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Design of case report forms based on a public metadata registry: re-use of data elements to improve compatibility of data

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Abstract

Background: Clinical trials use many case report forms (CRFs) per patient. Because of the astronomical number of potential CRFs, data element re-use at the design stage is attractive to foster compatibility of data from different trials. The objective of this work is to assess the technical feasibility of a CRF editor with connection to a public metadata registry (MDR) to support data element re-use.

Results: Based on the Medical Data Models portal, an ISO/IEC 11179-compliant MDR was implemented and connected to a web-based CRF editor. Three use cases were implemented: re-use at the form, item group and data element levels.

Conclusions: CRF design with data element re-use from a public MDR is feasible. A prototypic system is available. The main limitation of the system is the amount of available MDR content.

Keywords: CRF, Data element re-use, MDR, CDISC ODM, ISO/IEC 11179, Information infrastructure

Background

Data management in clinical trials is resource-intensive because many case report forms (CRFs) need to be collected: on average, about 180 pages per patient [1]. This article refers to a CRF as an individual documentation form; therefore, each trial applies a set of CRFs. Despite these extensive documentation efforts, combined analysis of data from different trials is complicated. Variability of CRFs is a major challenge when merging data from different clinical trials. In principle, an astronomical number of different CRFs can be designed [2]. Therefore, the overlap of data elements between two CRFs is very small when these CRFs are designed independently, even if the medical subject matter is similar. This problem of related but not matching data structures has been described in the literature, such as regarding clinical decision support: 'The largest barrier to linking knowledge-based medical decision support systems to heterogeneous [databases] is the variety of ways in which similar data are represented' [3, page 204]. More standardised and compatible CRF data structures would enable integrated data analysis using different sources. In addition, data transfer from electronic health records to databases in clinical research would be facilitated [4]. One approach to foster more standardised CRFs is re-using data elements from a metadata registry (MDR) at the CRF design stage.

The objective of this work was to assess the technical feasibility of this approach (proof of concept) (i.e., development and implementation of a CRF editor with connection to an MDR and support for re-use of data elements). The system should be compliant with regulatory standards and apply a realistic set of data elements.

Methods

Metadata registry

ISO/IEC standard 11179 [5, page V] describes a metadata registry as 'a database of metadata that supports the functionality of registration. Registration accomplishes three main goals: identification, provenance, and monitoring quality'. Identification is achieved by unique identifiers for metadata; provenance relates to sources of metadata. A data element according to this standard is specified regarding concept domain and value domain (i.e., a set of

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permissible values). Semantic information is needed for an MDR, because 'an MDR manages the semantics of data' [5, page V]. More specifically, an MDR enables researchers to compare objects (is a certain object already existing in the MDR?) and can 'identify situations where similar or identical names are in use for administered items that are significantly different in one or more respects' [5].

The Medical Data Models (MDM) portal [6] is a public repository based mainly on CRFs. It is a registered European research infrastructure [7]. Semantic annotations (predominantly Unified Medical Language System [UMLS] codes [8]) are available for a subset of these data models and their data elements. Therefore, MDM was enhanced by an MDR software component which is processing only MDM data elements with UMLS annotations. Figure 1 presents the high-level architecture of the system. Basically, all data elements with UMLS codes are transferred from the MDM database to the MDR using Structured Query Language (SQL) database commands.

Clinical Data Interchange Standards Consortium Operational Data Model

CRFs in clinical trials must comply with requirements of regulatory agencies. Standards of the Clinical Data Interchange Standards Consortium (CDISC) are being applied in this setting. Patient data items can be represented by CDISC Operational Data Model (ODM) [9], an open Extensible Markup Language (XML)-based transport format. Define XML (using CDISC ODM) is part of the U.S. Food and Drug Administration (FDA) Data Standards Catalog, which was announced to become mandatory for new drug applications by the end of 2016 [10]. Therefore, MDM and MDR are using internally ODM-compatible data structures.

CRF editor

Electronic CRFs are designed with CRF editors. The CRF editor of the MDM portal was enhanced to support re-use of data elements. Re-use can be applied at different levels: re-use of complete documentation forms, re-use of item groups and re-use of individual data elements. This CRF editor is a web-based system; Asynchronous JavaScript and XML (AJAX) in combination with database commands (SQL) was applied to generate a list of suggested data elements for re-use during CRF design. Because of the large number of coded terms in the MDR (approximately 1,040,000), an asynchronous technique was applied to avoid performance issues. Re-use at the item group level and at the form level is provided by dedicated web services.

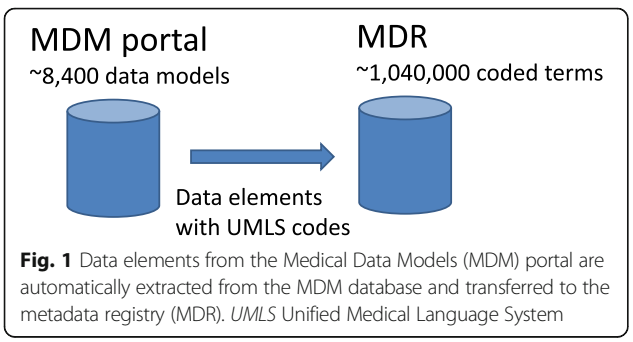


Fig. 1 Data elements from the Medical Data Models (MDM) portal are automatically extracted from the MDM database and transferred to the metadata registry (MDR). *UMLS* Unified Medical Language System

Results

Search function for MDR

A prototypic MDR implementation is available at http://mdr.uni-muenster.de. Figure 2 presents the graphical user interface (GUI). When an item name is entered, a table of matching data elements from the MDR is displayed. It is ordered by frequency and contains links to respective data models. By this means, users can review the context of each element. For each data element, a short name and more detailed text are provided, separated by a colon. The language of these texts can be selected. At present, most data elements are available in English and German. The concept domain is characterised by a UMLS code. The value domain is described by data type and, if appropriate, by unit, minimum/maximum or a list of permissible values.

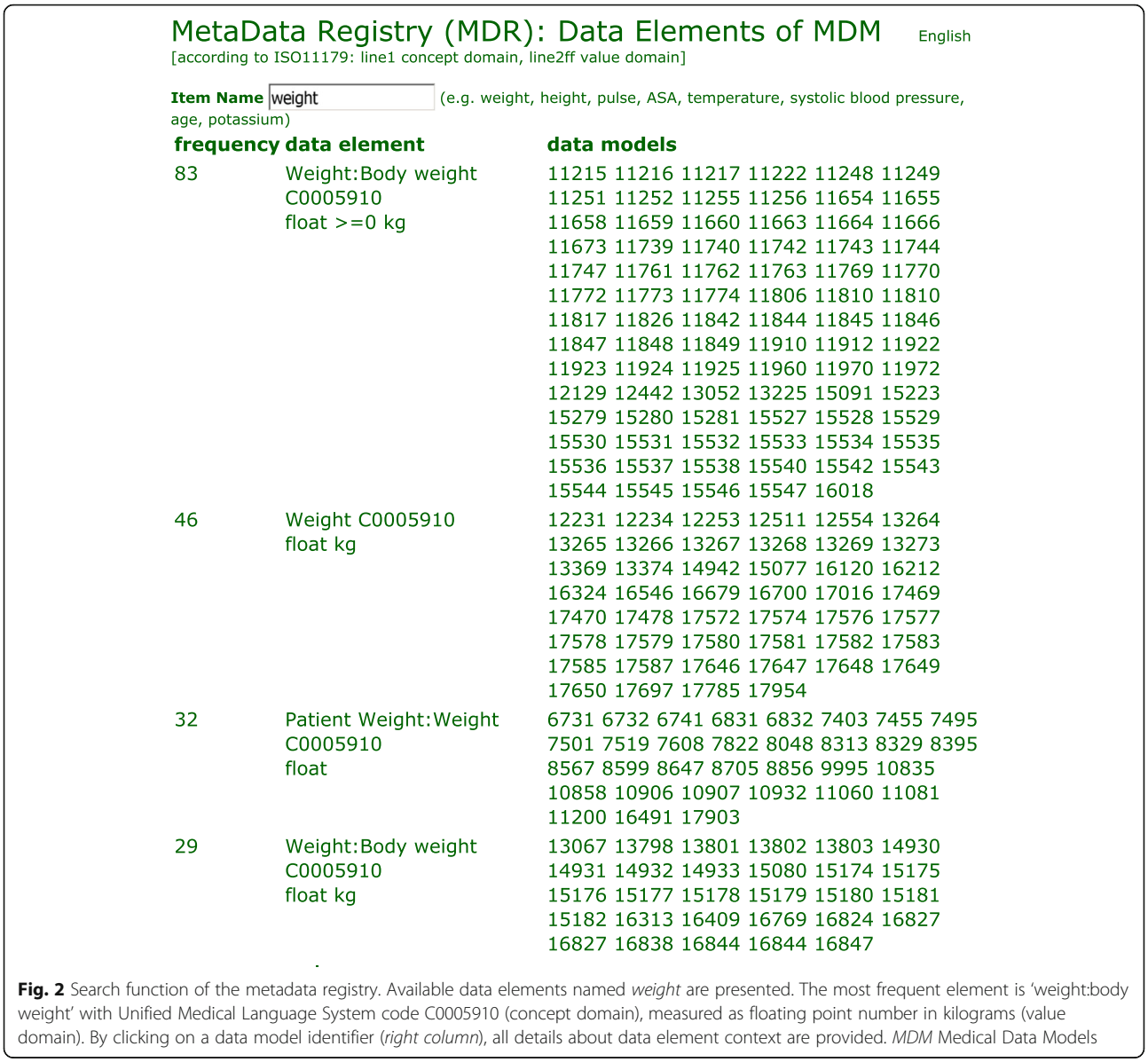
Overall, approximately 240,000 data elements with approximately 1,040,000 coded terms (UMLS codes) are available in the MDR. The number of terms is higher than the number of elements because each element can be translated into several languages (e.g., English, German, Dutch). This GUI can be used to look up data elements in the MDR.

Re-use of data elements at form, item group and item levels

A prototypic implementation of a CRF editor with re-use functionality is available at http://odmeditor.uni-muenster.de. Re-use of data elements during CRF design can occur at different levels. A study consists of a set of CRFs. In principle, a whole CRF from a previous study could be re-used for a new study. An example of this use case is provided in Fig. 3.

Another use case is re-use of an item group from a previous study (i.e., a list of related data elements). Figures 4 and 5 present screenshots from the prototypic implementation. Specific search terms for item groups should be applied because generic search terms such as *Physical examination* can produce a long list of results.

The third use case is re-use of data elements at the element level, illustrated in Fig. 6. A catalogue-based search of data elements is not efficient, because there are more than 240,000 elements in the MDR; the usability of the system would be limited because finding and selecting an appropriate data element would require many clicks and keystrokes. Therefore, an automated approach was implemented. While the user enters a new data element, a


MetaData Registry (MDR): Data Elements of MDM English

[according to ISO11179: line1 concept domain, line2ff value domain]

Item Name weight (e.g. weight, height, pulse, ASA, temperature, systolic blood pressure, age, potassium)

frequency	data element	data models
83	Weight:Body weight C0005910 float >=0 kg	11215 11216 11217 11222 11248 11249 11251 11252 11255 11256 11654 11655 11658 11659 11660 11663 11664 11666 11673 11739 11740 11742 11743 11744 11747 11761 11762 11763 11769 11770 11772 11773 11774 11806 11810 11810 11817 11826 11842 11844 11845 11846 11847 11848 11849 11910 11912 11922 11923 11924 11925 11960 11970 11972 12129 12442 13052 13225 15091 15223 15279 15280 15281 15527 15528 15529 15530 15531 15532 15533 15534 15535 15536 15537 15538 15540 15542 15543 15544 15545 15546 15547 16018
46	Weight C0005910 float kg	12231 12234 12253 12511 12554 13264 13265 13266 13267 13268 13269 13273 13369 13374 14942 15077 16120 16212 16324 16546 16679 16700 17016 17469 17470 17478 17572 17574 17576 17577 17578 17579 17580 17581 17582 17583 17585 17587 17646 17647 17648 17649 17650 17697 17785 17954
32	Patient Weight:Weight C0005910 float	6731 6732 6741 6831 6832 7403 7455 7495 7501 7519 7608 7822 8048 8313 8329 8395 8567 8599 8647 8705 8856 9995 10835 10858 10906 10907 10932 11060 11081 11200 16491 17903
29	Weight:Body weight C0005910 float kg	13067 13798 13801 13802 13803 14930 14931 14932 14933 15080 15174 15175 15176 15177 15178 15179 15180 15181 15182 16313 16409 16769 16824 16827 16827 16838 16844 16844 16847

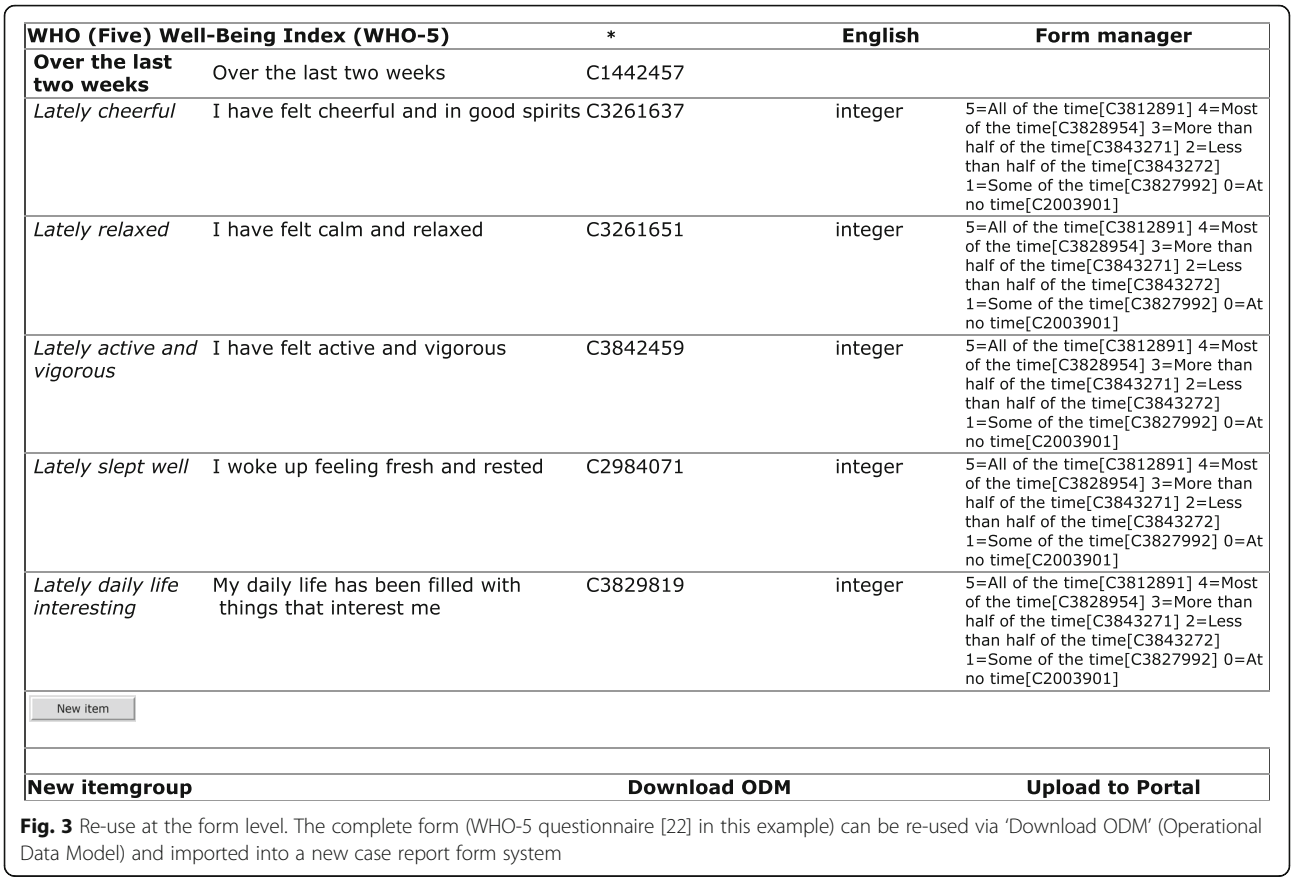
Fig. 2 Search function of the metadata registry. Available data elements named *weight* are presented. The most frequent element is 'weight:body weight' with Unified Medical Language System code C0005910 (concept domain), measured as floating point number in kilograms (value domain). By clicking on a data model identifier (*right column*), all details about data element context are provided. *MDM* Medical Data Models

list of matching elements for re-use is generated and updated. A data element for re-use can be selected at any time, or these suggestions are ignored and a new element is defined from scratch.

In principle, it is possible to predict the next element of a new CRF on the basis of context. The next element after surname is frequently first name; aspartate transaminase (AST) is documented often together with alanine transaminase (ALT). (AST and ALT are both liver parameters.) This contextual information (what data elements are used frequently on the same CRF like a given element?) can be extracted from the MDM portal. In the current prototype, information from two preceding data elements is analysed to generate suggestions for the next element.

Discussion

The theoretical benefits of re-using data elements for medical documentation have been described before [4, 11]. CRF quality could be improved, such as with fewer typing errors by re-using high-quality CRFs. CRF design could be more efficient, such as through less manual input by re-using code lists. From my perspective, the aspect of standardisation by re-use is of interest. It is known from the literature that an astronomical number of CRFs can be designed. This leads to incompatible data in different studies (i.e., not suitable for data integration). Therefore, re-use of data elements for CRFs seems attractive to avoid incompatible modelling of similar items; for example, a pain scale with four levels generates data incompatible with that from a



WHO (Five) Well-Being Index (WHO-5)		*	English	Form manager
Over the last two weeks	Over the last two weeks	C1442457		
Lately cheerful	I have felt cheerful and in good spirits	C3261637	integer	5=All of the time[C3812891] 4=Most of the time[C3828954] 3=More than half of the time[C3843271] 2=Less than half of the time[C3843272] 1=Some of the time[C3827992] 0=At no time[C2003901]
Lately relaxed	I have felt calm and relaxed	C3261651	integer	5=All of the time[C3812891] 4=Most of the time[C3828954] 3=More than half of the time[C3843271] 2=Less than half of the time[C3843272] 1=Some of the time[C3827992] 0=At no time[C2003901]
Lately active and vigorous	I have felt active and vigorous	C3842459	integer	5=All of the time[C3812891] 4=Most of the time[C3828954] 3=More than half of the time[C3843271] 2=Less than half of the time[C3843272] 1=Some of the time[C3827992] 0=At no time[C2003901]
Lately slept well	I woke up feeling fresh and rested	C2984071	integer	5=All of the time[C3812891] 4=Most of the time[C3828954] 3=More than half of the time[C3843271] 2=Less than half of the time[C3843272] 1=Some of the time[C3827992] 0=At no time[C2003901]
Lately daily life interesting	My daily life has been filled with things that interest me	C3829819	integer	5=All of the time[C3812891] 4=Most of the time[C3828954] 3=More than half of the time[C3843271] 2=Less than half of the time[C3843272] 1=Some of the time[C3827992] 0=At no time[C2003901]

Fig. 3 Re-use at the form level. The complete form (WHO-5 questionnaire [22] in this example) can be re-used via 'Download ODM' (Operational Data Model) and imported into a new case report form system

pain scale with five levels. This should be avoided wherever possible at CRF design stage. In the long run, the proposed re-use of data elements would also be beneficial for meta-analysis because more homogeneous data collection would be fostered and compatibility of patient data would be improved. Previous work [12] has shown that the 100 most frequent medical concepts cover 25% of all concept occurrences in clinical trials. However, owing to the semantic complexity of medicine, there is a large number of rarely used medical concepts in clinical trials.

A prerequisite for data element re-use is access to elements from previous studies. Open metadata is demanded by scientists [13, 14] but is not (yet?) the norm; therefore, currently, the vast majority of CRFs are not available to the scientific community. In recent years, more and more data elements are being made available via various MDRs, such as the cancer Data Standards Registry and Repository of the National Cancer Institute [15], the National Institute of Neurological Disorders and Stroke project [16], the Clinical Element Model [17] or the Metadata Online

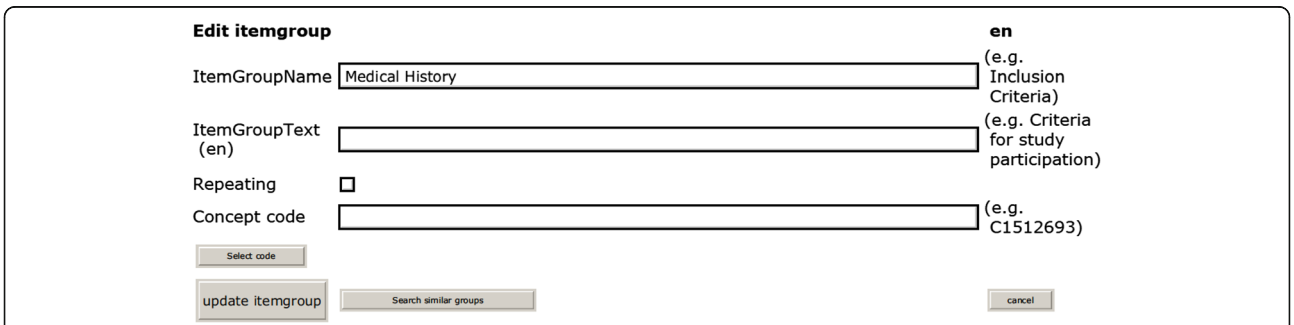


Fig. 4 Re-use at the item group level. Using the 'Search similar groups' button (*bottom left, second button*), similar item groups for 'Medical History' can be identified. (For this search result, see Fig. 5.)

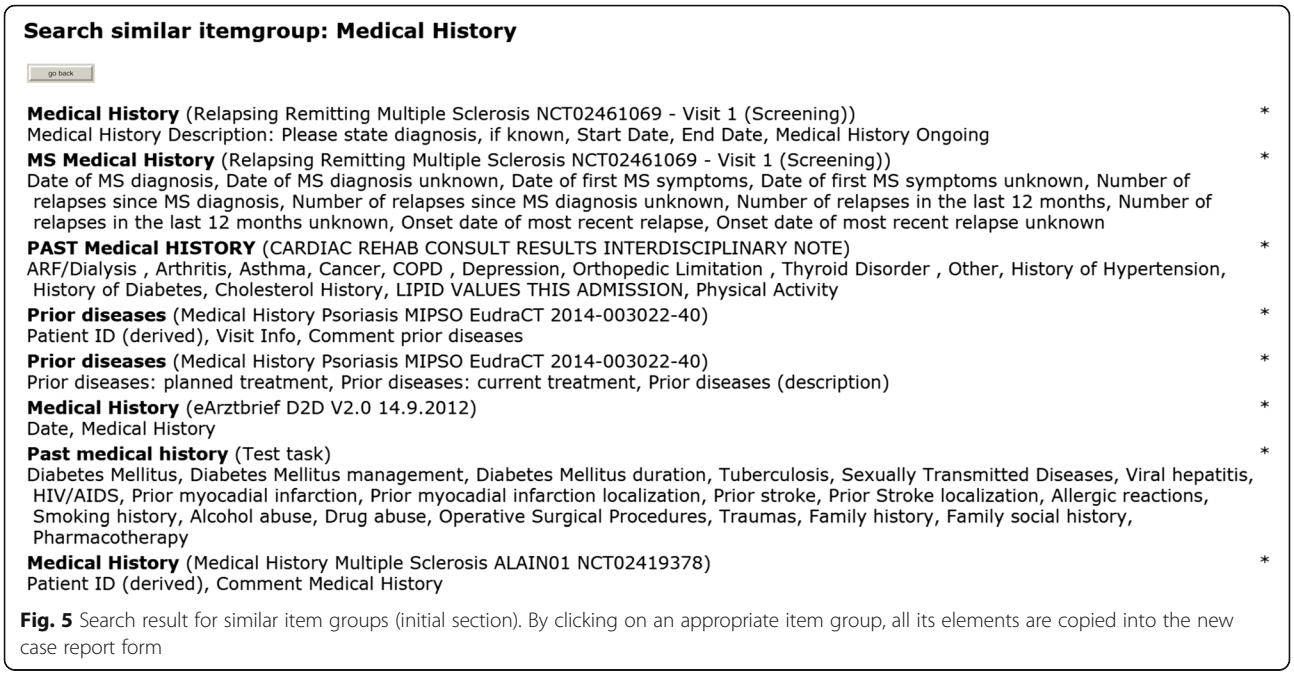


Fig. 5 Search result for similar item groups (initial section). By clicking on an appropriate item group, all its elements are copied into the new case report form

Registry of the Australian Institute of Health and Welfare [18]. A special feature of the MDM [6] is provision of complete CRFs (i.e., data elements with relationship to other elements).

In this context, the objective of this work was to develop, for the first time to my knowledge, as a proof of concept a CRF editor with connection to an MDR and support for re-use of data elements. This prototype is now available to the scientific community. It applies relevant international standards, in particular ISO/IEC 11179 for MDRs and CDISC ODM, which is supported by regulatory agencies.

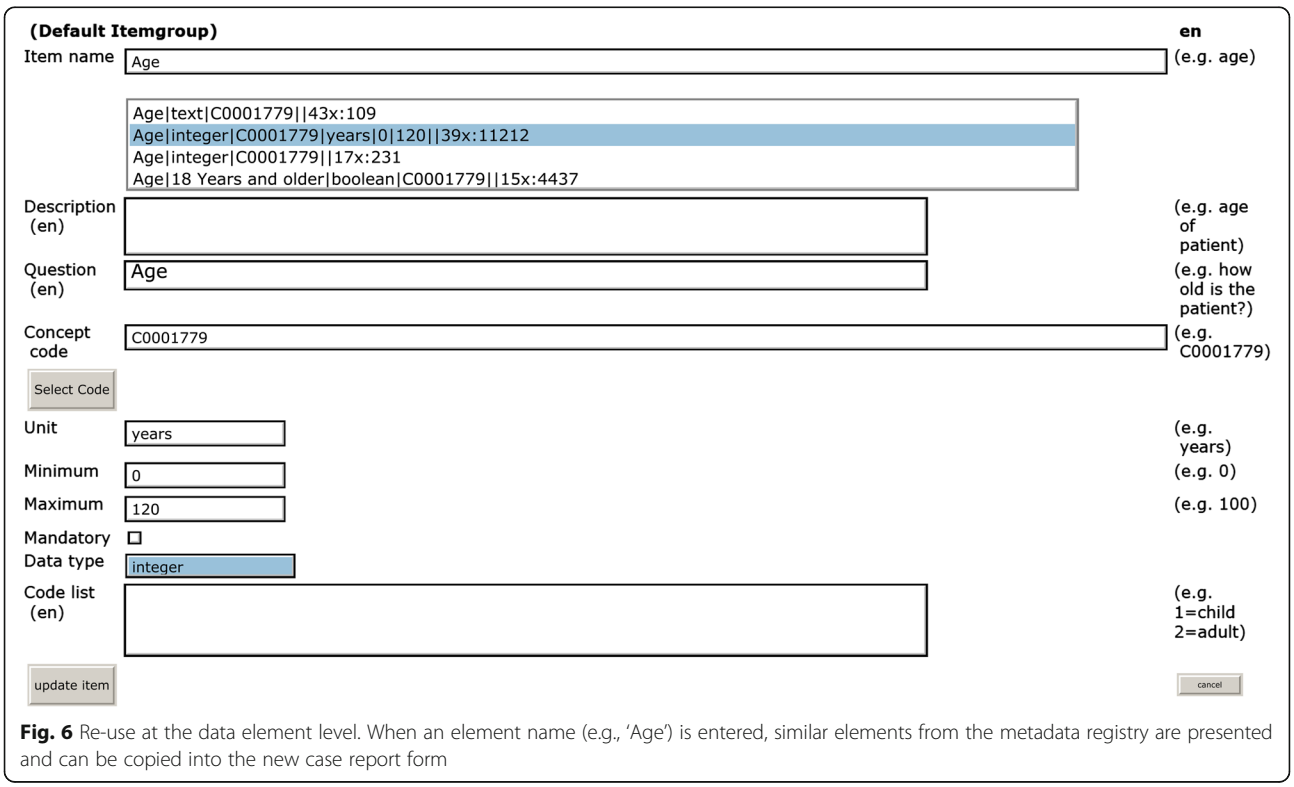


Fig. 6 Re-use at the data element level. When an element name (e.g., 'Age') is entered, similar elements from the metadata registry are presented and can be copied into the new case report form

Limitations and future work

This prototypic CRF editor has limitations. Most important, available data elements for re-use are derived from only about 8400 forms from the MDM portal. There are more than 227,000 registered trials [19] with approximately 180 pages each (i.e., about 41 million CRFs), corresponding to approximately 1.6 billion data elements (assuming, on average, 40 data elements per CRF). If current initiatives for more transparency in clinical trials [20, 21] are successful, public information infrastructures of data elements for CRFs will grow further. When more complete MDRs for CRFs are available, the approach of CRF design with data element re-use can be evaluated in realistic clinical research settings. Then it should be determined what proportion of CRF data elements can actually be re-used. This will also contribute to assessment of the benefit of data element re-use for data integration.

Conclusions

CRF design with data element re-use from a public MDR is feasible. A prototypic system is available. The main limitation of the system is the amount of available MDR content.

Abbreviations

AJAX: Asynchronous JavaScript and XML; ALT: Alanine transaminase; ASA: System for assessing the fitness of patients before surgery by AmericanSociety of Anesthesiologists; AST: Aspartate transaminase; CDISC: Clinical Data Interchange Standards Consortium; CRF: Case report form; FDA: U.S. Food and Drug Administration; GUI: Graphical user interface; MDM: Medical Data Models; MDR: Metadata registry; ODM: Operational Data Model; SQL: Structured Query Language; UMLS: Unified Medical Language System; XML: Extensible Markup Language

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Availability of data and materials

Supporting data are available from https://medical-data-models.org/.

Authors' contributions

MD designed the research, analysed data, programmed ODM editor and wrote the manuscript.

Competing interests

The author declares that he has no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Not applicable.

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