# Protocol - Version 6, 18th march 2016

# Pace of evidence generation in comparative effectiveness research and feasibility of live cumulative network meta-analysis Tania Martin-Montoya, Ludovic Trinquart, Philippe Ravaud INSERM U1153 Methods team

## Background

When several treatments are available for a given condition, a series of meta-analyses provide only partial information because they can answer questions about pairs of treatments at given point in time. Moreover, they become frequently out-of-date quickly, sometimes even by the time they are published. This inability to maintain currency leads to significant inaccuracy [2]. Hence, it has a direct impact for patient care and research planning [3].

A broader scope that aim to synthesize all randomized trial data available from all available treatments of a given condition, including the direct and indirect evidence, is the network metaanalysis (NMA) [4]. Compared with conventional meta-analyses, network meta-analyses allow for visualisation of a larger amount of evidence, estimation of the relative effectiveness among all interventions (even if direct comparisons are lacking), and rank ordering the interventions [5]. Thus, NMAs may yield more reliable and definitive results than would conventional meta-analyses [6]. However, NMA is also affected by the out-of-date issue. To counteract this, recently, Crequit et al. have proposed to push further the network meta-analysis into what they have called the "live cumulative network meta-analysis"[7].

Live cumulative network meta-analysis is a single systematic review and evidence synthesis (with meta-analyses and network meta-analyses) covering all treatments available for the same disease, and systematically updated when new trial results become available. Starting from an initial network meta-analysis, the updates take place trough an iterative process. The iterations consists in search for, screen, and select trials with new results and, if any, extract data, assess the risk of bias, and update the network meta-analysis. The updates in live cumulative network meta-analysis need to be performed at fixed regular intervals, nevertheless the determination of these intervals depends on the pace of evidence generation of each topic, that is to say that each live cumulative NMA may need a particular interval for being updated. For example, for the second line treatments of non-small cell

lung cancer (NSCLC) the authors determined that the interval needed to perform the iterations was 4 months [7].

The amount of work required to perform one network meta-analysis correspond to multiplying the amount of work required for several conventional meta-analyses. The feasibility of live cumulative network meta-analysis relies on the idea that the updating process is less-time consuming than the realization of the initial NMA. In this study, we aim to determine the pace of randomized evidence generation across a wide range of comparative effectiveness research (CER) topics and to assess the feasibility of, as well as the need for, live cumulative network meta-analysis across a range of CER topics.

## Methods

We will select a sample of network meta-analyses of different CER topics. For each corresponding CER topic, we will assess the pace of evidence generation, in terms of the evolution of the numbers of trials, treatments and treatment comparisons with time. Then, for each NMA we will estimate the amount of work needed to perform that initial NMA and the amount of work needed to perform the updates in the framework of live cumulative network meta-analysis.

# Search and selection of network meta-analyses

We will search for all network meta-analyses indexed in MEDLINE in 2015. We will use the search strategy reported in Appendix 1. Eligible NMAs will report the date of last search, flowchart (with the numbers of records screened on title and abstract, the numbers of records screened on full-text, and the numbers of trials included in each NMA), treatments arms assessed, and the citations to included trials.

We will exclude duplicates, comments, conference proceedings, methodological studies related to network meta-analysis, protocols, updates, other type of studies using data from a previous published NMAs (i.e cost-effectiveness, systematic reviews, etc.), NMAs that included less than 20 trials, and CER topic overlaps. Updates refers to a NMA that aimed to search of more recently published studies to incorporate and bring up to date a previously published NMA; we will exclude them because the amount of work required to perform such updates will underestimate the work required to perform a typical NMA. CER topic overlap refers to the situation when several NMAs address the exactly same indication; in that case, we will select the NMA that included the largest number of trials.

## Data extraction

We will develop a data extraction form. We will extract for each NMA: the first author, journal, title, the corresponding author and his email, the date of last search, the number of records screened on title and abstract, the number of records screened on full-text and the number of included trials. The included trials are those that met the eligibility criteria regardless of the outcome or the treatment arms. In other words, included trials are not necessarily those selected for the meta-analysis.

For a given NMA, we will extract for each included trial: the date when it became first available (e.g publication date, if any) and the treatment arms, regardless of the outcome assessed. If possible, we will retrieve automatically the publication date of the trials included in each NMA using the *Web of Science* database, otherwise we will retrieve them manually. We will extract only treatments that were considered in the NMA. If a trial assessed A versus B versus C, but C does not make part of the network, then we will not extract C as a treatment. Moreover, we will define treatments exactly as they were defined in the NMA, for example, if similar treatments were lumped in together we will maintain it [8].

For each NMA, we will contact by email the corresponding author to request the list of references of the records screened on title and abstract and the records screened on full-text. In absence of reply, we will send two reminders 7 and 14 days after the initial email. Those NMAs in which the list of references is not submitted by authors will be excluded for the analysis of the amount of work for the update of network meta-analysis.

Two reviewers will independently extract data from a random sample of 10% of reports. Disagreements will be resolved by discussion.

# Pace of randomized evidence generation in CER

For each NMA, we will identify the first available trial and we will assess the time of appearance of the subsequent trials using it as the reference. We will assess the cumulative numbers of trials, treatments and treatment comparisons with time; the time unit will be months. Then, we will produce growth curves. As each NMA represents one different CER topic, the growth curves we will estimate the pace of randomized evidence generation within each CER topic. Based on the pace of randomized evidence generation across all CER topics we will look for different clusters of CER topics through group-based trajectory modeling. Group-based trajectory modeling is an statistical method designed to identify cluster of individuals (here CER topics) called trajectory groups, who have followed a similar developmental trajectory (here pace of evidence generation) on an outcome of interest. This kind of modeling has been applied to answer several clinical research questions [9, 10, 11].

We will summarize data by estimating the average rate of appearance over month of new treatments, trials and treatment comparisons, for a given CER topic.

## Feasibility of live cumulative network meta-analysis

We will assess the feasibility of live cumulative network meta-analysis by quantifying the amount of work needed to perform the updates for each NMA.

The amount of work will be estimated as the equivalent of full-time work hours. We will assess this time through surveys of expert reviewers working in ongoing systematic reviews. We will ask them to measure the time needed to perform the following tasks: i) screening 500 records on titles and abstracts, ii) screening 100 records on full-text, and iii) data extraction and risk of bias assessment of 10 records.

#### Amount of work for the initial network meta-analysis

We will estimate the full-time work hours needed to perform each NMA through the number of records screened on title and abstract, the number of records screened on full-text, and the number of included trials, reported in the flowchart. We will multiply these numbers to the average time obtained from the expert reviewers survey, respectively. Then we will calculate the mean work needed and its variability across all the NMAs.

#### Amount of work for the update of network meta-analyses

We will perform a retrospective analysis. We will start from the initial network meta-analysis and we will evaluate backwards the amount of work needed to perform the updates through 5 iterations separately. The updating interval will be 4 months. In sensitivity analysis, we will use 6 and 12 months.

For the first iteration, the interval corresponds to the time between the date of last search and 4 months before the date of last search. For this interval, we will use the number of records screened

on title and abstract, the number of records screened on full-text, and number of included trials, from the list of references submitted by the corresponding authors and the list of references of included trials from the NMA report, respectively. For the next iteration, the interval corresponds to time between 4 months and 8 months before the date of last search. We will assess equally the numbers of records screened (on title and abstract, and on full-text) and the number of included trials for this interval and so forth. We will repeat this algorithm until the fifth iteration.

We will estimate the absolute full-time work hours needed to perform the update in each interval through the numbers of records screened on title and abstract, the numbers of records screened on full-text, and the number of included trials, submitted by the correponding authors. We will multiply these numbers to the average time obtained from the expert reviewers survey, respectively.

We will estimate the relative full-time work hours needed to perform the update in each interval. We will divide the absolute full-time work hours needed to perform the update in each interval out of the full-time work hours needed to perform each NMA. Finally, we will calculate the mean of absolute and relative full-time work hours and their variability within the 5 iterations and across all the NMAs.

#### References

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#### Appendix

#### 1. Search strategy

|    | MEDLINE  |
|----|--|
| #1 | "mixed treatment comparison"[tiab] OR "mixed treatment comparisons"[tiab] OR "network      |
|    | meta-analysis"[tiab] OR "network meta-analyses"[tiab] OR (multiple-treatments[tiab] AND    |
|    | meta-regression[tiab]) OR "multiple-treatment meta-analysis"[tiab] OR "multiple treatments |
|    | meta-analysis"[tiab] OR "multiple-treatment meta-analyses"[tiab] OR "multiple treatments   |
|    | meta-analyses"[tiab]   |