbol{\Lambda}|$
- $\boldsymbol{\Gamma}$ is the set of titles of subsections, $\boldsymbol{\Gamma} = \cup_{j=1}^{n} \gamma_j$, n = $|\boldsymbol{\Lambda}| = |\boldsymbol{\Gamma}|$
- $\boldsymbol{\Omega}$ is the set of fields of S_i ,$\boldsymbol{\Omega} = \{(\lambda_j, \Omega_j) \mid j \epsilon 1..n\}$ with: $n = |\boldsymbol{\Lambda}| =$

$|\boldsymbol{\Omega}|$; $\Omega_j = \cup_{k=1}^{p_j} \omega_k$ set of fields of subsection λ_j ; $\boldsymbol{p_j} = |\Omega_j|$ number of fields of subsection λ_j ; if $p_j = 0$, then λ_j is a blank subsection

- **Π** is the set of subfields where **Π=** $\cup_{l=1}^{n*p_j} \Pi_l$ | $\Pi_l = \cup_{m=1}^{k_l} \boldsymbol{\pi_m}$; **kl=** $|\Pi_l|$ number of subfields of field ω_k ; if $k_l = 0$, then ω_k is a blank field
- **Π=** $\boldsymbol{I_1} \cup \boldsymbol{I_2} \cup \boldsymbol{I_3} \cup \boldsymbol{I_3'} \cup \boldsymbol{I_4} \cup \boldsymbol{I_4}'$ **,** with
  - $\boldsymbol{I_1}$ ={0,1} the set of checkboxes that don't require a condition
  - $\boldsymbol{I_2}$ the set of input fields that don't require a condition
  - $\boldsymbol{I_3}$ ***and*** $\boldsymbol{I_3'}$ set of checkboxes that require verification of condition respectively "if yes" and "if no"
  - $\boldsymbol{I_4}$ ***and*** $\boldsymbol{I_4'}$ the set of input fields, that require verification of condition respectively "if yes" and "if no"

For each subsection $\lambda_j \in \Lambda$, it is associated with a title $\gamma_j \in \Gamma$ and a set of fields $\Omega_j \in \Omega$, where for each field $\omega_k \in \Omega_j$, it is associated with a set of subfields $\Pi_l \in \Pi$.

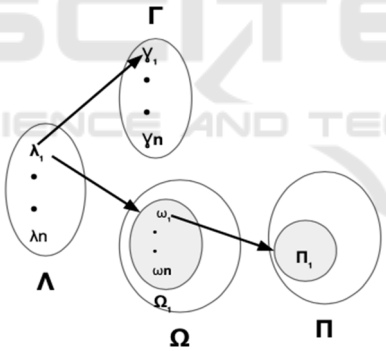

Figure 2: Relations between groups.

4.2 Entity-Relationship Disease Registries Form Pattern

For a deeper and more accessible understanding of the structure and easy interpretation of the connections and interdependencies between entities, as defined in the "Definition" section, we provide a visual representation using the entity-relationship diagram. This representation provides a clear and concise representation of various entities, their distinct attributes, and the connections between them, making it easier to understand the interactions within a given registry system (see "Figure 3").

The diagram in "Figure 3" illustrates the essential attributes for various entities. We use the attribute 'Name' for Register, Field, and SubField, while employing the attribute 'Title' for Section and Subsection. Additionally, Field and SubField have additional attributes defining their representation and data collection methods, as represented in the algorithm outlined in "Figure 4" and "Figure 5".

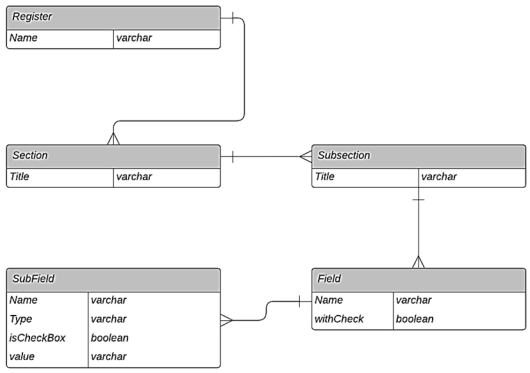

Figure 3: Diagram entity-relationship.

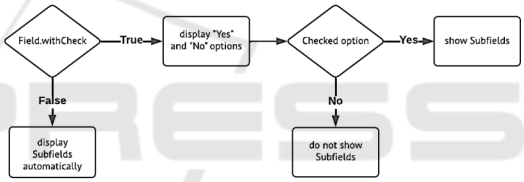

Figure 4: Field Attribute Constraints.

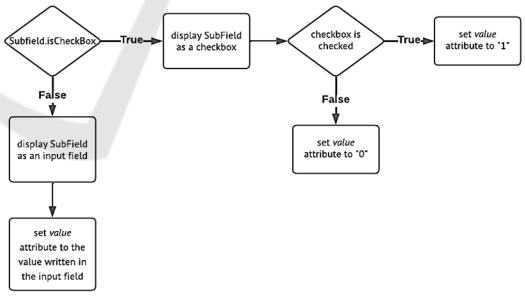

Figure 5: SubField Attribute Constraints.

4.3 Sample Structure of a Standardized Registry Form

To illustrate the structured representation of data, entities, and their connections, we present a sample format of a standardized registry form. This structured format is instrumental in ensuring consistency, efficiency, and uniformity in the capture, storage, and retrieval of information across the diverse domains of registry forms.

The example showcased in “Figure 6” delineates two sections within the registry. For instance, the first section comprises two subsections: the first subsection encompasses two fields, while the second subsection includes one field. Within the first subsection of the initial section, the first field has an attribute of "withCheck" set to false, and all its associated subfields possess the attribute "isCheckBox" set to true. Conversely, the second field has "withCheck" set to true, hence presenting options for 'Yes' and 'No'. Subsequently, by selecting “Yes”, the two subfields that appear have their “isCheckBox” attributes set to false.

This detailed example (in “Figure 6”) exemplifies how attributes like "withCheck" and "isCheckBox" impact the presentation and behavior of fields and subfields within the standardized registry structure, demonstrating various conditional display settings and attribute configurations.

Figure 6: Example of a standardized structure.

4.4 Universal Use of Proposed Standard Structure

For our validation process, we examined the structures of some registries actually in use alongside a set of standard questions and responses, comparing them to the standard structure proposed by our model representation. We chose to use the accuracy metric for this evaluation (see “Table 1”). In this simple binary classification scenario, our goal is to determine whether a given structure matches our model representation or not. The choice to use the accuracy metric is well-suited for this context. The classification task is straightforward, dividing structures into two categories: those that match (the positive class) and those that do not (the negative class), making accuracy a suitable measure. Furthermore, we observed that the consequences and costs associated with both false positives and false negatives are similar, which further supports the use of accuracy. Indeed, the accuracy metric measures the proportion of correctly classified instances among the total instances evaluated. It provides a straightforward measure of how well a model is performing overall in terms of classification accuracy. The formula for calculating accuracy is as follows:

$$\text{Accuracy} = (\text{Number of Valid Sections}) / (\text{Total Number of Sections}) \quad (1)$$

Table 1: Validation Results: Comparison with proposed Structure.

Register / standard	Number of Valid Sections	Total Number of Sections	Accuracy
Tunisian registry GUELT 2013	36	44	0.82
Maghreb group for the evaluation of large B cell lymphomas GEMLA	8	9	0.89
Tunisian registry of AMINOACIDOPATHIES	8	12	0.67
Tunisian registry of DIALYSIS	5	5	1
TFAR (Hadiji et al, 2012)	32	37	0.84
- (TARUSCIO ET AL, 2014) SET OF COMMON DATA ELEMENTS FOR THE EUROPEAN RDR PLATFORM	5	5	1
- SAMPLE OF PRISM QUESTIONS AND SELECTED METADATA (RICHESSON, SHEREFF AND ANDREWS, 2012). (224/2,200 QUESTIONS PRESENTED IN: **[PDF FILE (ADOBE PDF FILE), 318KB-MULTIMEDIA APPENDIX 1])**	22	22	1

We've noted complete adherence to the standardized structure model, reaching 100%, in the two standards used. However, this varies between 100% and 67% among other disease registries. Notably, even in cases where sections deviate from our proposed representation, there's potential to realign them with our standardized model. Nevertheless, the lack of standardization in section structures often leads disease registry form developers to create sections that diverge from the standardized form structure, presenting the initial obstacle toward achieving complete standardization of disease registries.

5 CONCLUSIONS

The paper proposes a standardized structuring of disease registry forms, providing a clear definition of various concepts and components within these forms, as well as the relationships among these different elements. Such structuring is crucial in progressing towards the standardization of disease registries. Adhering to this standard will result in a uniform structural representation of disease registry forms, a valuable uniformity for subsequent data analyses, and a detailed guide for generating new disease registry forms.

This work aims to simplify and unify the structure of disease registry forms, establishing a standardized representation that is universally applied. This standardization represents the initial phase in a broader effort to create a unified approach for data collection and analysis across different disease registries. By doing so, we not only enhance the efficiency of this process but also facilitate the cross-comparison of data and findings from various sources.

The work represents the initial step towards standardizing disease registries. A more generic standardization will require further work on the nature of different registry sections and their contents. This will be our focus in future endeavors.

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