CHAPTER III
ESTIMATION OF TIME TO UPDATE OF COCHRANE PREGNANCY AND CHILDBIRTH REVIEWS: A SIMULATION METHOD

1. Abstract

1.1 Background: Updating is an important procedure for keeping systematic reviews as the best source of healthcare evidence. However, most CRs are not updated within the 2-year guideline proposed by the Cochrane Collaboration. The reviews which were frequently updated were mostly found little changes in the results and conclusions. Few methods were developed as guidelines of strategies, techniques and statistical methods for updating. However, they still could not recommend the timeframe for updating. The aim of this study is to estimate median simulated times for updating under various scenarios.

1.2 Methodology: We simulated times to update using parameters from the estimated effect of associated factors of time to update analyzed in 101 updated PCG reviews of the Cochrane Library 2007, issue 3. We generated 1000 sample times to update of each scenario of all possible combinations of factors on the Cox proportional hazard models with Weibull distribution. Updating was defined as 1) most recent amendment and 2) at least 50% quantitative change in effect sizes or called out-of-date. Monte Carlo procedure was used to simulate times to update of each scenario.

1.3 Results: A median of 60000 simulated times to update for the PCG reviews with most recent amendment was 2.56 years (95% CI, 2.54 to 2.58). The fastest time to update was founded in the reviews of postpartum issues (1.02 years; 95% CI, 0.96 to 1.08). The simulated time to update with non-additional database was faster than those with additional database. Simulated time to update was increased when increasing number of trials. A median of 7000 simulated times to update for the PCG reviews with out-of-date was 4.16 years (95% CI, 4.05 to 4.27). The simulated

times were less when increasing the percentage of additional participants from original published reviews.

1.4 Conclusion: Updating PCG reviews within the 2 year period of Cochrane suggested policy may not find much change in estimate effects or conclusions. The out-of-date PCG reviews were longer than 2 years. Cochrane policy guidelines should be considered updating period that is appropriate with each review topic.

2. Introduction

Updating is the important procedure for keeping SRs as the best source of healthcare evidence [1]. CRs are suggested to be continuously updated every two-year after original publication [2]. Three studies on updating of CRs found that 30% to 70% of the reviews were updated with additional the new trials [3, 4, 5]. They were frequently updated but only small proportion (3 to 9%) has changed the results and conclusions [3, 6, 7, 8]. A few methods were developed as guidelines for updating the SRs. Moher and colleagues identified methods describing when and how to update SRs which composed of four strategies, one technique and two statistical methods [9]. The broad strategies for updating SRs were generally description of steps, maintaining and assessing an updated review. However, some strategies still lack of crucial detail for practices, could not determine whether a review is out of date. Searching technique is the main activity for assessing new relevant evidence. It applies multi-dimensional searching procedures including MeSH terms, entry date field and/or related and cited article function. These techniques could help finding new relevant evidence to update the review.

CMA is a statistical method whereby existing evidence is sequentially updated by incorporating results from each newly available study. CMA trend is usually used to define the earliest time of interventions in term of efficacy or harm. Another statistic method is that of Barrowman and colleagues [10] is able to detect out-of date meta-analyses and decide to update a review with available resources. This method is less resource intensive than CMA, but it limited application to only meta-analyses with statistically non-significant results. Various methodologies for updating SRs could help reviewers to consider updating a review with new evidence. Current

updating methods may be time and resource consuming for monitoring the emerging of new evidences. Statistical methods could detect whether SRs are out-of-date or not. However, it could not recommend the timeframe for updating. There is only a Cochrane policy, which recommends every 2 years timeframe for updating. It is applied as a policy recommendation for updating. However, a 2-year updating policy may be wasted of resources in slow-developing fields, or outdated in fast-developing fields [11].

Our recent study [5] was completed using 276 Cochrane pregnancy and childbirth reviews published in the Cochrane Library 2007, issue 3. We aimed to describe the time to update and identify predicting factors associated with time to update. We found that only 36.6% (101/276) of the reviews were updated with a median time to update of 3.3 years (95% CI, 2.7 to 3.8 years). From 101 updated reviews, 53.5% (54/101) had quantitative changes in effect size and 95% CI width. Most of the changes were less than 50% from the magnitudes at original published. Their median changes in effect size were only 18.2% and the median changes of 95% CI width were 30.8%. Another study of survival update time by Shojania and colleagues [12] was found that the update reviews with quantitative changes more than 50%, have a median update time of 5.5 years (95% CI, 4.36 to 7.67 years). Both studies indicated that only few reviews (11% and 32.7%, respectively) could be updated within two years. The time to update from both survival time studies showed overall situation but could not recommend specific situations.

Simulation application can help generating time to update under various situations with adequacy sample size. The associated factors for updating such as clinical topics, number of including trials, additional searching databases, and percent of participants increase also contribute to prediction of time to update for updating SRs with or without quantitative change $\geq$ 50%. Simulation method which focuses on identifying time to update SRs could recommend the timeframe for updating and keep SRs up-to-date. This study aims to estimate medians of simulated times to update under various scenarios.

3. Methods

We used Monte Carlo procedure to simulate times to update. Parameters were from the results of associated factors of time to update on Cox proportional hazard model of our previous study [5] carried out in 101 updated reviews (pregnancy and childbirth) in the Cochrane Library 2007, issue 3. We defined updating when each review had most recent amendment (most recent update) without considering its change in effect size and conclusion. The median time to update was 3.3 years (95% CI, 2.7 to 3.8 years).

3.1 1st Simulation parameters of time to update: most recent update

The potential associated factors of time to update which were entered in the Cox Proportional Hazard model were PGC topic classification, number of additional trials, number of additional participants and additional database. Only the number of additional trials was significant associated with time to update (p-value = 0.03). The interaction between number of additional trials and number of additional participants was not significant associated with time to update (p-value = 0.18).

The contributions of different rate of new trials developments of PGC topic classification and increasing time to update when searching information in new database might be effect on time to update. Our finding did not show their association because of small samples of the reviews. We, however, simulated time to update by using the model as following

$$h(t|x) = \lambda_0 \exp(\beta_0 + \beta_1' \text{PCG topic}' + \beta_2 \text{ number of additional trials} + \beta_3 \text{ additional database}) \gamma t^{(\gamma-1)} \quad (1)$$

Estimated coefficients of individual factors of function (1) were presented in Table 6. Only number of additional trials was showed negative effect, a shorter time to update was associated with fewer trials in the update. They were used as parameters to generate the estimated time to update.

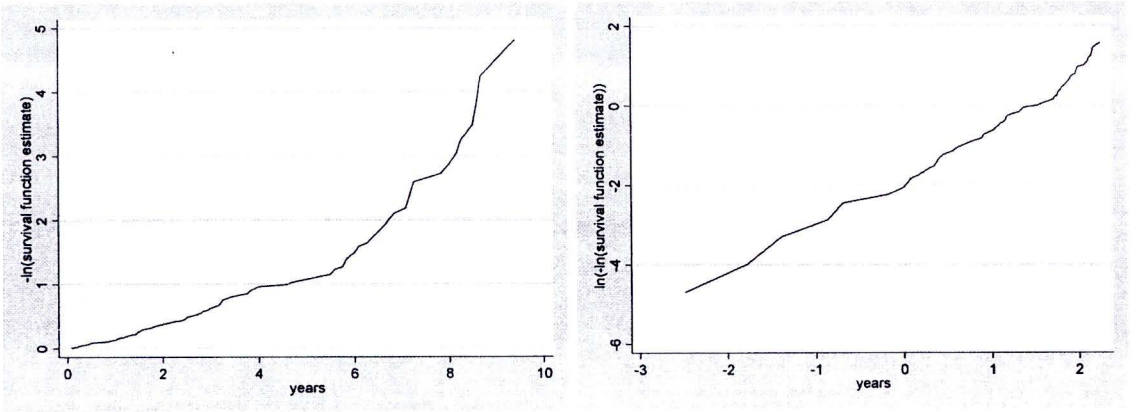
Table 6 Coefficients and standard error of Cox proportional hazard model in 101 updated reviews

Factors	Parameters	
	Coefficient	**S.E.**
PCG topic classification (β_1')		
Antenatal care	ref.	
Pregnancy complications	0.18	0.33
Fetal complications	0.08	0.33
Intrapartum issues	0.52	0.30
Postpartum issues	0.89	0.52
Increasing trials (β_2)	-0.06	0.03
Additional database (β_3)	-0.37	0.24
Constants (β_0)	-2.12	0.34
Shape parameter (γ)	1.52	0.12

For selecting distribution to simulate time to update we tested the observed time to update data S(t) for fitting with two survival distributions; exponential and Weibull distributions,

- by plotting –(ln(S(t)) versus t for exponential distribution and
- plotting the ln(-ln(S(t))) versus ln(t) for Weibull distribution.

The plots of empirical check were more straight line for Weibull distribution (see Figure 4). We then simulated each time to update using estimated function with the distribution.



a) Exponential distribution b) Weibull distribution

Figure 4 Empirical check for the parametric hazard model with exponential and Weibull distributions of 101 updated reviews

The simulation scenarios were conducted using three factors in function (1). The assigned numbers of increasing trials were estimated under observed data of our previous study [5]. The scenarios are all possible combinations of the following factors:

1) PCG topic classification: antenatal care, pregnancy complications, fetal complication, intrapatum issues, and postpartum issues
2) Number of additional trials: 1, 5, 10, 15, 20, and 25 trials
3) Additional database: added database, and non-added database

3.2 2nd Simulation parameters of time to update: 50% quantitative change in effect size as updating definition

From the 101 updated reviews, 54 showed changes in magnitude of effects (effect size and 95% CI). We used 50% change as the cut point for out-of-date reviews. We analyzed time to out-of-date in these reviews and found the median was 7.2 years (95% CI, 6.3 to 8.0 years).

The potential associated factors of PCG topic classification, percentage of increasing trials and participants, and additional database for the time to update were assessed again in these 54 reviews. Using Cox proportional hazard model, only percentage of increasing participants was significant associated with time to update (p-value = 0.02). For the simulation we did not add other non significant factors to the

model as of previous situation because coefficients of the factors were very small and their 95% confidence intervals were unreliable. This difficulty might be because our small sample size of the reviews.

The estimate hazard function with Weibull distribution was given by

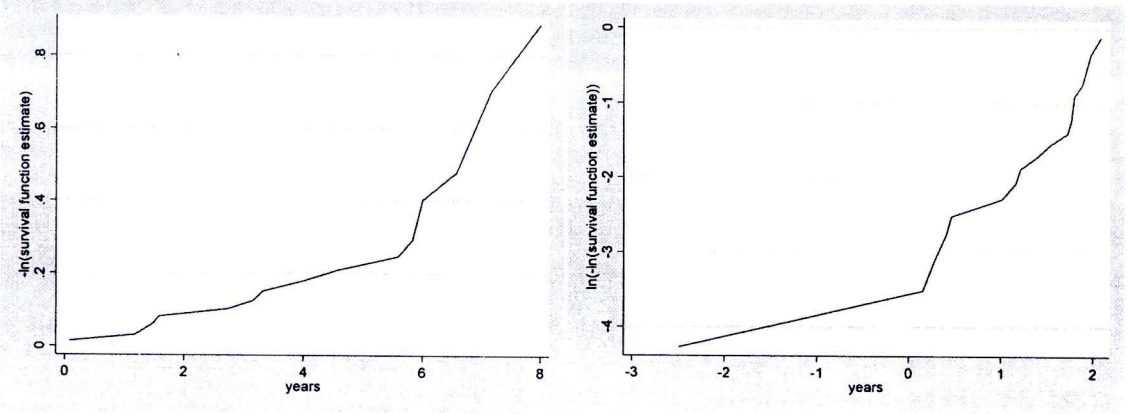
$$h(t|x) = \lambda_0 \exp(\beta_0 + \beta_1 \text{ percentage of additional participants}) \gamma t^{(\gamma-1)} \qquad (2)$$

Estimated coefficients of individual factors of function (2) were presented in Table 7. They were used as parameters to generate the estimated time to update.

Table 7 Coefficients and standard error of Cox proportional hazard model in 54 updated reviews having quantitative change

Factor	Parameters	
	Coefficient	**S.E.**
Percentage of increasing participants (β_1)	0.0009	0.0004
Constants (β_0)	-3.66	0.62
Shape parameter (γ)	1.55	0.30

The observed times to update data, S(t), were also tested for fitting with two survival distributions; exponential and Weibull distributions. The same result of more straight line was seen in the Weibull distributions (Figure 5), which was use to simulate time to out-of-date.



a) Exponential distribution b) Weibull distribution

Figure 5 Empirical check for the parametric hazard model with exponential and Weibull distributions of 54 updated reviews having quantitative change

Simulation scenarios were conducted by various assigned values of percentage of additional participants based on the range of our observed situation of update reviews. Function (2) was used to simulate the time to update using percentage of increasing participants as the percentage of additional participants as 50, 100, 200, 500, 1000, and 2000 percents according the observation from the first phase.

3.3 Simulation process

We simulated the time to update under the estimated function (13)

$$T = \left(-\frac{\log(U)}{\lambda_0 \exp(\beta' x)} \right)^{1/\gamma} \tag{3}$$

with a Weibull distribution for each scenario.

The values of γ determined the shape of the distribution curve of Weibull distribution from Table 6 and Table 7,

λ_0 determined the baseline hazard function,

β' is a vector of parametric hazard coefficients from function (1) and (2), and

U is a random variable of a uniform distribution which had 0 to 1 interval for survival function proportion.

For each scenario, 1,000 simulated time to update samples with 10,000 iterative loops were generated by using Monte Carlo procedure in STATA version

10.0 (StataCorp 2007. Stata Statistical Software: Release 10.0. College Station, TX: StataCorp LP.).

3.4 Data Analysis

Kaplan-Meier survival curve was used to estimate the median time to update and their 95% CI for each scenario.

4. Results

4.1 Time to update at most recent amendment

Overall 60000 simulated times to update the median was 2.56 years (95% CI, 2.54 to 2.58, Figure 6). Median times to update and their 95% CIs for individual scenario are shown in Table 8. Fast updating of the simulated times was seen in postpartum issue for all scenario. Latest updating of the simulated times was seen in antenatal care. The median times to update were increase with additional new searching database and trials. The fastest updating was seen in the simulated time to update of postpartum issues without additional database but increasing of one trial (median 1.02 years; 95% CI, 0.96 to 1.08 years). The latest updating was almost 5 years in antenatal care topic with additional database and increasing of 25 trials (median 4.83 years; 95% CI, 4.59 to 5.07 years).

Table 8 Median and 95% CI of simulated times to update at most recent amendment

PCG topic classification	Additional database	Median survival time (95% CI) (years)					
		Number of increasing trials					
		1	5	10	15	20	25
Antenatal care	Add database	2.4 (2.2 - 2.5)	2.7 (2.6 - 2.8)	3.4 (3.2 - 3.6)	4.1 (3.9 - 4.3)	4.4 (4.2 - 4.7)	4.8 (4.6 - 5.1)
	Non add database	1.8 (1.7 - 1.9)	2.2 (2.1 - 2.3)	2.8 (2.6 - 2.9)	3.3 (3.1 - 3.5)	4.1 (3.8 - 4.4)	4.4 (4.1 - 4.6)
Pregnancy complications	Add database	2.2 (2.1 - 2.3)	2.5 (2.3 - 2.6)	2.9 (2.7 - 3.1)	3.7 (3.5 - 3.9)	4.1 (3.8 - 4.4)	4.8 (4.5 - 5.0)
	Non add database	1.6 (1.5 - 1.8)	1.9 (1.8 - 2.0)	2.4 (2.3 - 2.6)	2.9 (2.7 - 3.1)	3.5 (3.3 - 3.7)	4.3 (4.1 - 4.6)
Fetal complications	Add database	2.2 (2.0 - 2.3)	2.6 (2.5 - 2.8)	3.3 (3.2 - 3.5)	3.7 (3.5 - 3.9)	4.6 (4.3 - 4.9)	4.8 (4.5 - 5.2)
	Non add database	1.8 (1.7 - 1.9)	2.1 (2.0 - 2.2)	2.6 (2.4 - 2.7)	3.2 (3.0 - 3.3)	3.7 (3.4 - 3.9)	4.2 (4.0 - 4.4)
Intrapartum issues	Add database	1.7 (1.6 - 1.8)	2.0 (1.9 - 2.1)	2.4 (2.3 - 2.5)	3.1 (2.9 - 3.3)	3.5 (3.3 - 3.8)	4.2 (4.0 - 4.5)
	Non add database	1.3 (1.2 - 1.4)	1.6 (1.5 - 1.7)	1.9 (1.8 - 2.0)	2.3 (2.1 - 2.4)	2.9 (2.7 - 3.1)	3.4 (3.2 - 3.6)
Postpartum issues	Add database	1.3 (1.2 - 1.4)	1.5 (1.4 - 1.6)	1.9 (1.8 - 2.0)	2.4 (2.2 - 2.5)	2.8 (2.7 - 3.0)	3.6 (3.4 - 3.8)
	Non add database	1.0 (0.9 - 1.1)	1.2 (1.1 - 1.3)	1.6 (1.5 - 1.7)	1.8 (1.7 - 1.9)	2.3 (2.2 - 2.4)	2.9 (2.7 - 3.0)

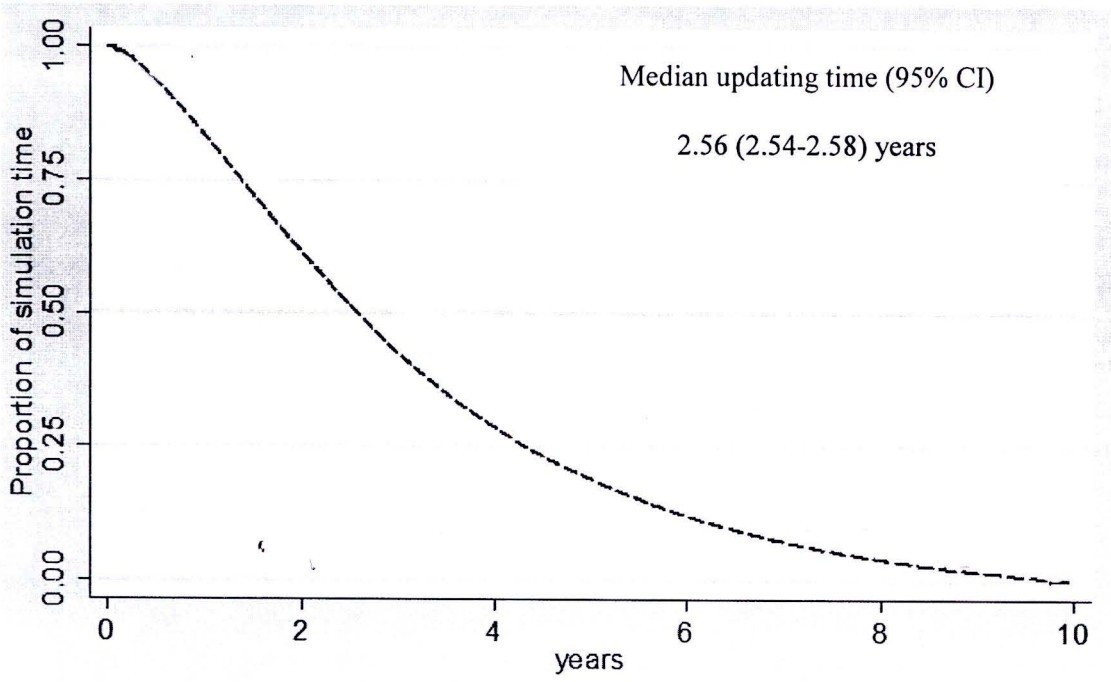


Figure 6 Time to update curve of simulated data compare with original data of 101 updated reviews

4.2 Time to out-of-date at 50% quantitative change in effect size

We simulated 7000 times to update with various percents of increase participants. The median time to update was 4.16 years (95% CI, 4.05 to 4.27, Figure 7). Median simulated times to update were shown less when increase percents of additional participants from original published review (Table 9). The median time to update was 8.23 years (95% CI, 7.66 to 8.81 years) when increase 50% of additional participants from original published review. The median time to update decreased to 2.60 years (95% CI, 2.46 to 2.74 years) when increase up to 2000% of additional participants from original published review.

Table 9 Median and 95% CI of simulated times to out-of-date reviews

% additional participants	Simulated time (years)	
	Median	**95% CI**
50	8.23	7.66 - 8.81
100	7.76	7.40 - 8.12
200	7.37	6.95 - 7.79
500	6.39	6.10 - 6.67
1000	4.56	4.31 - 4.81
1500	3.22	3.00 - 3.44
2000	2.60	2.46 - 2.74
Overall	**4.16**	**4.05 - 4.27**

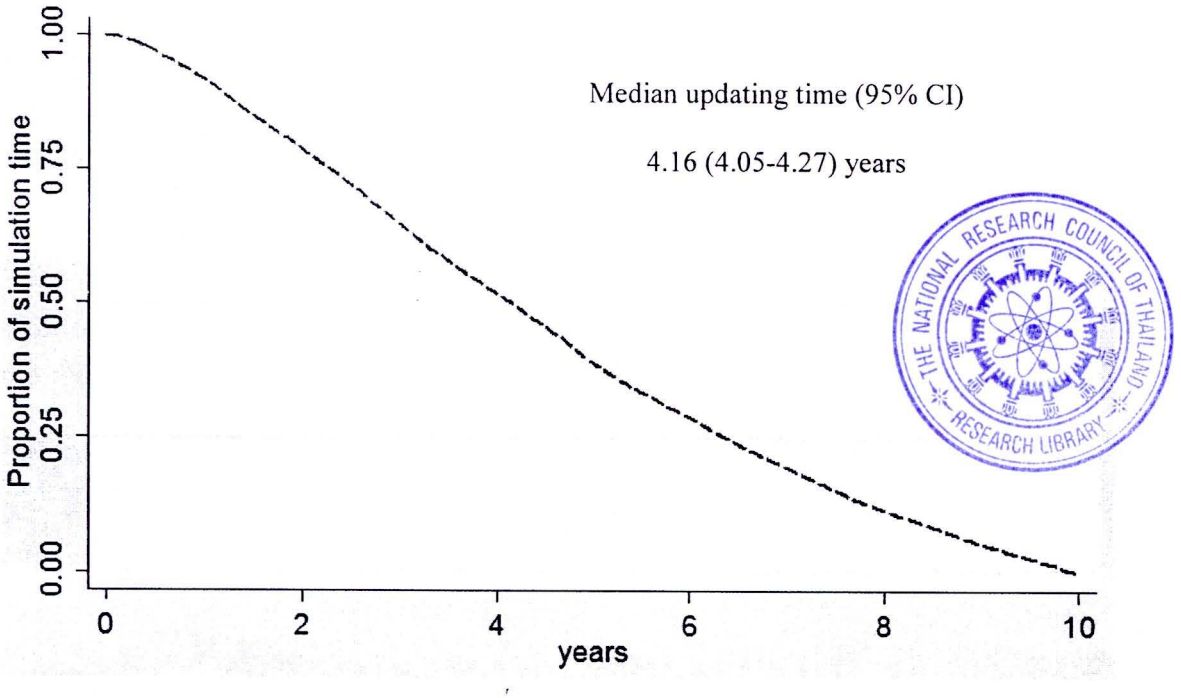


Figure 7 Time to update curve of simulated data compare with original data of 54 updated reviews having quantitative changes

5. Discussion

Our simulations of time to update were based on the parameters from the effects of associated factors on updating time of our previous study in the 101 PCG reviews [5]. The results of simulating time to update at most recent update indicated the median time to update of 2.56 years (95% CI, 2.54 to 2.58 years). The median was lowest in the estimated times to update of postpartum issues and highest in the estimated times to update of antenatal care issues. The results of simulating times to out-of-date when use 50% quantitative change in effect size as the cut-off indicated the median time to update of 4.16 years (95% CI, 4.05 to 4.27 years). The simulation results show shorter time to out-of-date when increase percents of additional participants at update period.

The simulated time to update at most recent amendments indicated that PCG reviews could be updated within the 2-years recommendation of Cochrane policy. However, the different simulated times to update of various PCG topics were seen. This may be reflected the different frequencies of trial development among the PCG areas.

The median simulated time to out-of-date, 4.16 years (95% CI, 4.05 to 4.27 years), is longer than the median simulated time to update at most recent amendments, 2.56 years (95% CI, 2.54 to 2.58 years). The results indicate that the time to update of 2 years after first publication may be inappropriate if changes in conclusions are expected with an update. The result of the median simulated time to out-of- date is relevant to the findings reported by Shojania and colleagues [12] in the 100 updated reviews with wide range of clinical areas. They report median time to out-of-date with the 50% quantitative change cut-off was 5.5 years (95%CI, 4.6 to 7.6 years). The median simulated time to out-of-date results also support our previous review findings [5]. It was found that the median change of 18.2% in effect size estimates and 30.8% in 95% CI width were seen in the 54 update PCG reviews at a median of 3.3 years.

Increasing number of trials and participants may be very difficult when frequency of trial development in some clinical areas were slow. Thus, updating every 2 years in some clinical areas such as pregnancy and childbirth may not affect to the results and change interpretation of conclusion. Reviewers may waste time, money and other resources for updating activities. Our results may be the beneficial

information to the Cochrane Collaboration in reconsideration updating time frame for each clinical area to maximize benefit and make the CRs as the best source of evidence for healthcare practices.

The simulated times to update increased when applied new search in new databases. However, reviewers should improve search strategy and add new databases because the new relevant trials might not be found by insensitive original search strategy.

A limitation of our study is the simulation parameters were from the results in a cohort of 101 update PCG reviews published in the Cochrane Library 2007, issue 3. Of these 53.5% (54/101 reviews) had quantitative change. The small sample size limited the potential associated factors to be significantly predicted time to update by Cox proportional hazard model. However, some non-significant associated factors of PCG topic, additional database and trials with time to update were still added to the Cox model for the simulation. It was because there was evidence of their significant effects on time to update [5, 12]. The PCG topic classification was used rather than trial development rate because it was difficult to study trial development rate in this study since data collection was time consuming. However, PCG topic had different trial development rate and could affect the accuracy of time to update. This is only a sample in a CR group but we believe the results could reflect to other CRs.

Our study used Cox proportional hazard model to simulate time to update. The model could give specific time to update in various situations using the effects of model predictive factors as parameters. The times to update were simulated in the Weibull distribution. The generated times to update had slope closer to the slope of the original time to update comparing to those simulated in the exponential distribution. Two previous studies of method to identify time to update were differed from our study. Berkey and colleagues (14) studied the estimated time of first significance in CMA. They simulated information of treatment effect using regression model with normal distribution. Berkey's study did not identify variables which influence the first-time to update and did not have specific criteria for out-of-date. The study of Barrowman and colleagues [10] was to determine when meta-analyses are out-of-date. They used *z*-statistics to test null meta-analysis whether the review was out-of-date or not and used new participant ratios as the best candidates for updating.

It simulated number of trials using binomial distribution with event rate sampled from a uniform distribution between 1% and 50% and simulated number of participants using Poisson distribution with expected value *E*. Both studies did not relate to time function in the simulation model.

The recent study of Sutton and colleagues [15] was done to prioritize the updating of CRs 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. This study showed that the two approaches were close agreement in update priority. Our simulation finding was consistent with this study, i.e. the shorter simulated time to update also related to the higher percentages of additional participants from original SRs.

In conclusion, our study indicated useful information for those who produce, publish, and use PCG reviews. Updating reviews within 2 years period as the Cochrane updating policy recommendation may not show the change in effect estimate or conclusion which would be waste of resources. Cochrane policy guidelines should be reconsidered in the appropriate time to update for each CR topic.

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7. Author Contributions

Conceived and designed study: WJ DM ML. Collected and performed data analysis: WJ. Drafted paper: WJ ML interpreted the data: WJ DM ML. Edited and approved the paper: DM ML.

8. References

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