CHAPTER I
INTRODUCTION

1. Introduction

Evidence based medicine (EBM) is the integration of current best evidence from systematic research with clinical expertise and patient values in making decisions about the care of patients [1]. Healthcare practitioners must have ability to use their clinical skills and past experience with EBM for rapid diagnosis, best beneficial intervention selection, and patient values expectation. They must keep looking at the best research evidence for interventions that are effective. The research with scientific methodology to identify relevant evidence, appraise, and summarize their results is systematic review (SR). It is accepted as the best source of research evidence for EBM.

SR is a form of synthesis of healthcare research literature [2]. A single healthcare question is first identified by this technique. Then existing individual studies including gray literatures are searched under eligibility criteria and search strategy. All of included studies are appraised and assessed quality. All high quality studies relevant to the question are synthesized and combined. Sometime these valid studies are integrated by meta-analysis (MA). The smaller sample size studies may have a rigorous design but lack the precision of effect (power of statistically significant effect). The pooling of statistical results in a MA can lead to improve statistical power of a significant effect.

SR can help healthcare practitioners to keep up-to-date with efficient use of reading time [3]. It has been accepted as a process which produced top high quality evidence-base in health (level 1a) [4]. SR has become increasingly popular in recent years [5] and is recommended by many as the best source of evidence to guide such decisions. SR can also help healthcare practitioners and researchers in finding the most effective treatments for patients. Policy makers use SR as a powerful tool to develop policy guidelines and technology development. Funding agencies also use SR to identify the gap of evidence for further studies [6].

2. Updating SR, the best resource

The information of interventions is dynamic and emerging over time. Effective and safe interventions may be shown ineffective or harmful, in the future or vice versa [7]. As well, new interventions will be developed and well planned randomized controlled trials to supersede other intervention. Some interventions may be reported in delayed publication or gray literature [8]. The potential availability of new evidence may result in the need to revise a SR. Therefore, SR is less useful and even misleading if it is not up-to-date [9, 10]; Updating systematic review is necessary for keeping the best evidence overtime. A formal definition of updating SR has been proposed by Moher and Tsertsvadze [9]. Updating SR is "a discrete event with the aim to search for and identify new evidence to incorporate into a previously completed SR". This definition could help reviewers to determining whether or not any given SR has been updated.

Keeping Cochrane reviews (CRs) up-to-date is an explicit policy of the Cochrane Collaboration. SRs published for two years or more in The Cochrane Library were suggested to be updated [3]. They defined the term "update" is "any modification to the published document that includes the findings (including that of no new studies) from a more recent search for additional included studies than the previous published review". The updating SR is incorporating additional studies as they become available may, on occasions, change the results and/or conclusions of a SR. There is a risk that updating SR is too frequent when the pace of reported research is slow might be unnecessary and will probably result in wasted resources, whereas low updating frequency in a fast-developing specialty could render the results of systematic reviews outdated, misleading, or both [9]. The two years updating time may not be appropriate to all SRs. The updating SR time should be appropriated with each research fields that can gain the maximum benefit to using in healthcare. However, the Cochrane Collaboration recommended that the reason why the review is not being updated in line with the Collaboration policy should be stated in the "Published notes" section of the review.

3. Empirical evidence of updating SR

Only half of the completed reviews published in The Cochrane Library were updated [11]. About 3-9% of updated reviews were changed fixed or random effects MA on the primary outcome [11, 12, 13]. Some reviews had increased and some reviews had reversed precision and statistics significance of the primary outcomes. The cross-sectional updated tag in The Cochrane Library of the year 2003 found that 3% of 181 updated reviews were changed in conclusion [14]. The survey of first published SRs in The Cochrane Library in 1998, issue 2 to 2002, issue 2 found that 70% of 362 identified SRs were updated. Of these updated SRs, 9% had changes in their conclusions [11]. The cross-sectional searched MEDLINE for SRs indexed during November 2004, 17.7% of 300 reported SRs were the updates of previous completed reviews [6]. Of these, 37.6% published by the Cochrane group had been updated compared to 2.3% of those published in peer-reviewed journal.

The study of 100 cohort SRs that published in ACP Journal Club between year 1995-2005 shows the median survival time to update was 5.5 years (95% Confidence interval (CI), 4.6 to 7.6 years). The signal was conducted from concept of potential changes in evidence. It is sufficiently threshold to warrant updating SR. Twenty-three percent of the SRs were seen signals for updating within 2 years, and 15% were seen signals within 1 year [15]. The time to update was associated with cardiovascular topics factors which were increased number of trials. The SRs in this topic should be updated rapidly. This is only the empirical evidence presents time to update.

4. Evidence of methodologies needed for updating SR

There are many methodologies for updating and presenting the SR. The fundamental of updating SR processes starts from defining what constitutes an update of review. The routine search, monitoring of trials registries and expert opinion must be extensively searched as scientific study using basic strategies. The conditions which could affect the confidence in the updating review will be identified as trigger points. Triggers are specific factors that prompt the initiation of whether or not to commence and update. The above process is essential for making decision formal whether to perform updating SR or not. New relevant trials and number of participants in the new trials will be used as factors for updating decision. The

updating process might be costly and time-consuming, however, updating SR is necessary to up-to-date and keeping the best evidence. Updating methodologies is necessary for addressing the updating problems. Moher and colleagues [16] summarizes strategies and methods described when and how to update SR into four strategies, one technique, and two statistical methods.

Four methodologies were suggested for updating SRs: steps in maintaining an update review, maintaining an updated review, assessment of the need to update, and strategies for updating a review. Chalmers and colleagues [17] described the maintaining SRs of perinatal care in seven steps. The seven steps for continuously update were 1) identify potentially eligible studies; 2) obtain copy of the report, check allocation "random" or "quasi-random" and intervention "perinatal"; 3) Enter eligible trials on central database; 4) distribute topic-specific work lists to reviewers; 5) describe tasks to reviewers; 6) update the core database; and 7) prepare data for dissemination. Maintaining process describes the identification, and obtaining gray literature and contacting authors for further information. Lutje and colleagues [18] described the editorial strategies of updating SRs of the Cochrane Infectious Disease group in two steps. The assessment of whether or not a given updating SR is consideration of age of review, availability of new relevant trails, and number of participants in the new trials. Weller [19] proposed updating strategies applicable to SR, clinical practice guidelines, and health technology assessments. This strategy suggests considering clinical endpoints (short- and long- term clinical outcomes), treatment characteristics (state of evolution of the field), statistical methodology (the conduct of cumulative MA), public health impact of treatment, and availability of resources. The Cochrane Collaboration [3] recommends updating SRs every two years. This is only the strategy mentions time to update. The mechanism to identify relevant new trials is literature searching in the CR Group's specialized register, CENTRAL, and MEDLINE. The 2-year updating cycle may lead to inefficient use of resources in slowly developing fields or out of date in rapidly developing fields. These strategies are broadly applicable but lack the detail needed for practical utility. The general description of actions is inefficiency, and unclear for how to determine whether a review is out of date and importance of the topic in order to reach editorial consensus.

A searching strategy is the main activity for maintaining and updating SRs. This is methods used to identify published and unpublished relevant evidence to be included in the review. Some relevant evidence may be delayed or gray literature, for reasons related to the publication bias. Although, indexing terms available for searching MEDLINE for randomized clinical trials have improved, but sensitivity of searching still remains unsatisfactory [20]. Therefore, many searching techniques were presented for help reviewers identified relevant evidence. Using the "entry date" field when updating a review [21] is suggested techniques for updating SRs. The suggestion to use the "entry date" field in search strategies performed for retrieve all relevant evidence rather than the publication year, could help minimizing publication bias in SRs. More than 25% of the lifespan of a review was spent in production and publication [22]. The updating search prior to submission and electronic publishing had been recommended as a promising technique to minimize time lags and may maximize the useable life of SRs. In addition, new evidence can emerge during the production and publication process, the surveillance search is the important practice for monitoring the emerging evidence that signals the need to update SR. The subject search technique combined with PubMed's related article function and citing reference search can help specifying relevant evidence [23]. The search with indexing terms of specified fields such as the MeSH terms as a search strategy could increase the relevancy of evidence [24]. A method of checking reference lists [25] is one utility to supplement poorly developed search strategies that miss relevant indexed citations and detect document type not usually indexed within bibliographic databases. However, most SRs have major weakness of the poor reporting and inadequate search strategies used [26]. The consensus regarding optimum reporting of SR search methods are not clear. However, there is a trend toward mandating more complete reporting. The reporting guidelines and instruments should be developed [27]. Reporting on searching information in SRs should contain enough detail for reviewers to monitor the updating SRs. In addition, the validation of performance of search such as MEDLINE search should be modified for improved recall before being used in the update [28].

Various statistical methods were developed for updating SRs. Cumulative meta-analyses (CMA) [29, 30, 31, 32] is a statistical procedure in which the combined

effect estimate is sequentially updated by incorporating results from each newly available study. CMA trend is used to define the earliest time at which an intervention can be shown the efficacious, non-inferior, or harmful. This technique can be used for monitor the effect size and direction over time. Thereby, CMA can be useful for providing up-to-date SRs, and serving as signal to planning future trials or stopping ongoing trials. Other techniques of CMA, such as; CMA using the cumulative slope as an indicator of stability [33], CMA using sequential monitoring boundaries [34], and Recursive CMA [35, 36], were developed for solving limitation of conventional CMA. The limitation of type I error that inflated due to multiple testing and affecting of publication bias can be solved by these techniques. However, all of CMA techniques may show the inefficiency, if an update is conducted every time a new study becomes available and they consume the resource for updating many SRs. The identifying "null" meta-analyses that are ripe for updating technique [37] can reduce type I error related to conventional CMA and use less resources than CMA technique. This technique is not widely used because of its limitation in application to only meta-analyses with statistically non-significant results. The recent study of Sutton and colleagues [38] was done to prioritize the updating of Cochrane SRs in infectious diseases. They applied two statistical methods, Barrowman and simulation-based power approaches, to rank priority for updating SRs. The prioritization was related to size of participants.

They are very few existing efficient methods, techniques, and strategies for updating SRs. Most of the strategies are generally descriptive, unclear in practice, others are specific for each clinical field, and limitation on MA. All of these strategies and methods are time and resource consuming. Therefore, methodologies for updating SRs which proved to be practical and efficient should be developed. Moher and colleagues [16] recommended that identifying predictors and triggers are needed for update SRs. Such important information would help estimating the probability of new study that indicates the need for an update within a specified period of time after completing the original SR.

5. The framework of updating SR is a guideline for updating procedure and policy

Empirical updating method is becoming imperative. The framework of updating SR [39] has been developed by experts of various areas, such as; clinical researchers, healthcare organization executives, and other methodologists with funding from the Canadian Agency for Drugs and Technologies in Health (CADTH). The objective is to be a guidance for researchers, and healthcare organizations to perform optimal decision-making of when and how to updating SR based on current information. The elements of updating framework can be explained in seven areas, including 1) surveillance and monitoring; 2) triggers; 3) update action; 4) context; 5) definition of update; 6) update procedures; and 7) research. Framework is essential to understand that combined factor effect determining the need to update. Systematic reviewers could be used relative to various research settings and contexts under which is considered updating. However, the various updating methods do not appear to specific predictor variables for "when" to update.

6. Cochrane pregnancy and childbirth reviews, a studying setting

The Cochrane Pregnancy and Childbirth Group (PCG) is, in October 1992, the first group to register with the Cochrane Collaboration [40]. PCG has a mandate to establish the evidence for clinical practice [41] as the best available evidence. The updating methods in PCG that was described by Chalmers in year 1993 [17] was the general methods. The method of updating must be improved and developed for SRs to ensure the best evidence in healthcare.

In January 2007, there were 301 PCG full text reviews and 68 PCG protocols [42]. The number of reviews and protocols has been increasing continuously. There were 399 reviews and protocols published in The Cochrane Library version 2007 issue 3 [43]. The clinical trial registration has important role in reducing the ethical problems, delayed reporting of the results, and obtaining information about ongoing and completed trials [44]. There have been increasing numbers of clinical trial registrations annually [45]. The information on clinical trial registers can be used for predicting time which will be spent for updating SRs and help reviewers in designing the updating process.

The simulation modeling is used extensively to model healthcare systems. This is particularly useful when the system is very complex or when experimentation is not possible. This process can be used to predict the outcome of a change in various strategies. The best strategy should be selected and can improve healthcare service. Simulation modeling can help SR to keeping up-to-date. The intrinsic uncertainties of healthcare evidence have been changed over time. Updating period of each SR is undertaken in health care areas and difference factors. Therefore, conducting of simulation modeling for updating SR process will be done for the appropriate time for when to updating SR. At each decision, the variety of choices is available for researcher can make an updating time for keeping SR as strong evidence.

7. Objective

7.1 To estimate average survival times to update of PCG reviews by simulation technique.

7.2 To identify the time to update and to describe updating situation of complete PCG reviews and ascertainment of factors associated with updating.

8. Benefit of the study

The estimated average survival updating time from the simulated data will be the suggested information for time to update SRs in pregnancy and child birth topics.

9. Sequences of further chapters

This study covers 4 chapters. Chapter II describes the updating situation of complete PCG reviews and ascertainment of factors associated with updating. Chapter III presents a simulation method for estimating average time to update. Chapter IV presents the summary and conclusion of the study, and suggestions for practice and future studies.

10. References

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