REVIEW

The Use of Prospective Meta-Analysis

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Abstract

Meta-analysis is a powerful statistical instrument to summarize the knowledge in a research field, and to estimate overall measures of effects based on reported or unreported results. In performing meta-analysis is generally used the results of the reported trials. Knowing the results before the meta-analysis may affect the description of the review query, the entry and exclusion specifications because the researchers may also be prejudiced in selecting favor of reports supportive for their own thoughts. With these problems the retrospective meta-analysis is becoming a controversial tool in terms of "bias". The prospective meta-analysis can cope with these problems of the retrospective meta-analysis. A prospective meta-analysis is a type of next-generation systematic reviews where studies are investigated to be eligible before reporting their original studies. Prospective Meta-Analysis is unaware of the results of all studies because of the prospective identification and application of selection criteria for trials. In this paper, it is aimed to give information about Prospective Meta-Analysis, and to promote the use.

Key words: Meta-Analysis, Prospective Meta-Analysis, Randomized controlled trial, Publication bias, Researcher bias

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Introduction

The combining the results of studies on the same subject is continuing for long time as a scientific tradition (Berlin and Colditz, 1999). The utilization of meta-analysis is becoming increasingly prevalent for combine methodological and formally similar studies.

Meta-analysis, a notion coined by Glass (1976), is purposed to ensure the statistical investigation of a wide compilation of analysis outcomes from independent researches for the aim of combination the outcomes. Meta-analysis, or research synthesis, or research combination is a scientific method of achieving this goal through certain statistical methods, and really it has a long and former history (Hartung et al., 2008).

Meta-analysis, which is a complicated statistical method containing the generation of data obtained from related researches to determine impact size or result, has more and more noticed and influence evidence-based medicine, particularly in the area of health sciences. Through the arrival and unfulfilled

needs of the evidence-based medicine, the initial registerable article of a meta-analysis that addresses the efficiency of the typhoid vaccine in 1904, the quality and number of meta-analyses published in relative to health sciences have increased significantly (Mak et al., 2010).

Upon the emergence of evidence-based medicine approach in the recent two decades, meta-analysis has turned into a widespread study instrument to compound inputs from different studies and process them collectively. Meta-analysis ensures crucial data for creating clinical outlines and generating health policy suggestions (Turok et al., 2011; Tu and Faggion, 2012). Conventional meta-analysis, however, suffers from the heterogeneousness of the including studies of where tests a distinctive interference and evaluates a particular main result. While attempting to include all relevant data, other traps associated with meta-analysis contain discriminative reporting biases and reluctance of investigators' project data (Turok et al., 2011).

Assembling the results of many randomized studies in a meta-analysis ensures a strong and systematic tool to reliably predict modest but valuable developments in therapy. However, traps in the meta-analysis can further be run across because of the strength of this approach in determining small biases. Some of the traps in meta-analysis contain:

- the selection bias of patients;
- the selection bias of studies;
- the bias owing to the post hoc choice of study queries, suitability criteria, result description, or subgroups (Simes, 1995).

Bias in Meta-Analysis

Meta-Analysis is a statistical method used by researchers to quantify methodologically similar studies. In other words, Meta-analysis is a quantitative systematic review used "to combine the results of a number of different reports into one report to create a single, more precise estimate of an effect" (Ferrer, 1998). With the Meta-Analysis developed as an alternative to traditional literature review, new conclusions are generally made from the results of the previous research. Before applying the meta-analysis, the researchers decide which studies and which statistical methods to use. In this decision phase, they learn the results of previous studies, and this may cause the selection to be made in favor of the own ideas. This potential case arises

the problem of bias in meta-analysis (Eysenck, 1994; Egger, 1998).

Typical retrospective meta-analysis looks like investigative rather than corroborative study. Decisions regarding researches to be subsumed, statistical investigations, and moderating elements are generated after the researchers recognize the results of the researches. These retrospective decisions have high probability for bias. For ensure confirmatory proof, methodological decisions in meta-analysis must be carried out prospectively, before the outcomes of the studies are known and ideally before studies are made (Watt and Kennedy, 2017). Multi-center randomized controlled trials and meta-analysis are the gold standard for evidenced-based medicine. However, multi-center trials are expensive and relatively uncommon in the literature. Recently, the use of meta-analysis is popular, because it combines inputs from many trials and processes them in the aggregate. Yet, selective reporting biases when trying to incorporate all thematic input (Turok et al., 2011).

In the meta-analysis, bias is a very important issue. The potential sources of publication bias are "researcher bias", "selection bias of subjects and trials" and "bias due to post hoc selection of study questions", "eligibility criteria", "outcome definitions or subgroups" (Alderson et al., 2004; Askie et al., 2011). Publication bias may cause critical results, particularly in the areas of epidemiology and medicine (Weiss and Wagner, 2011). Dickersin (2005) notes that there are some studies that is influenced by meta-analyses that suffer from publication biases in the even the treatment of life-threatening diseases (Weiss and Wagner, 2011).

Prospective Meta-Analysis

A meta-analysis may be performed by retrospective or prospective. While, a retrospective meta-analysis is performed on data extracted from the literature, a prospective meta-analysis (PMA) is performed on the actual raw data from the various studies. "Patient-level data" that have been directly and individually collected during a clinical trial as individual will only be available in a prospective analysis (Herson, 2009). This chance of using patient-level data is one of the advantages of PMA.

PMA analysis plans are unaware of the results of all studies. This prevent possibly biased, data-dependent emphasis on specific subgroups or specific endpoints. Most widely, PMA has been

practiced to randomized studies, but it is a method that could be practiced to the PMA of observational studies as well (Berlin and Ghersi, 2004). They have joint properties with both aggregate meta-analyses

and including individual patient data. PMA may help to tackle some of the known troubles of retrospective meta analyses;

- indicating hypotheses that are unaware of the results of individual studies;

- to ensure that the study election criteria are implemented prospectively;

- to ensure that a priori declaration of planned analysis, including subgroup analyses, to be generated before the outcomes of individual studies are known. This prevent probable challenges in explication relevant to the data-dependent emphasis on specific subgroups (Ghersi et al., 2011).

PMA is a meta-analysis where studies (generally randomized controlled trials) are defined, evaluated and specified to be suitable before the results of any of the studies become known. This is distinct from a systematic review because the included studies are usually determined after completion and reporting of results (Ghersi et al., 2011; Anonymous 2, 2018; Anonymous 2, 2018)

Retrospective meta-analysis rises the statistical strength and ensure more exact predictions of the therapy influence by incrementing sample size. While meta-analysis use widespread in medical literature, PMA is a comparatively new methodology. In PMA, the certain interferences as well as the primary and secondary results are stated before data from certain studies are published (Turok et al., 2011). PMAs enable the identification of hypotheses before the results of individual studies, and provide a prospective execution of study selection criteria; and perform the pre-definitions of the intended analyses. PMAs are generally undertaken by a common group and generally collect and analysis individual patient data (Ghersi et al., 2011).

Watt and Kennedy (2017) reported that there are three options for PMA:

1. The most apparent choice is to pre-register the meta-analysis plan and include in the meta-analysis only researches handled after the plan was registered. The meta-analysis plan would determine the statistical investigations and the criteria for detecting which studies are included. Next studies that abide by the inclusion/exclusion criteria would be included in the meta-analysis. Unhappily, that

choice is probably to keep remarkable retrospective deciding.

2. A more powerful alternative for PMA is to pre-determine the protocols of studies included as part of the meta-analysis plan. In multicenter studies, all researchers generally need to adopt the same protocols.

3. It is recommended that a registration-based PMA in which the decision to include or exclude a specific research study prospectively based on preliminary records for the research.

PMA ensures statistical strength to study substantial queries about rare cases and subgroups. The skill to examine subgroups is not specific to PMA, but a pre-description of subgroups in a PMA submits the benefit of preventing the bias in the post hoc description of prevalently used subgroups (Rothstein et al., 2005).

A PMA must be planned meticulously and should be registered a protocol such as that sustained by the Cochrane Collaboration from the outset (Reade et al, 2010; Anonymous 8, 2018). There are several PMAs maintained over decades, with new trials adding to the enlarging data compile (Porgue and Yusuf, 1998). If the meta-analysis is finished prematurely, there is little instance to conduct the reactions of researchers in trials still underway (Reade et al., 2010).

A PMA should have a openly obtainable guideline. Berlin and Ghersi, (2004) and Ghersi et al. (2011) note that the contents of this protocol can be summarized as in Table 1.

An Example for the Use of PMA

Askie et al. (2018) performed a study to compare the influences of varying target intervals for oxygen saturation as determined via pulse oximetry (SpO2) on major morbidity or death. A prospectively planned meta-analysis named as Neonatal Oxygenation Prospective Meta-analysis (NeOProM) composed of independent participators' input for five clinical trials (Anonymous 1-6, 2018) These researches were assessed as suitable to include in the meta-analysis before the outcomes of any of the trials given (Ghersi et al. 2011). 4965 newborns were included to this study. The study protocol was published in 2011 and registered on "ClinicalTrials.gov". The statistical analysis plan was finalized in 2015. In this PMA results of independent participators' input from highly preterm newborns, no significant difference was detected in a comparison between

lower SpO2 target interval and higher SpO2 target interval on the early combined result of major disability or death at an adjusted age of 18 to 24 months. The lower SpO2 target interval was related with an elevated threat of necrotizing enterocolitis and death, however a lower risk of retinopathy during premature therapy. All in all, the use of PMA provided in this study that the researchers can comply to take advantage of the identical tool to define a specific result, and to determine the results at the identical check-points in the trials.

Table 1. Contents of a PMA as stepwise (Berlin and Ghersi, 2004)

Objectives
- Specify the particular hypotheses.

Methods

Criteria according to the studies for this review
- Suitability criteria for trial designation (e.g. needs for randomization).
- Suitability criteria for the target population.
- Suitability criteria for each comparator and intervention.
- Result information: determination of definitions, primary and secondary endpoints, timing, measurement instruments.
- Details of subgroups.

Search methods for identification of studies
- Describe efforts made to identify ongoing trials.

Data collection and analysis

· *Trial details:*
- List details of trials specified to include.
- An expression outlining if, at the time of submission for registration of the PMA, any trial results were known; Trials should be included only if their results were unknown at the time they were identified and added to the PMA
- Whether a signed agreement to cooperate has been obtained from the appropriate reference of each trial (e.g. the principal researcher or sponsor).·

Analysis Plan:
- Sample size and power calculation, subgroup analyses etc.

Management and Coordination:
- Details of management structure and committees.
- Data management (data to be collected, format required, quality assurance procedures, etc).
- Responsibility for statistical analyses.

Publication Policy:
- Policy of authorship (e.g. publication in 'group' name).
- Writing Committee (membership, responsibilities).
- Policy of manuscript (e.g. shared to all collaborators for interpretation).

Conclusion

In this paper, it is aimed to give information about PMA, a type of next-generation systematic reviews, and to promote the use.

In recent years, the use of meta-analysis has become increasingly popular, as it has ability to combining the results of different studies in one study. However, publication bias is a serious problem in meta-analysis, which can affect statistical power. Thus, PMA with some distinct advantages should be preferred rather than retrospective meta-analysis of published data.

As a result, PMA can used in the medical research to establish causative links between treatment and results. Planning a PMA of collected data from associated researches and the usage of real data will help a more accurately prediction of the influences of treatment methods in health sciences.

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