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Leveraging Advanced Analytics to Generate Dynamic Medical Systematic Reviews

Prem Timsina
Dakota State University

Omar F. El-Gayar
Dakota State University

Nevine Nawar
Dakota State University

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Research-in-Progress

Prem Timsina
Dakota State University
ptimsina@pluto.dsu.edu

Omar El-Gayar
Dakota State University
omar.el-gayar@dsu.edu

Nevine Nawar
Dakota State University
nevine.nawar@dsu.edu

Abstract

According to Khan et al, "a review earns the adjective systematic if it is based on a clearly formulated question, identifies relevant studies, appraises their quality and summarizes the evidence by use of explicit methodology". Conducting systematic reviews tend to be resource intensive and may suffer from problems such as publication bias, time-lag bias, duplicate bias, citation bias, and outcome reporting bias. This research aims to develop a system to facilitate the creation of systematic reviews. Starting with a clinical question, the proposed system will query ClinicalTrial.gov to search published RCTs. The system will exploit advanced data analytics techniques to systematically mine clinical trials obtained from the ClinicalTrial.gov. From the theoretical perspective, the system provides context for exploring the feasibility and efficacy of using advanced analytics techniques for generating machine readable, real time medical evidence. From a practical perspective, the system is expected to produce cost efficient medical evidence.

Keywords

Systematic Review, Evidence Based Medicine, Health Information Technology, Text Analytics, Medical Informatics

Introduction

The United States spends more than $2.3 trillion per year in healthcare and is the second largest nation (just below Sierra Leone) in healthcare spending as a percentage of GDP (The World Bank 2012). However, such spending has not translated into quality of care. The Institute of Medicine (IOM) report of 1999 estimated that as many as 98,000 people die annually in hospitals because of preventable medical errors (Institute of Medicine 1999). Furthermore, estimates of deaths due to preventable errors increased by four folds from 1999 to 2013 to reach 400,000. (James 2013). On the other hand, the "Centers for Medicare and Medicaid Services" & "Kaiser Family Foundation" predict an increase in future health spending; by 2020 healthcare spending will reach 4.6 trillion dollars (2 trillion dollars increase from 2010) and by 2050 US will spend 40% of its GDP on healthcare (National Public Radio 2012). One of the principal causes of this rising cost and diminishing quality is a gap between knowledge and practice. For example, the US spends over 136 billion dollars annually in clinical research. Through this spending, over 7,500 "Applicable Clinical Trials" and other studies are published annually, which are then used to generate medical evidence. Yet, the usage of medical evidence in frontline practice is limited. In a survey of 2148 treatments, 15% were rated beneficial, 21% likely to be beneficial, 8% tradeoff between beneficial and harmful, 5% unlikely to be beneficial, 4% likely to be harmful, and critically, 47% of treatments were with unknown effectiveness (Garrow 2007). It is, therefore apparent that the US spends a substantial amount of funds for basic medical research that lack effective translation into medical evidence and later into medical practice.

In response to this situation, the federal government has shown interest in healthcare informatics. President Obama in his inauguration address in 2009 said, "We will wield technology's wonders to raise health care's quality and lower its cost". IOM proposed several recommendations to increase the quality of

care & reduce cost. One of the highly sought areas is the usage of business intelligence and data analytics (BI&A) techniques to collect, analyze, curate, and present evidence at the point of care, i.e., the support the practice of computerized evidence based medicine (EBM). For the purpose of this study, we refer to EBM as the "conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients" (Sackett et al. 1996). In other words, EBM refers to medical practice based on the concrete knowledge of what works and what does not.

Supporting the practice of EBM is the systematic review of the medical literature. According to Khan et al, "a review earns the adjective systematic if it is based on a clearly formulated question, identifies relevant studies, appraises their quality and summarizes the evidence by use of explicit methodology" (Khan et al. 2003). Again, Cochrane illustrates seven steps for generating systematic reviews (Cochrane 2013) (a) Defining the review question and developing criteria for inclusion (b) Searching for studies (c) Selecting studies and collecting data (d) Assessing risk of bias in included studies (e) Analyzing data and undertaking meta-analyses (f) Addressing reporting biases: (g) Presenting results and 'Summary of findings' tables (h) Interpreting results and drawing conclusions. Moreover, Cochrane indicated that the following resources as essential for conducting systematic reviews: (i) Topic of relevance or interest (ii) Team of coauthors (at least 2 to reduce bias) (iii) Training and support (iv) Access to/understanding of the likely users of the review (v) Funding—Cochrane estimated that the cost of review can go up to a quarter of million dollars (vi) Time (average of 1139 hours) (McGowan et al. 2005) (vii) Access to electronic searching databases and the internet (for unpublished literature) (viii) Statistical software (if appropriate) (ix) Bibliographic software (e.g. Endnote) (x) Word processing software. Despite the significant resources needed to generate and update systematic reviews, such reviews may suffer from problems such as publication bias, time-lag bias, duplicate bias, citation bias, and outcome reporting bias (Cochrane 2013).

In that regard, several initiatives have been taken by both governmental & private organizations to optimize evidence dissemination. One such attempt is the US federal government's mandate that all "*Applicable Clinical Trials*" be published in ClinicalTrial.gov web site. ClinicalTrial.gov serves as a repository for clinical trials in a semi-structured format (XML format). This mandate, coupled with recent advances in data mining and analytics, creates an opportunity for exploring the use of these technologies to facilitate the generation and update of systematic reviews.

In this research we propose to develop a "Dynamic Systematic Review Generator," which overcomes problems of classical systematic review generation approach. Specifically, the objective of this research is to develop computer methods for producing machine-readable, real-time & cost-effective systematic review. Starting with a clinical question, the proposed system will query ClinicalTrial.gov to search published RCTs. The system will exploit advanced data analytics techniques to systematically mine clinical trials obtained from the ClinicalTrial.gov. The mining will be systematic in the sense that the system will replicate the systematic review procedure done by the human researcher (following Cochrane methods (Cochrane 2013)). Here, all RCTs will be analyzed, appraised, and finally combined to generate scientific evidence. The generated scientific evidence will be stored in a knowledge base, that is machine-readable. To the authors' knowledge (based on the comprehensive literature review), no study has been conducted that automatically and systematically mines RCTs from ClinicalTrial.gov and generates systematic review in real time.

The remainder of the paper is organized as follows: the next section provides a brief overview of the literature review followed by Theory & Artifact Design. Next, we illustrate evaluation & validation Method. After that we present expected results, contributions & discussion. The last section presents the conclusion of the research.

Related Work

Evidence Based Medicine is the practice of medicine based on relevant knowledge and evidence of potential benefit & harms associated with alternative drugs, devices, and other healthcare services. Evidence sources include randomized-controlled trials (RCT), clinical guidelines, cohort studies, Quasi-Experimental studies, descriptive studies, expert opinions and systematic review (West et al. 2002). Systematic review of medical research is one of the most reliable ways to identify harms and benefits associated with various treatment options. Specifically, a systematic review (SR) is the scientific investigation that focuses on a specific clinical question, and uses explicit and prescribed scientifically

proven techniques to identify, select, and combine the findings of similar research questions by different studies (Eden et al. 2011). Let us illustrate the importance of systematic review in the medical domain. Multiple studies related to same clinical questions are published each year, and those studies may vary on population, intervention, design, quality, and findings. An example, a systematic review may aim to identify, assess, and combine the finding of all randomized controlled trials that investigate the harms and benefits of pharmacological treatment to diabetic neuropathy patients.

Often times, the finding of one study may challenge the finding of other studies. Again, the finding of most cited studies may be refuted or challenged over time. As a result, clinical decision-making requires reconciliation and combination of various studies that provide different answers to the same question. Accordingly, conducting systematic review is resource intensive. For example, a single SR generation requires an average of 1139 human hours, and the cost can go up to a quarter of a million dollars (McGowan et al. 2005). Special training and various tools and techniques (statistical analysis tools, reference manager etc.) are required for conducting SR. It is thus almost impracticable for individual clinicians to track down and analyze all the primary studies (often as unpublished clinical trials), thus, highlighting the need for an organized approach for conducting and disseminating systematic reviews (Garg et al. 2008).

Guideline	Description
Guideline 1: Problem Relevance	The procedure of creating systematic reviews is very effort and time intensive. Moreover, generated review is complicated to consume and misses many recently published RCTs. Again, physician may not find a systematic review relevant to their clinical question. Therefore, there is an opportunity to leverage advanced analytics and dynamically generate dynamic systematic reviews that is machine-readable.
Guideline 2: Research Rigor	The proposed system will be firmly grounded in in existing guidelines for conducting systematic reviews, e.g., (Cochrane 2013). Analytic techniques will be based on existing algorithms and will be validated as described in guideline 5. The study will assure formative and summative validity by following the instructions by Lee et al. (2009). Formative validity will be assured by a) Comprehensive Literature Review & discussion with medical informatics researcher for problem identification (b) Well-established technology for system development (c) Well-suited software development methodology (d) Good Data Source—ClinicalTrial.gov. Also, summative validity will be assured through observational and experimental evaluation of the system
Guideline 3: Design as a Search Process	Problem Identification and generation of system requirements was done in iterative fashion. Moreover, optimum design requirements were finalized from comprehensive review of literature; moreover, gray literature and news articles were also reviewed.
Guideline 4: Design as an Artifact	The research will develop methods (novel techniques for generating systematic review) and Instantiation (Dynamic Systemic Review Generator).
Guideline 5: Design Evaluation	Observational Evaluation, Experimental Evaluation
Guideline 6: Research Contribution	The artifact can act as the front-end computation engine of ClinicalTrial.gov.
Guideline 7: Research Communication	The research will be published in IS and Medical Informatics Journals and Conferences.

Table 1: Design Science Research Methodology based on Hevner et al (2004)

In regard to this problem, there have been some attempts in literature to leverage the information technology and automate SR generation procedure (Aphinyanaphongs et al. 2003; Frunza et al. 2010; Kim et al. 2011; Liu et al. 2008; O'Sullivan et al. 2010; Verbeke et al. 2012; Westbrook et al. 2007). The most common usages of technology is to automate the generation of systematic reviews were (a) analyze abstract and classify articles as relevant or not (Frunza et al. 2010) (b) identify key sentences in articles relevant to clinical questions (Kim et al. 2011) (c) automatically annotate sentences in the abstract of articles in PICO (Population, Intervention, Comparison and Outcome) criteria (Aphinyanaphongs et al. 2003) (d) link clinical problems of patients with Medical Literature (O'Sullivan et al. 2010). For example, Cohen et al. (2010) proposed a text-mining based pipelining framework that supported the creation and

updating of evidence reports that provided assistance for the literature collection, collation, and triage steps of the systematic review process. Essentially, they automate the abstract review procedure of systematic review. In another instance, Kim et al. (2011) classify the key sentences in the PICO criteria (population, intervention, comparison, & outcome). Authors' research achieved micro-averaged f-scores of 80.9% and 66.9% over datasets of structured and unstructured abstracts respectively. One important outcome authors' research showed—it is easy to mine the structured abstract than unstructured abstract. Essentially, existing literature attempts to solve some part of the puzzle; however, they have rarely provided the comprehensive solution to the complicated task of systematic review generation and dissemination. Also, existing studies have not taken any advantages of opportunities created by newer initiatives (like, ClinicalTrial.gov), and they do not support the emerging concept of medical practice—"Computerized Evidence Based Medicine". Therefore, there is an immediate need by the research community to optimize the time and cost intensive task of systematic review generation and dissemination. Research communities have an opportunity to demonstrate the advantages of newer initiatives like, ClinicalTrial.gov. Therefore, in this study we propose to develop a system and associated techniques for the dynamic generation of systematic reviews which take advantage of newer federal initiative (ClinicalTrial.gov), and produce systematic review that is real-time, machine readable, and cost efficient.

Research Methodology

This study embraces the design science research approach as research methodology. The widely accepted guidelines for design science research methods have been articulated by Hevner et al. (2004) and Peffers et al. (2007). These guidelines layout the steps for conducting design science research and explicitly state the requirements for any study to be qualified as design science research. Table 1 illustrates the Design Science Research Methods Based on the Hevner et al (2004) and shows how our study fits into their approach.

Design & Development

The design and development will be based on established software development processes, design science research guidelines, and firmly grounded in established protocols for conducting systematic reviews. Figure 1 depicts the system architecture of Dynamic Systematic Review Generator. In the following sections, we illustrate the system architecture.

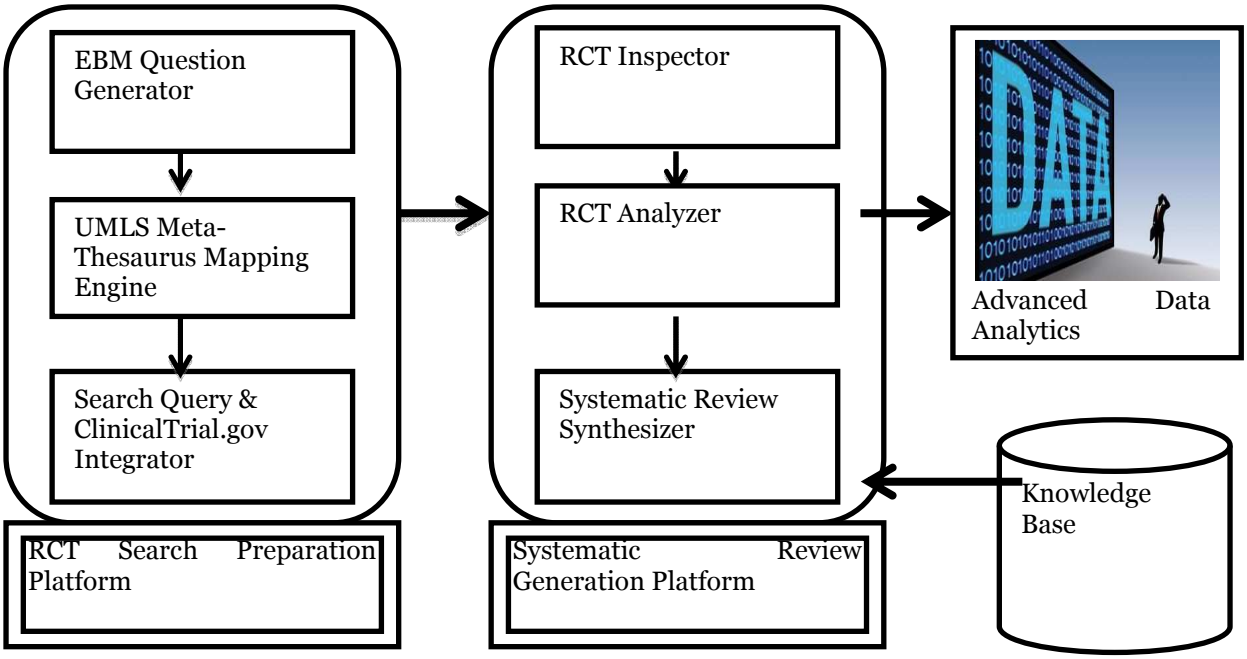

Figure 1: System Architecture

RCT Search Preparation Platform

EBM Question Generator: After clinicians enter the clinical question into the system, the "EBM Question Generator" proceeds with synthesizing that clinical question into EBM Question. One of the most popular ways to structure the EBM question is through the Population-Intervention-Comparison-Outcome (PICO) criteria. *Population* refers to the demographic and clinical information of patient; *intervention* refers to the possible course of action; while *comparison* refers to comparing between alternative interventions, or between "intervention" and "no intervention"; finally, *outcome* means output, which we want to access (clinical, economic or social).

An example of a clinical question may be: What are the harms and benefits of various pharmacologic therapies for diabetic peripheral neuropathy (pDPN) to patients greater over 18 years old? Here, "EBM Question Generator" Converts this Question into EBM Question like,

Population—condition: neuropathy, Diabetes; Age: >18 years
Intervention— Pharmacologic
Comparison—Placebo
Outcome—Benefit; Harm

Table 2: Example EBM Question

We will use Topic Modeling as the primary approach in this step—here, Topic Modeling will be used to mine the clinical question and summarize the question into a structured format that is PICO criteria. In essence, topic-modeling assist in creating new methods to browse, search and summarize large archives of text into a structured format (based on topic) (Blei 2013). We plan to use "Latent Dirichlet Allocation" as topic modeling algorithm (Blei et al. 2003), and Mallet (MALLET 2013), Stanford Topic Modeling Toolkit (The Stanford Natural Language Processing Group 2013) as topic modeling toolkit.

UMLS Meta-Thesaurus Mapping Engine: In the clinical domain, the same concepts may be referred to by multiple names. For example, Arthritis can be referred to as Gout, Ankylosing spondylitis, Scleroderma etc. Therefore, if we search RCTs with a single name, we may miss many articles. In that regard, UMLS provides a mapping structure among different vocabularies and thus allows one to translate among the various terminology systems; it may also be viewed as a comprehensive thesaurus and ontology of biomedical concepts. Table 3 presents an example of outcome of "UMLS Meta-Thesaurus Mapping Engine". The input to Meta-Thesaurus engine corresponds to Table 2.

Population—Condition: Neuropathy; Demyelinating Diseases, Polyneuropathies, Nerve Compression Syndromes, Neurologic Manifestations, Neurotoxicity Syndromes, Peripheral Nervous System Diseases, Neuromuscular Diseases, Nervous System Diseases, Type 2 Diabetes, Diabetes Complications, Diabetes Mellitus, Endocrine System Diseases; Age: 48,Sex: Male; Wt: overweight; BP: high
Intervention— Pharmacologic, Molecular Mechanisms of Pharmacological Action; Antidepressive drugs; Pharmacologic Actions; Psychotropic Drugs; Therapeutic Uses; O-desmethylvenlafaxine
Outcome—Outcome; benefit; Adverse Events; Physiological Effects of Drugs

Table 3: Example of Outcome of "UMLS Meta-Thesaurus Mapping Engine"

Search Query & ClinicalTrial.gov Integrator: We will employ the Application Program Interface (API) given by the ClinicalTrial.gov to integrate our application with ClinicalTrial.gov. The API is fairly easy; it allows the connection of a third party application to ClinicalTrial.gov, search & browse RCTs. It also allows the download of trials (single or multiple trials) in the form of txt, XML, and Oracle extract

formats (ClinicalTrial.gov 2013). "Search Query & ClinicalTrial.gov Integrator" performs the following tasks (a) take the EBM questions (from "UMLS Metathesaurus Mapping Engine") and generates the search query relevant to ClinicalTrial.gov's API (b) search relevant RCTs via ClinicalTrial.gov integrator (c) download identified RCTs in XML format.

Systematic Review Generation Platform

This platform attempts to imitate the systematic review procedure as performed by a human researcher following Cochrane guidelines (Cochrane 2013). However, instead of producing systematic reviews in a textual format, this platform produces systematic review in a structured format (machine readable) and store it in a knowledge base.

RCT Inspector: This component proceeds after clinical trials are queried and downloaded from the ClinicalTrial.gov. The primary task of this component is to either select or deselect the articles based on the inclusion and exclusion criteria. The inclusion criteria are formulated from the Population, Intervention & Comparison criteria of EBM question; whereas, exclusion criteria should be explicitly mentioned by the user. In the case of "Dynamic Systematic Review," most of the inclusion criteria can be accounted for by the search query. Nevertheless, mining of RCT records will be used to exclude articles based on the exclusion criteria.

RCT Analyzer: After the "RCT inspector" inspects and decides which RCT should be considered (for final analysis), this component comes into play. Here, protocols will be employed to analyze RCTs and extract information relevant to the clinical question. The protocols will be developed based on the analysis of systematic review generation guidelines (Cochrane 2013; Eden et al. 2011; Khan et al. 2003). However, we will principally follow systematic review creation protocols given by Cochrane (Cochrane 2013). These guidelines are meant to generate systematic review by human researchers; nevertheless, we expect to adapt these guidelines. The outcome of this component is to (a) Collect data and synthesize a structured format (b) calculate Jadad Score for each trial to assess the quality (Jadad et al. 1996) (c) Address the risk of reporting bias in included trials. Table 4 illustrates the functionalities of this component in details.

Functionality	Illustration
Collecting data relevant to clinical question in structured format (Sim et al. 2004)	Some of the example of data attributes that will be collected are: Study design, Eligibility, Exclusion criteria, Treatment comparators, Dosage and Duration, Patient Demographics (gender, age, and ethnicity), Outcome of Interest.
Calculate Jadad Score for each trial to assess quality (score range from 0 to 5, where 0 means very poor and 5 means very rigorous) (Jadad et al. 1996)	The Jadad Score can be calculated through the identification of three kind information: Randomization, Blinding, and Withdrawals & dropout
Addressing risk of reporting bias	Due to use of machine to produces systematic review and the rules of ClinicalTrial.gov; our system is immune to following reporting bias found in classical systematic review: Publication bias, Time-lag bias, Duplicate bias, citation bias, and outcome reporting bias.

Table 4: Functionalities of RCT Analyzer

Systematic Review Synthesizer: The primary task of this component is to combine and synthesize the information extracted from individual RCTs and generates evidence. The generated evidence will be disseminated in the structured format (machine readable) and stored in knowledge base. The functionalities of this component are illustrated in table 5.

Functionality	Illustration
Analyzing data and undertaking meta-analyses	Identifying and measuring homogeneity; if homogenous, study conduct meta-analysis.
Generating results and 'Summary of findings	Following summary will be created: (a) Result of Search and selection of studies; (b)Summary finding table—section of summary finding table includes: table title, outcomes, comparative risk, relative effect, number of participant, and quality of evidence (Cochrane 2013) (c) Forest plot, in case of systematic review
Interpreting results and drawing conclusions	The GRADE approach will be used to evaluate overall evidence.
Representing the results and summary in a structured format	
Storing the results and summary in a knowledge base	

Table 5: Functionalities of Systematic Review Synthesizer

Evaluation and Validation

The study follows Hevner et al. (2004) criteria for the evaluation of the research. First, we will conduct observational evaluation, the primary focus of which is to demonstrate improvement over classical methods of systematic review generation and dissemination. Here, (a) A clinical question will be chosen; then, medical informatics researchers will be asked to perform the systematic review manually (Trials from ClinicalTrial.gov) (b) the "Dynamic Systematic Review Generator" system will be employed to generate a systematic review of the same clinical question (c) a comparison will then be conducted between the systematic review generated by the human researcher and "Dynamic Systematic Review. Second we will conduct usability testing of the system based on the following metrics (Sauro 2010): Completion Rate, Usability Problem, Task Time, Task Level Satisfaction, Overall Ease of Use, Errors, Expectation, Clicks to complete task. The study will assure formative and summative validity by following the instructions by Lee et al. (2009). Formative validity will be assured by a) Comprehensive Literature Review & discussion with medical informatics researcher for problem identification (b) Well-established technology for system development (c) Well-suited software development methodology (d) Good Data Source—ClinicalTrial.gov. Also, summative validity will be assured through observational and experimental evaluation of the system.

Expected Results, Contributions and Discussion

The research will produce novel artifacts for creating dynamic systematic reviews. On completion of the project, the following final results can expected.

- Instantiation—computer application that takes a clinical question as input and produces machine readable systematic review as output.
- Methods—Novel approaches to harness data analytics to query clinical question, identify RCTs and generate the dynamic systematic review. As of the authors' knowledge there are no techniques for creating dynamic systematic reviews.

Conclusion

This study proposes a dynamic systematic review generation system. We identified five key issues with the existing approaches of systematic review generation: (a) existing reviews are largely in the form of lengthy text documents and are therefore difficult to consume at frontline of practice (b) generating systematic reviews is a costly and effort intensive endeavor (c) there is a significant time lag between publication of basic research and publication of systematic review (d) due to textual format, it is difficult to integrate systematic reviews with computerized evidence based medicine (e) human-generated systematic reviews are susceptible to multiple bias. The proposed system is an attempt to overcome those issues. Specifically, some of the key characteristics of proposed system are (a) real time evidence generation (b) machine

readable evidence format, and (c) cost effectiveness. From a practical perspective, the system is expected to produce cost efficient medical evidence, and promote evidence-based medicine. Moreover, the research proposed system and techniques can also be adapted to mine health records to produce relative evidence. From the theoretical perspective, the system provides context for evaluating acceptance and diffusion computerized evidence based medicine; as well as explores the possibility and efficacy of using advanced analytics techniques for generating machine readable, real time medical evidence.

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