Adverse Events from clinical studies in pharmaceutical research and development

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Abstract
A statement of interest to participate in the workshop Representing Adverse Events, arranged together with the International Conference on Biomedical Ontology (ICBO), July 2011. Introducing the business needs in handling safety issues and regular ongoing pharmacovigilance in pharmaceutical research and development. An outline of the proposed solution and two examples of different adverse event cases as a background to the authors wishes to understand a more ontological approach.

1 Business need

R&D and the Patient Safety department have a strategic focus to develop predictive ways to handle safety issues and regular ongoing pharmacovigilance. That is, the detection, assessment, understanding and prevention of adverse effects, particularly long term and short term side effects of medicines. Regulatory authorities require well designed and proactive risk management plans to be in place from launch throughout the whole lifecycle of a product. The new IND (Investigational New Drug) regulation from FDA, for routine review of incidence rates of all serious and non-serious adverse events in all clinical programs.

Many clinical study programs run several studies worldwide in parallel, which could result in a high worldwide exposure; hence it is extremely important to have continuous access to ongoing clinical study data. To successfully handle ongoing pharmacovigilance a prerequisite is access to continuous relevant pooled clinical study data in a format that make it possible to review, search and answer questions in a very short time frame. This requires consistent coding, pre-prepared pools and derived variables. Furthermore, the result of the searches in the pooled clinical study data should be put in context of other results both inside and outside the pharm company. In addition it is required to keep track of each single data point through the data collection and refinement chain as this contributes to the final result.

The overall business problem as stated for the ongoing AstraZeneca project called Quest: No global automatic way to access, structure and analyze safety related clinical study data (including ongoing study data) at drug product/project level.

Below an outline of the proposed solution for representation of adverse events influences by existing standards focused on data exchange and coding. This overview and two examples of cases provide some background to our interest in better understanding a more ontological approach to represent adverse events in the context of pharmaceutical research and development. We also explore semantic web standards and linked data principles to improve the research utility of data in clinical studies.

2 Solution overview

A safety analysis environment has been proposed by the Quest project. It includes: Clinical study data (legacy, completed, ongoing), Structure (optimized for Patient Safety queries), Analyze – (descriptive statistics and graphical output), Processes (how to work using these new options).

A relational database design, building on the experiences of two large Adverse Events databases in production for approximate 20 years have been proposed for the central Quest database.

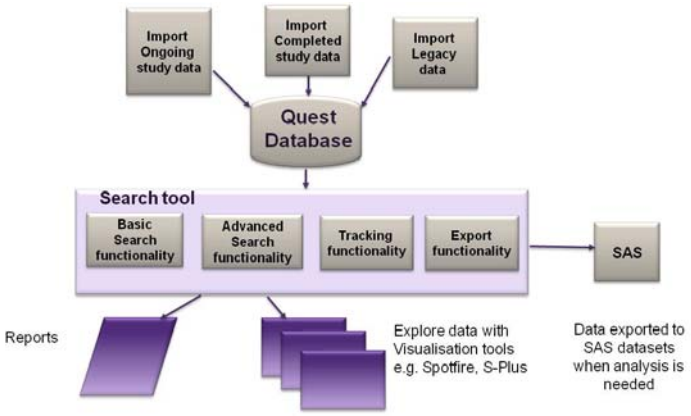

Figure 1: Proposed Quest solution

A key concept in the design of the Quest database is periods e.g. run-in, on treatment, wash-out, follow-up and the sequence of these periods. The periods will also reflect the half-life of the drug studied. All findings, events and interventions need to be linked to one or several periods.

This is also an example of how existing data exchange standards have influenced the mindset in pharmaceutical research and development on how adverse events should be represented. In this case it is the general classification of "observations" i.e. data exchange records, in terms of findings, events and interventions according to CDISC's (Clinical Data Interchange Standards Consortium) standard called SDTM (Study Data Tabulation Model). Another example is SDTM standard for data structures and elements, e.g. the extended AE domain for safety analysis. Together

with CDISC's controlled terminology with lists of codes (text strings to be used as submission values) for safety analysis such as the Severity/Intensity Scale for Adverse Events, with text strings: "MILD", "MODERATE", "SEVERE".

The dictionary for coding of explicit AE records in clinical trials sponsored by pharmaceutical companies is MedDRA. Adverse events can also be the implied consequence of a combination of measurements. Below two examples issues when it comes to versioning of MedDRA terms and an example of a lab measurement based adverse event case.

Issue #1

A main issue is the use of different MedDRA versions with potentially new so called preferred terms (PT:s) and new hierarchies. However no low level terms (LLT) are deleted/reused.

Original Coded MedDRA LLT	Original Coded MedDRA PT	Current MedDRA PT
Heaviness of head	Headache	Head discomfort
Headache vasomotor	Headache	Cluster headache
Headache unilateral	Headache	Hemicephalalgia

Figure 2: Example of MedDRA terms and versions

Issue #2

Adverse events can also be the consequence of a combination of measurements. For example FDA's document "Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation" from July 2009 describes the Hy's Law (PHL).

- A Potential Hy's Law (PHL) case is defined as any situation where a study subject
  - Has an increase in both alanine or aspartate aminotransferase (ALT or AST) ≥ 3xULN and total bilirubin (TBL) ≥ 2xULN
  - Irrespective of alkaline phosphatase (ALP), at any point during the study
  - The elevations do not have to occur at the same time or within a specified time frame