Decision Support Systems 55 (2013) 459–475

Contents lists available at SciVerse ScienceDirect

Decision Support Systems

journal homepage: www.elsevier.com/locate/dss

ADDIS: A decision support system for evidence-based medicine

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ARTICLE INFO

Available online 16 October 2012

Keywords:
Evidence-based medicine
Evidence synthesis
Data model
Clinical trial
Decision analysis

ABSTRACT

Clinical trials are the main source of information for the efficacy and safety evaluation of medical treatments. Although they are of pivotal importance in evidence-based medicine, there is a lack of usable information systems providing data-analysis and decision support capabilities for aggregate clinical trial results. This is partly caused by unavailability (i) of trial data in a structured format suitable for re-analysis, and (ii) of a complete data model for aggregate level results. In this paper, we develop a unifying data model that enables the development of evidence-based decision support in the absence of a complete data model. We describe the supported decision processes and show how these are implemented in the open source ADDIS software. ADDIS enables semi-automated construction of meta-analyses, network meta-analyses and benefit–risk decision models, and provides visualization of all results.

1. Introduction

Two kinds of decision support systems for evidence-based medicine can be distinguished: rule-based systems for supporting operational decisions of practicing physicians and strategic decision support systems. The rule-based systems represent clinical knowledge and include inference rules for aiding professional decision making in clinical practice. They have been in existence since the 1970s [61]. The most common of these are Computerized Physician Order Entry (CPOE) systems which contain evidence-based rules that enable issuing warnings when an inappropriate combination of medicines is prescribed. To the best of our knowledge, there are no established systems that inform strategic (rather than operational) decisions such as identifying the best treatment practices based on the consideration of benefit–risk trade-offs.

Strategic health care decision making, with or without a supporting system, depends heavily on the availability of unbiased evidence from controlled clinical trials [27]. One of the core activities and sources of

Abbreviations: OCRe, Ontology of Clinical Research; OBX, Ontology Based Extensible Conceptual Model; DED, Data Element Definitions; OWL, Web Ontology Language; ADaM, Analysis Data Model; ADE, Adverse Drug Event (an injury resulting from a medication); ADR, Adverse Drug Reaction (any unexpected, unintended, undesired or excessive response to a drug, with or without an injury); AMIA, American Medical Informatics Association; ANSI, American National Standards Institute; BRIDG, Biomedical Research Integrated Domain Group; caBIG, Cancer Biomedical Informatics Grid; CDASH, Clinical Data Acquisition Standards Harmonization; CDISC, Clinical Data Interchange Standards Consortium; CDMS, Clinical Data Management System (sophisticated EDC system); CHMP, Committee for Medicinal Products for Human Use (EMA); CPOE, Computerized Physician Order Entry; CRF, Case Report Form; CRO, Clinical Research Organization; CTIS, Clinical Trial Information System; CTMS, Clinical Trial Management System (sophisticated CDMS); DB, Database; DIS, Drug Information System; DSS, Decision Support System; EAV, Entity Attribute Value; EBM, Evidence-Based Medicine; eCRF, Electronic Case Report Form; EDC, Electronic Data Capture; EHR, Electronic Health Record; eLab, Electronic Laboratory Data; EMA, European Medicines Agency (EU, formerly EMEA); EPAR, European Public Assessment Report; ePRO, Electronic Patient Reported Outcome; FDAAA, FDA Amendments Act of 2007; FDA, Food and Drug Administration (US); GCP, Good Clinical Practice; HL7, Health Level 7; HSDB, Human Studies Database; ICMJE, International Committee of Medical Journal Editors; ICTRP, International Clinical Trials Registry Platform; JAMA, Journal of the American Medical Association; LAB, Laboratory Data Model; NCI, National Cancer Institute (US); NDA, New Drug Application; NIHUS, National Institutes of Health; ODM, Operational Data Model; PhRMA, Pharmaceutical Research and Manufacturers of America; PIM, Product Information Management (EMA); PMDA, Pharmaceuticals and Medical Devices Agency (Japan); PRM, Protocol Representation Model; QRD, Quality Review of Documents (EMA); RIM, Reference Information Model; SDTM, Study Data Tabulation Model; SEND, Standards for Exchange of Nonclinical Data; SmPC, Summary of Product Characteristics; SPL, Structured Product Labeling (FDA); TDM, Trial Design Model; WHO, World Health Organization; GUI, Graphical User Interface; DOI, Digital Object Identifier; MCDA, Multi-criteria Decision Analysis; ICD, International Classification of Diseases; MedDRA, Medical Dictionary for Regulatory Activities; MeSH, Medical Subject Headings; SNOMEDCT, Systematized Nomenclature of Medicine, Clinical Terms; UMLS, Unified Medical Language System; ATC, Anatomical Therapeutic Chemical Classification System; SMAA, Stochastic Multi-criteria Acceptability Analysis.

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http://dx.doi.org/10.1016/j.dss.2012.10.005

information in evidence-based medicine is the systematic review [70], a literature review that attempts to identify and synthesize all empirical evidence that fits pre-specified eligibility criteria in order to answer a specific research question [31]. Currently the process of systematic review is extremely labor intensive and error prone due to the lack of a comprehensive source of clinical trials, the inaccuracy of literature searches, interpretation issues, tedious manual data extraction and, importantly, the duplication of effort that is necessary for every review [62]. The emergence of clinical trial registries [82] and the move towards a more open clinical research community [25,63], as well as the initiatives of the Cochrane foundation [26] to share and update meta-analysis data sets offer opportunities for more efficient approaches to evidence synthesis. Still, to date there is no single complete collection of performed clinical trials and outcome data, and importantly none of the available sources store results in a format that is suited for re-analysis [80,82].

Thus, although suitable methods for evidence-based strategy decision support exist [15,53,74,78], evidence-based decision making is difficult to implement because of the substantial effort required to systematically review the literature for relevant studies and to manually extract the data from these studies, which has to be done on a case by case basis. Even when a relevant published systematic review exists, evidence-based decision making including multiple (possibly conflicting) objectives is difficult and in practice often done ad hoc due to a lack of supporting information technology. In addition, sometimes it will be necessary to incorporate additional studies to the body of evidence present in the systematic review, e.g. in the regulatory context where the manufacturer sponsors studies to prove the efficacy and safety of a newly developed drug. Moreover, the analyses reported in the published systematic review may not be valid for the decision at hand, so re-analysis of the included clinical trials may be needed. Text-based reports of systematic reviews do not support such use cases. There do exist methods for automated extraction of trial design and results from the literature, but although the field is rapidly evolving (see e.g. [37]), their accuracy is not yet sufficient to be directly used in systems supporting strategic decisions.

In this paper, we present ADDIS (Aggregate Data Drug Information System, http://drugis.org/addis), an open source evidence-based drug oriented strategy decision support system. It is an integrated software application that provides decision support for strategic decisions such as guideline formulation, marketing authorization, and reimbursement. ADDIS stores aggregate clinical trial results with a unifying data model, and implements semi-automated evidence synthesis and benefit–risk modeling. These use cases were derived from direct discussion with experts from pharmaceutical industry, regulatory authorities, and academia, and from their feedback to early prototypes of the system. Before the models can be applied, trial results must be available in the system; for this, we present an assisted procedure for importing study designs from an existing database. The evidence synthesis and decision models of ADDIS allow decision makers to visualize and understand the available evidence and the trade-offs between different treatment options, thus addressing information overload and reducing the complexity of strategy decisions informed by clinical evidence. We stress that ADDIS does not aim at operational decision support, but aids in strategic decision making and provides a platform for computational methods in clinical trial informatics. In addition, the generation of the models cannot be completely automated: some steps require decisions from a domain expert, but can be supported by ADDIS as will be shown in this paper. To the best of our knowledge, ADDIS is the first system to allow on demand generation and use of the evidence synthesis and decision support models in a suitable way for strategic decision making.

We start by discussing existing systems and standards for clinical trial design and results in Section 2. The unifying data model is presented in Section 3. After that, in Section 4, we present ADDIS and the assisted procedures of study import and generation of evidence synthesis and benefit–risk models. In Section 5 we summarize our principal findings and propose directions for future research.

2. Background

Several systems and standards dealing with clinical trial information exist. We provide an overview of these systems and standards in Sections 2.1 and 2.2, respectively. Subsequently, in Section 2.3, we briefly describe the current state of methods for extraction of information from predominantly text-based sources of clinical trial designs and results. Finally, Sections 2.4 and 2.5 give an overview of the most relevant evidence synthesis and decision modeling approaches for strategic decision making.

2.1. Clinical trial information systems

In this section we briefly summarize the information systems that deal with clinical trials information, first those in operational management of trials and the regulatory environment, then the dissemination to the scientific community through publication in journals and registration, and finally how the results are summarized in systematic reviews.

2.1.1. Operational management and regulatory submission

Operational management refers to the administrative and data-gathering activities for a single trial. The operational management of clinical trials can be automated by using a Clinical Trial Management System (CTMS). Until circa 2000, the management and data collection of the vast majority of clinical trials were paper-based activities [6], but the use of a CTMS has quickly become the norm [21,77]. The automation of operational management is now a mature field, and increasingly standardized (see also Section 2.2). However, CTMS are data-centric single study systems that are focused on enabling the efficient operation of the trial and, often, submission of data to the US Food and Drug Administration (FDA). As of yet these systems do not enable cross-study analyses, data integration and data sharing.

After drug development, the pharmaceutical company compiles the evidence collected from clinical trials (and other research) into an electronic dossier that is submitted to the regulators who decide upon its market authorization. The dossier, especially the clinical trial results, forms the basis on which regulators assess the benefit–risk profile of a new drug. Submissions to the European Medicines Agency (EMA) and most other regulatory agencies worldwide are mainly text-based, containing aggregate-level results of clinical trials based on the applicant's statistical analyses. The FDA, on the other hand, requires an electronic submission of individual patient data to be able to perform independent analyses [23], and is currently building JANUS, a standards-based clinical data repository specifically designed for the integration of data [7].

2.1.2. Results dissemination

Pharmaceutical companies and clinical research organizations may choose to publish the results of clinical trials in peer-reviewed scientific articles that do not include the underlying data set. Abstracts of publications are indexed in databases such as PubMed (http://pubmed.com/), which includes over 20 million citations from over 5000 journals, of which more than 600,000 were published in 2009 [PubMed, 2011-05-02]. Although large in size, PubMed contains only a selected subset of the biomedical literature [52]. Abstract databases include metadata that might be incomplete due to being provided by external parties; for example, to achieve high sensitivity in searching for clinical trials in PubMed, restricting the search to the 'clinical trial' publication type is too restrictive [30], and a broader query is recommended [31]. The Cochrane CENTRAL database of clinical trials is dedicated to indexing reports of clinical trials only, and